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Three Consecutive OnabotulinumtoxinA Cycles in Cervical Dystonia and Primary Hemifacial Spasm: A Retrospective Cohort Study

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Abstract

OnabotulinumtoxinA (onaBoNT-A) is used to treat cervical dystonia (CD) and primary hemifacial spasm (HFS), but real-world outcomes across repeated treatment cycles are less well described. This retrospective single-center study analyzed 74 adults who completed three consecutive injection cycles (34 with CD and 40 with HFS; 222 cycles); 56 had received botulinum toxin before the first recorded cycle. Clinical scores were recorded by the treating neurologist before injection and approximately four weeks afterward. Changes were analyzed with mixed-effects models accounting for repeated observations within patients; patient-level bootstrap confidence intervals were calculated. In CD, the model-estimated reduction in the Toronto Western Spasmodic Torticollis Rating Scale total score was 12.8 points (95% CI 11.4–14.4). In HFS, the Jankovic Rating Scale total score decreased by 4.2 points (95% CI 3.9–4.5). Descriptive responder proportions were 73.5% and 90.0% of cycles, respectively. Patient-reported effect duration was approximately 11–12 weeks in both cohorts. Adverse events were predominantly transient and anatomically localized; however, 29.4% of patients with CD reported neck weakness and 20.6% reported dysphagia at least once, whereas ptosis and dry eye predominated in HFS. Because only treatment completers were included, most patients were prevalent users, and outcomes were rated by an unblinded injector from routine records; these findings describe outcomes in patients who continued treatment and do not establish treatment effectiveness or safety in all patients starting therapy.

Keywords: onabotulinumtoxinA; botulinum toxin; cervical dystonia; hemifacial spasm; real-world evidence; repeated treatment cycles; safety

Key Contribution: Among patients who completed three consecutive onabotulinumtoxinA cycles, symptom scores improved after each cycle in both cervical dystonia and hemifacial spasm, with a small, secondary decline in hemifacial-spasm response across cycles. Neck weakness and dysphagia affected 29.4% and 20.6% of patients with cervical dystonia; completer selection and unblinded assessment preclude conclusions about effectiveness in all patients starting treatment.

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1. Introduction

Cervical dystonia (CD) causes involuntary neck postures and pain, while primary hemifacial spasm (HFS) produces intermittent or sustained unilateral facial contractions [1,2]. Population-based estimates indicate that HFS is uncommon [3].

Botulinum neurotoxin type A (BoNT-A) reduces muscle activity by inhibiting presynaptic acetylcholine release, and its effects usually wane over several months [4,5]. The 2016 American Academy of Neurology guideline recommended considering onabotulinumtoxinA (onaBoNT-A) for CD (Level B) [6]. Expert consensus and systematic-review evidence also support BoNT-A treatment in CD [7,8], while botulinum neurotoxin (BoNT) therapy remains an established symptomatic treatment for HFS [9,10]. Repeated injections are, therefore, common in both conditions.

Injection technique differs between the indications. Deep, overlapping cervical muscles are typically targeted with electromyographic (EMG) guidance, which increases the magnitude of benefit in CD [11], while superficial periocular and perioral muscles in HFS are reliably reached with anatomical-landmark guidance. Standardized instruments exist for each: the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) for CD [12], and the Jankovic Rating Scale (JRS) [13] for HFS, for which a disease-specific seven-item quality-of-life questionnaire (HFS-7) has been validated in its original version [14].

Registries and long-term studies describe repeated BoNT treatment for CD [15,16] and HFS [10,17–19]. However, some series summarize outcomes per injection rather than per patient [19], and patient-reported onset and duration of effect and patient-level adverse-event frequencies are less often reported across consecutive cycles for both disorders within the same real-world setting. Observations from the same patient are correlated, so treating injection cycles as independent may give misleadingly narrow confidence intervals. This study therefore described changes in symptom scores, patient-reported onset and duration of effect, and cycle- and patient-level adverse events over three recorded consecutive onaBoNT-A cycles in separate CD and HFS cohorts treated in routine practice using analyses that account for repeated measurements. The study was restricted to patients who completed three cycles and was not designed to estimate effectiveness in all patients starting treatment. The two indications were not compared for relative efficacy because they were assessed using different scales.

2. Results

2.1. Cohort Characteristics

Seventy-four eligible patients who completed three consecutive injection cycles (222 cycles) were analyzed: 34 with CD (102 cycles, all EMG-guided) and 40 with primary HFS (120 cycles, all anatomical-landmark-guided), all treated with onaBoNT-A between January 2024 and January 2025 (first to last recorded injection). Only patients completing three consecutive cycles were included; the total number of patients who received onaBoNT-A during this period, including those who discontinued earlier, could not be retrieved, so the proportion of treated patients represented by this cohort is unknown (see Section 3). Patients with HFS were older than those with CD (59.0 ± 7.6 vs. 50.1 ± 13.2 years), while sex distribution was comparable (female 77.5% vs. 73.5%). In CD, torticollis predominated (21/34); in HFS, the right side was affected in 27/40, and magnetic resonance imaging (MRI) documented neurovascular contact in 28/40. Eighteen patients (12 with CD and 6 with HFS) had no prior BoNT exposure at the first recorded cycle; the remaining 56 patients (75.7%; 22/34 with CD and 34/40 with HFS) were prevalent users (Table 1).

Table 1. Baseline characteristics of the three-cycle completer cohort, by cohort.

Characteristic	Cervical Dystonia (*n* = 34)	Hemifacial Spasm (*n* = 40)
Age, years (mean ± SD)	50.1 ± 13.2	59.0 ± 7.6
Female, n (%)	25 (73.5)	31 (77.5)
Disease duration, years	7.3 ± 3.9	6.9 ± 4.2
Prior BoNT exposure, years	1.9 ± 1.9	2.9 ± 2.8
No prior BoNT exposure, n (%)	12 (35.3)	6 (15.0)
Phenotype/affected side	Torticollis 21; mixed 9; antero-/laterocollis 4	Right 27; left 13
MRI neurovascular contact, n	—	Yes 28; no 7; N/D 5
Injection guidance	EMG-guided	Anatomical landmarks
Toxin product	OnabotulinumtoxinA	OnabotulinumtoxinA
Cycles analyzed	102	120

SD, standard deviation; BoNT, botulinum neurotoxin; EMG, electromyography; MRI, magnetic resonance imaging; N/D, not documented.

2.2. Dosing

Mean dose per cycle was 161.3 ± 37.1 U in CD (median 160, range 80–245) and 23.0 ± 5.2 U in HFS (median 23.5, range 11.5–34.0). Dose by injected muscle is given in Table 2. There was no clear association between total dose and percentage symptom reduction in either cohort (CD: +0.03%/U, 95% confidence interval [CI] −0.05 to +0.11, $p = 0.44$; HFS: −0.52%/U, 95% CI −1.29 to +0.24, $p = 0.18$). Because doses were individualized according to clinical presentation and previous response, this analysis is subject to confounding by indication and is reported descriptively.

Table 2. Mean onabotulinumtoxinA dose per injection cycle by target muscle (units, mean ± SD, computed over injected cycles).

Cohort	Injected Muscle	Dose, U (Mean ± SD)
CD	Sternocleidomastoid	38.2 ± 10.1
CD	Splenius capitis	50.7 ± 13.2
CD	Levator scapulae	23.2 ± 6.7
CD	Trapezius	18.1 ± 5.2
CD	Semispinalis capitis	22.9 ± 6.2
CD	Obliquus capitis inferior	9.5 ± 4.4
CD	Total per injection cycle	161.3 ± 37.1
HFS	Orbicularis oculi	14.6 ± 3.5
HFS	Corrugator	3.0 ± 0.9
HFS	Zygomaticus	2.1 ± 0.7
HFS	Orbicularis oris	1.3 ± 0.6
HFS	Platysma	1.3 ± 0.7
HFS	Procerus	1.0 ± 0.5
HFS	Total per injection cycle	23.0 ± 5.2

Per-muscle means are computed over the cycles in which that muscle received a non-zero dose. Muscles injected in every cycle: all CD muscles except obliquus capitis inferior (injected in 88/102 cycles); in HFS, orbicularis oculi, corrugator, zygomaticus, and orbicularis oris (all cycles), procerus (106/120), platysma (107/120). Total dose is the mean of the per-cycle sums across all cycles.

2.3. Effectiveness

Symptom scores declined from the pre-injection assessment to the scheduled follow-up in both cohorts. In CD, mean TWSTRS-total change was −12.8 points (95% CI −14.4 to

−11.4), including improvements in severity (−7.1), disability (−3.0), and pain (−2.7). In HFS, mean JRS-total change was −4.2 (95% CI −4.5 to −3.9). The exploratory HFS-7 score, collected with a Turkish translation that had not been formally validated, decreased by 9.1 points (mean change −9.1; 95% CI −9.9 to −8.4). Mean percentage reductions were 31.5% (95% CI 28.3–34.6) for TWSTRS, 68.5% (64.1–73.1) for JRS, and 70.1% (66.3–73.7) for HFS-7. In the score-change mixed models, the cycle slope was +0.03 TWSTRS points (95% CI −0.39 to +0.45; $p = 0.890$) in CD and +0.24 JRS points (95% CI +0.08 to +0.39; $p = 0.003$) in HFS, indicating a small decline in HFS improvement over successive cycles (secondary analysis, not adjusted for multiplicity). Scores by cycle are shown in Table 3 and Figure 1; summary estimates are in Table 4.

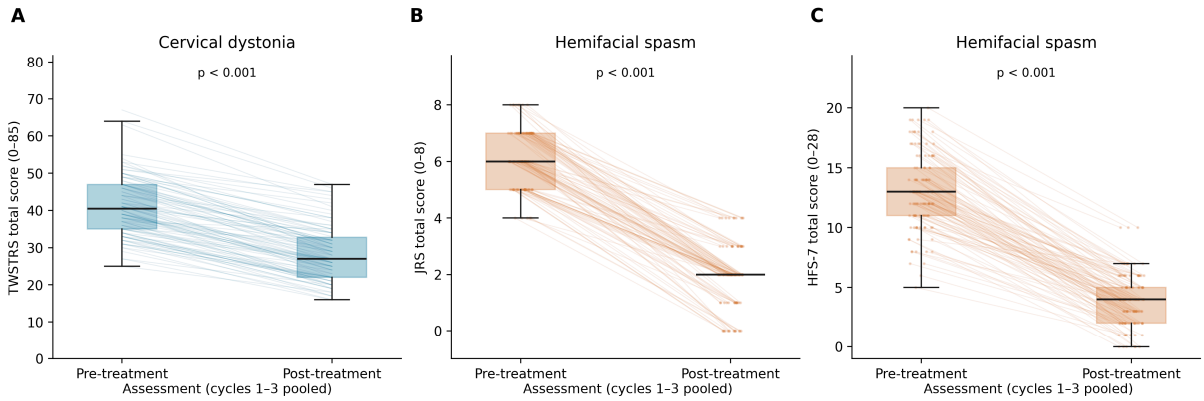


Figure 1. Scores before and approximately four weeks after injection across three treatment cycles. (**A**) TWSTRS total in cervical dystonia; (**B**) JRS total and (**C**) exploratory HFS-7 in hemifacial spasm. Lines connect measurements before and after each injection; each patient contributed three cycles, and the three cycles are pooled in each panel. Boxes show the median and interquartile range (IQR), with whiskers extending to 1.5 × IQR; outliers are not shown as separate boxplot symbols. Horizontal offsets in panels (**B**,**C**) help distinguish overlapping observations without changing their scores. The p values refer to within-cycle changes tested using patient random-intercept models (all $p < 0.001$). TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; JRS, Jankovic Rating Scale; HFS-7, seven-item hemifacial spasm questionnaire (Turkish translation not formally validated).

Table 3. Observed pre-treatment and post-treatment scores across three onabotulinumtoxinA injection cycles.

Cohort	Cycle	Measure	Pre-Treatment (Mean ± SD)	Post-Treatment (Mean ± SD)
CD	1	TWSTRS	41.5 ± 8.8	28.5 ± 8.0
CD	2	TWSTRS	41.2 ± 7.7	28.7 ± 7.6
CD	3	TWSTRS	40.6 ± 8.2	27.6 ± 6.9
HFS	1	JRS	6.2 ± 1.0	1.8 ± 1.1
HFS	1	HFS-7	13.3 ± 3.4	4.1 ± 2.2
HFS	2	JRS	6.2 ± 1.1	1.9 ± 1.0
HFS	2	HFS-7	13.1 ± 2.9	3.9 ± 1.7
HFS	3	JRS	6.0 ± 0.9	2.0 ± 1.0
HFS	3	HFS-7	12.7 ± 3.1	3.6 ± 2.3

Table 4. Summary of effectiveness, treatment kinetics, and safety outcomes by cohort.

Outcome	Cervical Dystonia	Hemifacial Spasm
Primary scale, pre-to-post change (95% CI)	TWSTRS: −12.8 (−14.4 to −11.4)	JRS: −4.2 (−4.5 to −3.9)
HFS-7, pre-to-post change (95% CI; exploratory)	—	−9.1 (−9.9 to −8.4)
TWSTRS or JRS mean reduction, % (95% CI)	31.5 (28.3–34.6)	68.5 (64.1–73.1)

HFS-7 mean reduction, % (95% CI; exploratory)	—	70.1 (66.3–73.7)
Responder rate, % of cycles (bootstrap 95% CI)	73.5 (60.8–86.3)	90.0 (82.5–96.7)
Patient-reported global improvement, % (95% CI)	50.0 (46.8–53.3)	74.6 (70.4–79.0)
Patient-reported onset latency, days (95% CI)	7.1 (6.7–7.6)	5.0 (4.7–5.2)
Patient-reported effect duration, weeks (95% CI)	11.3 (11.0–11.7)	12.4 (12.0–12.7)
Score-change cycle trend, points/cycle (95% CI; primary)	+0.03 (−0.39 to +0.45)	+0.24 (+0.08 to +0.39)
Percentage-reduction cycle trend, percentage points/cycle (95% CI)	+0.1 (−0.9 to +1.1)	−2.6 (−4.7 to −0.5)
Any adverse event, % of cycles	17.6	10.0
Patients with ≥1 adverse event, % (95% CI)	47.1 (31.5–63.3)	25.0 (14.2–40.2)
Patients with neck weakness, % (95% CI)	29.4 (16.8–46.2)	0.0 (0.0–8.8)
Patients with dysphagia, % (95% CI)	20.6 (10.3–36.8)	0.0 (0.0–8.8)

Change estimates and percentage reductions are calculated from repeated cycle observations. Mean-outcome and responder confidence intervals are patient-level percentile bootstrap intervals (5000 resamples; fixed seed). Cycle-trend intervals are from patient random-intercept mixed models using residual degrees of freedom. Adverse-event percentages are observed cycle proportions; patient-level adverse-event confidence intervals use the Wilson method. Responder thresholds are ≥25% TWSTRS-total reduction in CD and ≥50% JRS-total reduction in HFS. Patient-level adverse-event proportions are the percentages of patients with at least one event during the three cycles. HFS-7 results are exploratory because the Turkish translation had not been formally validated. Between-cohort differences in onset and duration are descriptive.

2.4. Responder Rates and Stability Across Cycles

Using descriptive response thresholds of ≥25% TWSTRS reduction in CD and ≥50% JRS reduction in HFS (rationale in Section 4), 73.5% and 90.0% of injection cycles, respectively, met the criteria. Patient-level bootstrap 95% confidence intervals were 60.8–86.3% and 82.5–96.7%. At least one cycle met the threshold in 85.3% of CD patients and 97.5% of HFS patients; all three cycles met it in 64.7% and 80.0%, respectively. Two cycles from one CD patient were marked as secondary non-response; none were marked in HFS. In the percentage-reduction sensitivity models, the cycle slope was +0.1 percentage points (95% CI −0.9 to +1.1; $p = 0.823$) for CD and −2.6 (95% CI −4.7 to −0.5; $p = 0.016$) for HFS. These secondary tests were not adjusted for multiplicity. In the MRI subgroup (35 patients), mean JRS percentage reduction was 69.4% with and 66.0% without documented neurovascular contact (mixed-model difference 3.5 percentage points; 95% CI −9.3 to 16.3; $p = 0.591$). This comparison was imprecise.

2.5. Kinetics

Patient-reported onset averaged 7.1 days (95% CI 6.7–7.6) in CD and 5.0 days (4.7–5.2) in HFS (descriptive mixed-model difference −2.2 days; 95% CI −2.6 to −1.7). Mean patient-reported effect duration was 11.3 weeks (95% CI 11.0–11.7) and 12.4 weeks (12.0–12.7), respectively (difference +1.0 week; 95% CI 0.6–1.5). Estimates changed little in sensitivity analyses including age, sex, and previous BoNT exposure. Because indication, target muscles, injection guidance, and dose range were inseparable, these between-cohort contrasts describe the two clinical settings and do not isolate an effect of the toxin, the technique, or the disorder. Mean injection intervals were 13.7 and 13.4 weeks in CD and HFS, respectively, exceeding the patient-reported duration of benefit in both groups. Patient-reported global improvement (%) averaged 50.0% (95% CI 46.8–53.3) and 74.6% (70.4–79.0), respectively. Treatment kinetics are shown in Figure 2.

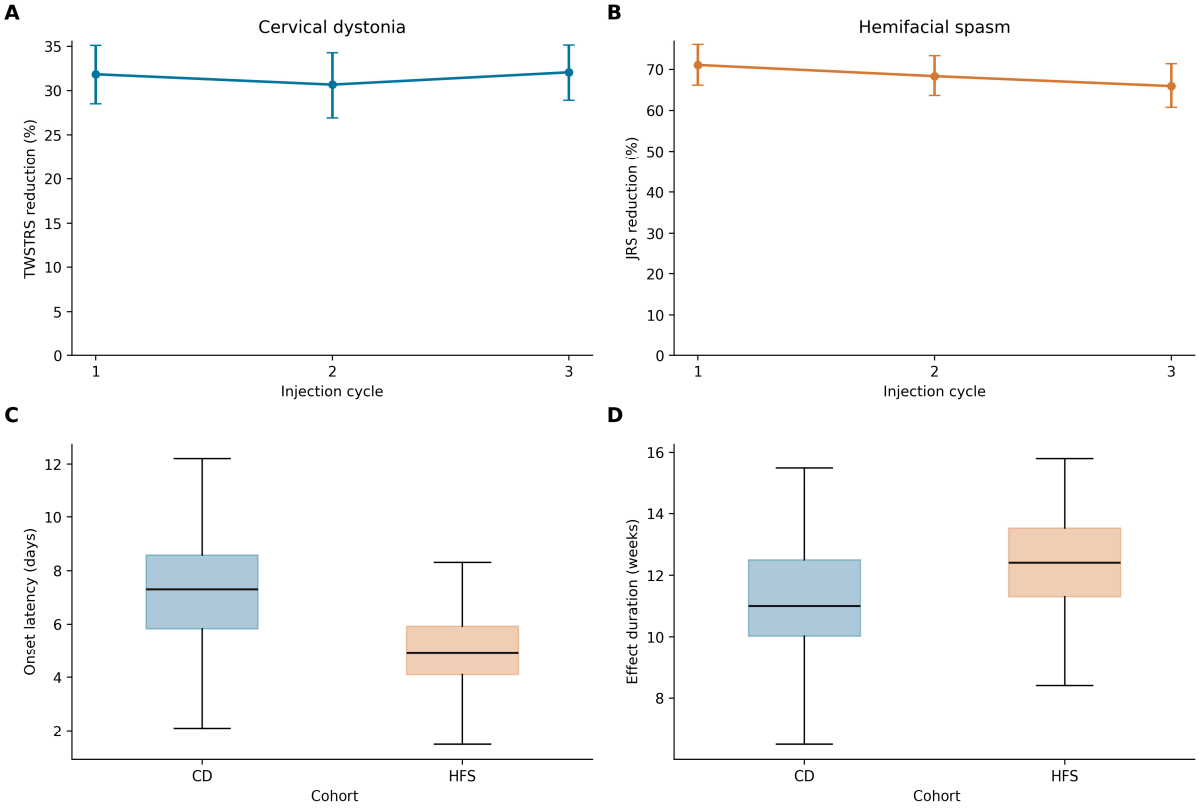


Figure 2. Changes across three injection cycles and patient-reported treatment kinetics. (**A**) Mean TWSTRS percentage reduction in CD and (**B**) mean JRS percentage reduction in HFS with patient-level bootstrap 95% confidence intervals (5000 resamples per cycle). (**C**) Patient-reported onset latency in days and (**D**) patient-reported effect duration in weeks, using 102 CD and 120 HFS cycle-level observations; boxplots show the median and interquartile range. The two symptom scales are not directly comparable, and the between-cohort contrasts in (C) and (D) are descriptive. CD, cervical dystonia; HFS, hemifacial spasm; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; JRS, Jankovic Rating Scale.

2.6. Safety

Recorded adverse events were mainly transient and related to the treated region; no serious or systemic events were documented in the clinical records. In CD, an event occurred in 18/102 cycles (17.6%) and in 16/34 patients (47.1%). Neck weakness was reported in 10 cycles (9.8%) and 10 patients (29.4%; 95% CI 16.8–46.2); dysphagia in 7 cycles (6.9%) and 7 patients (20.6%; 95% CI 10.3–36.8). Thus, although per-cycle rates were below 10%, nearly one in three patients with CD experienced neck weakness and one in five experienced dysphagia at least once during the three cycles. One CD cycle included injection-site pain or hematoma. In HFS, events occurred in 12/120 cycles (10.0%) and 10/40 patients (25.0%): ptosis in 7 cycles (5.8%), dry eye in 3 (2.5%), facial weakness in 2 (1.7%), and an injection-site event in 1 (0.8%). Because events can overlap within a cycle, category counts need not sum to the total. No lagophthalmos was recorded in either group. Because severity was not systematically graded, the proportion of events that interfered with daily activities cannot be reported. Cycle-level rates are shown in Figure 3, and patient-level proportions in Table 4.

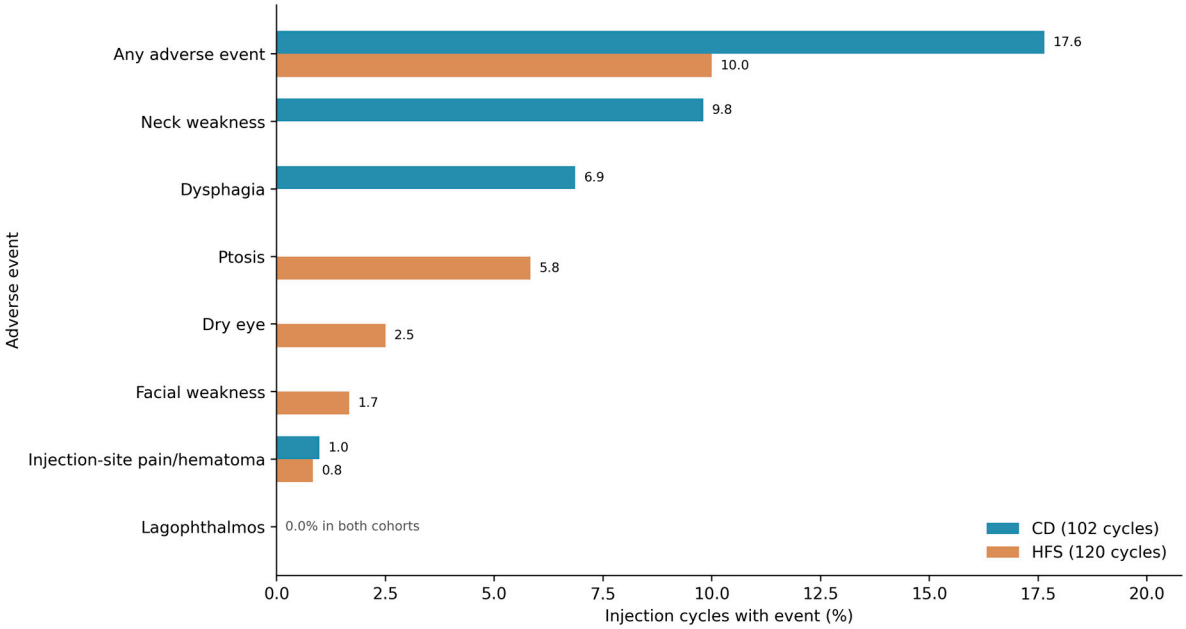


Figure 3. Recorded adverse events per injection cycle in CD (n = 102 cycles) and HFS (n = 120 cycles). Bars show observed percentages of injection cycles, not patient-level risks; patient-level proportions are reported in Section 2.6 and Table 4. No lagophthalmos was recorded in either cohort. Formal severity grading was not performed.

3. Discussion

In this retrospective cohort of 74 adults who completed three consecutive treatment cycles, symptom scores improved after each onaBoNT-A injection in both CD and primary HFS. Patient-reported benefit lasted approximately 11–12 weeks, and the main adverse events differed according to the injected region. These findings should be read as outcomes among patients who continued treatment rather than as estimates of treatment effectiveness: the cohort was restricted to three-cycle completers, three-quarters of patients were prevalent users, and outcomes were rated by the unblinded treating neurologist.

These results are broadly consistent with previous clinical series. In the CD PROBE registry, mean TWSTRS total among the 479 patients who completed all assessments decreased from 39.2 at baseline to 27.1 at the final visit [15,20]. Dashtipour and colleagues also identified a clinically meaningful reduction of approximately eight points [20]. The mean within-cycle change in this cohort was 12.8 points, although direct comparison is limited by different populations and follow-up schedules. Other CD reports, including studies of acquired dystonia, describe benefit during repeated treatment [16,21–23]. Published HFS series report fewer spasms and improved quality of life after BoNT treatment [10,17–19,24–26]. These reports provide context but do not remove the limitations of this uncontrolled study.

Patient-reported onset was approximately two days earlier in HFS than in CD, and reported effect duration was around one week longer. Because indication, target muscles, injection technique, and dose range were inseparable in this cohort, these descriptive contrasts cannot be attributed to the toxin, the injection technique, or the disorder itself, and mechanisms were not evaluated. Variation in onset and duration after BoNT treatment has been described previously [27]. Percentage reductions in TWSTRS and JRS should not be interpreted as a comparison of drug efficacy, because the scales measure different outcomes.

The mean symptom reduction was similar across CD cycles, whereas a small decline was observed in HFS. This secondary finding was not accompanied by dose escalation or recorded secondary non-response in HFS. Previous reports describe sustained benefit with repeated injections [10,28], and neutralizing antibodies to onaBoNT-A are uncommon [22,29]. Within the doses used, total dose was not clearly associated with response; however, because doses were individualized according to clinical presentation and previous response, this null association is subject to confounding by indication and does not indicate that dose is unimportant. Tunç and colleagues reported greater improvement in idiopathic HFS [30]; the MRI subgroup in this study was too small to confirm or refute that finding. The mean injection intervals of 13.7 weeks in CD and 13.4 weeks in HFS were close to the 13–15-week median intervals reported by Hast et al. [31], although the populations and summary statistics differ. In both cohorts, the patient-reported duration of benefit was shorter than the actual injection interval, which is consistent with a survey of patients with CD in which symptoms commonly re-emerged before reinjection, with a mean reported onset of about 12 days and symptom re-emergence at about 10.5 weeks [32].

The cycle-related decline in HFS response should be interpreted cautiously. It was a secondary finding, small in absolute terms (0.24 JRS points, or 2.6 percentage points, per cycle), observed over only three cycles, and none of the secondary analyses were adjusted for multiplicity. As a post hoc illustration, a Bonferroni correction across the eight secondary hypothesis tests reported in this article ($\alpha = 0.05/8 \approx 0.006$) would retain the score-change slope ($p = 0.003$) but not the percentage-reduction slope ($p = 0.016$). Reports on whether the duration of benefit changes during long-term treatment of HFS have been inconsistent [33]; a 12-year single-injector series found that JRS improvement and duration of effect were maintained or increased between the first and last injections [34], and a 16-year series from Türkiye reported BoNT to be effective and safe across 470 treatment sessions [35]. Antibody-induced secondary treatment failure has been described during long-term BoNT therapy [36], but neutralizing antibodies were not assessed in this analysis, and three cycles are insufficient to determine whether the trend persists.

Adverse events followed the anatomical distribution of the injections. Neck weakness and dysphagia, recognized adverse effects of BoNT treatment in CD [8,37], were the main concerns in CD, whereas ptosis and dry eye were recorded after HFS injections. Although per-cycle rates were below 10%, 29.4% of patients with CD experienced neck weakness and 20.6% experienced dysphagia at least once during three cycles, and nearly half experienced at least one adverse event. In the ANCHOR-CD registry, dysphagia and muscle weakness were also among the most frequently reported adverse events, although at a lower patient-level frequency [38]; differences in product, dose, ascertainment, and follow-up limit direct comparison. Because severity was not graded, it cannot be determined how many of these events were clinically limiting. Even if transient, dysphagia and neck weakness at this frequency warrant explicit discussion during patient counseling and active inquiry at follow-up visits. No serious events were documented, although routine records may under-capture events managed elsewhere.

This study has several limitations. First, it was retrospective and restricted to patients who completed three consecutive cycles. Patients who discontinued treatment earlier because of limited benefit or adverse effects were not represented, and the overall number of patients receiving an injection during the study period was not available for a full enrollment flow diagram. This selection is expected to bias response estimates upward and adverse-event frequencies downward and to attenuate any decline in response across cycles; in long-term CD cohorts, up to about one-third of patients discontinue treatment, and lack of efficacy and adverse events are among the most common reasons [16,37,39].

Second, 56 of 74 patients had previously received BoNT. Prevalent users have already passed through the early treatment period in which intolerance or lack of benefit leads to discontinuation, which can bias observational estimates [40]; the 18 BoNT-naïve patients were too few for a separate analysis. Third, all treatments and assessments were carried out by one unblinded neurologist at a single center, without an untreated or alternative-toxin comparison group, so expectation and detection bias cannot be excluded. Fourth, onset, duration, and patient-reported global improvement were abstracted from routine clinical documentation rather than prospective diaries and are subject to recall error (a limitation also acknowledged in retrospective real-world BoNT research [41]) and to rounding; the narrow confidence intervals for these outcomes reflect sampling precision rather than measurement accuracy. Fifth, the two indications required different clinical scales, injection techniques, target muscles, and dose ranges, which are fully confounded with diagnosis; between-cohort contrasts are, therefore, descriptive. Sixth, doses were individualized, so the dose–response analysis is subject to confounding by indication. Seventh, severity was documented only for serious adverse events, none of which occurred, so the severity of the recorded non-serious events could not be graded; in addition, the Turkish HFS-7 had not undergone formal cross-cultural adaptation or psychometric validation. Eighth, the several secondary analyses were not corrected for multiple testing. Finally, the interval to the post-injection assessment was approximately four weeks rather than identical for every visit; injection laterality and reasons for variation in reinjection timing were not examined; no prospective sample-size calculation was performed; and follow-up was limited to three cycles at a single Turkish center. Consequently, the findings cannot be generalized to all patients beginning treatment or to long-term outcomes beyond three cycles.

Future studies should use prospective inception cohorts that record every patient starting treatment, including discontinuations and their reasons; blinded or video-based rating by an independent assessor; standardized diaries for onset and wearing off; graded adverse-event reporting; a formally validated Turkish HFS-7; and follow-up beyond three cycles, with antibody testing in patients whose response declines. Dose–response analyses that account for baseline severity and muscle selection, and studies of whether individualized reinjection intervals improve end-of-cycle symptom control in patients with early wearing off, would also address questions raised by these findings.

4. Conclusions

Among adults completing three consecutive onaBoNT-A cycles in routine practice, CD and HFS symptom scores improved after each treatment cycle. The patient-reported benefit lasted approximately 11–12 weeks, generally ending before the next injection, and local adverse events differed between the two indications. In CD, neck weakness and dysphagia affected 29.4% and 20.6% of patients, respectively, during three cycles, which supports explicit counseling about these effects and active inquiry at follow-up. The small decline in HFS response across cycles was a secondary, unadjusted finding and requires confirmation over longer follow-up.

These observations describe patients who continued treatment and were assessed by an unblinded treating neurologist; they do not establish treatment effectiveness or safety in all patients starting onaBoNT-A, and they cannot be used to compare efficacy between the two indications. Prospective inception cohorts with complete enrollment records; blinded outcome assessment; standardized recording of onset, duration, and graded adverse events; and a validated Turkish HFS-7 are needed to confirm these findings.

5. Materials and Methods

This single-center retrospective study included 74 adults aged 18 years or older with CD or primary HFS who had complete clinical records for three consecutive onaBoNT-A cycles between January 2024 and January 2025. Patients with secondary HFS or incomplete three-cycle assessment records were not included. Patients were eligible regardless of previous BoNT exposure. The cohort comprised 34 patients with CD (102 cycles) and 40 with HFS (120 cycles); patients who stopped before completing three cycles were not represented, and the total number of patients injected during the study period could not be retrieved from the available records. No prospective sample-size calculation was undertaken. Analyses were restricted to this three-cycle completer cohort.

All injections were administered, and all clinical ratings were performed, by the same neurologist, who was not blinded to treatment history. OnaBoNT-A (BOTOX; Allergan/AbbVie, North Chicago, IL, USA) was reconstituted with 2 mL of preservative-free 0.9% sodium chloride per 100 U vial, yielding a concentration of 5 U/0.1 mL. In CD, injections were guided by EMG. The treated muscles included the sternocleidomastoid, splenius capitis, levator scapulae, trapezius, and semispinalis capitis; the obliquus capitis inferior was added in selected cycles. Injection laterality and dose distribution were individualized according to the predominant dystonic posture and EMG findings, with unilateral or bilateral injections as clinically indicated. In HFS, injections were guided by anatomical landmarks and targeted the orbicularis oculi, corrugator, zygomaticus, and orbicularis oris, with the procerus and platysma treated in selected cycles. Muscle-specific and total doses are reported in Table 2. Repeat injections were generally scheduled at approximately three-month intervals, taking symptom recurrence and response to the previous treatment into account. Actual reinjection intervals were calculated from follow-up records and analyzed descriptively.

The primary outcomes were within-cycle changes (post-injection minus pre-injection) in TWSTRS total score for CD and JRS total score for HFS, from the pre-injection assessment to the scheduled visit approximately four weeks later. TWSTRS includes severity (0–35), disability (0–30), and pain (0–20) subscales (total 0–85) [12]. JRS comprises severity and frequency scores (each 0–4; total 0–8) [13]. The HFS-7 (0–28) [14] was administered in routine care using a Turkish translation that had not undergone formal cross-cultural adaptation or psychometric validation; HFS-7 results are, therefore, reported as exploratory and were not used to support the conclusions. Additional variables included percentage score reduction, patient-reported global improvement (%) documented on a 0–100 scale, onset latency, effect duration, reinjection interval, dose, response status, and adverse events. The three consecutively numbered cycles recorded for each patient were analyzed. Secondary non-response was identified from cycle-level clinical records.

Onset latency and effect duration were patient-reported estimates obtained by the treating neurologist at routine visits and recorded in the clinical notes; no symptom diaries were used. Onset latency was defined as the number of days from injection to the first improvement noticed by the patient and effect duration as the number of weeks from injection until the patient reported that the benefit had worn off. Both were abstracted as recorded and analyzed as continuous variables; they are, therefore, subject to recall and rounding.

Response was defined descriptively as a ≥25% reduction in TWSTRS total score in CD or a ≥50% reduction in JRS total score in HFS. A ≥25% reduction in TWSTRS scores (total or severity subscale) has been used as the magnitude-of-effect criterion for response in observational CD studies [38,42], and failure to reach a 25% improvement over consecutive treatments has been proposed as a reason to consider immunoresistance [37]; with mean pre-injection TWSTRS totals of approximately 41 points in this cohort, it corresponds to a reduction of about 10 points, which exceeds the minimal clinically

important change of approximately 8 points reported from the CD PROBE registry [20]. No consensus rating scale has been established for HFS, and outcome assessment in HFS studies has been heterogeneous [43]; no validated JRS responder threshold has been reported for HFS. Because the JRS ranges from 0 to 8 and pre-injection scores averaged approximately 6 points, a ≥25% threshold would be met by a 2-point change; the ≥50% threshold, corresponding to at least halving of combined spasm severity and frequency, was used to identify a clearly perceptible response. Both thresholds are pragmatic and have not been validated in this population; responder results are, therefore, descriptive.

Adverse events were captured per cycle as present/absent for ptosis, dry eye, lagophthalmos, facial weakness, dysphagia, neck weakness, and injection-site pain or hematoma with an "any adverse event" indicator; formal severity grading was not performed. In routine practice, adverse events were recorded as present or absent, and severity details were documented only for serious adverse events; because no serious adverse events occurred, no severity information was available, and retrospective grading was not possible. Adverse events were summarized as the proportion of cycles with an event and the proportion of patients with at least one event during the three cycles; patient-level 95% CIs were calculated with the Wilson method.

The two cohorts were analyzed separately because different clinical rating scales were used.

Linear mixed-effects models with patient-specific random intercepts were employed to account for correlations among repeated treatment cycles. Cycle number was treated as a continuous variable and centered at cycle 2. The model intercept represented the estimated treatment-associated change at the second cycle, corresponding to the average predicted change across the three equally spaced cycles, while the cycle coefficient quantified changes in treatment response across successive cycles. Models based on percentage score reduction were performed as sensitivity analyses.

Mean score changes, percentage reductions, treatment kinetics, and responder proportions were accompanied by percentile 95% confidence intervals derived from 5000 patient-level cluster bootstrap resamples (fixed random seed: 20261010). Resampling was performed at the patient level to preserve the within-patient correlation structure. Separate mixed-effects models were used to examine associations between total onaBoNT-A dose and percentage improvement within each cohort; because doses were individualized, these associations are susceptible to confounding by indication and were interpreted descriptively.

Between-cohort contrasts in onset latency and effect duration, which were recorded in the same units in both cohorts, were estimated descriptively using mixed-effects models incorporating diagnosis and treatment cycle as fixed effects and patient as a random intercept and are reported as differences with 95% CIs. Additional adjusted models included age, sex, and duration of previous BoNT exposure. Dose, injection guidance, target muscles, and muscle depth were not entered as covariates because they were determined by the indication (all CD injections were EMG-guided into deep cervical muscles at 80–245 U per cycle, and all HFS injections were landmark-guided into superficial facial muscles at 11.5–34.0 U per cycle), and therefore, could not be separated from diagnosis. Among patients with HFS, the association between MRI-documented neurovascular contact and percentage reduction in JRS scores was evaluated using a mixed-effects model with neurovascular contact and centered cycle number as fixed effects and patient as a random intercept.

All statistical tests were two-sided. Secondary analyses were considered exploratory, and no adjustment for multiple comparisons was applied. Eight secondary hypothesis tests are reported (four cycle-trend slopes, two dose associations, one MRI-subgroup

comparison, and the within-cycle HFS-7 change), and their *p* values should be interpreted in light of this multiplicity.

Statistical analyses were primarily performed using IBM SPSS Statistics for Windows, version 32.0 (IBM Corp., Armonk, NY, USA). Linear mixed-effects models were fitted using the MIXED procedure with restricted maximum likelihood estimation. Patient-level cluster bootstrap calculations and independent verification of analytical results were conducted using Python 3.13.5.

Generative artificial intelligence tools were used as follows. ChatGPT (GPT-6; OpenAI) was used to prepare the graphical abstract from results reported in this manuscript. The graphical abstract was reviewed and approved by the author, who takes full responsibility for its accuracy and content.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the responsible institutional ethics committee (Approval Date: 15 September 2026; Approval Number: HÜ-GOEK-2026-00383).

Informed Consent Statement: The requirement for informed consent was waived by the ethics committee because of the retrospective design and the use of de-identified clinical data.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author. The patient-level clinical data are not publicly available due to patient confidentiality, privacy considerations, and institutional data protection requirements. De-identified data may be shared upon reasonable request, subject to applicable ethical and institutional restrictions.

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Abbreviations

The following abbreviations are used in this manuscript:

BoNT	botulinum neurotoxin
BoNT-A	botulinum neurotoxin type A
CD	cervical dystonia
CI	confidence interval
EMG	electromyography
HFS	hemifacial spasm
HFS-7	seven-item hemifacial spasm quality-of-life questionnaire
IQR	interquartile range
JRS	Jankovic Rating Scale
MRI	magnetic resonance imaging
onaBoNT-A	onabotulinumtoxinA
SD	standard deviation
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
U	unit

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