Neurological Sciences (2020) 41:131–138
https://doi.org/10.1007/s10072-019-04061-5

ORIGINAL ARTICLE

Sensorimotor Perceptive Rehabilitation Integrated (SPRInt) program: exercises with augmented movement feedback associated to botulinum neurotoxin in idiopathic cervical dystonia—an observational study

Anna Castagna[1] · Antonio Caronni[1] · Alessandro Crippa[1] · Luciana Sciumè[2] · Giulia Giacobbi[1] · Chiara Corrini[1] · Angelo Montesano[1] · Marina Ramella[1]

Received: 11 June 2019 / Accepted: 28 August 2019 / Published online: 2 September 2019

Abstract

Background Idiopathic cervical dystonia (ICD) is a focal dystonia affecting neck muscles. Botulinum neurotoxin (BoNT) is the first-line treatment of ICD and different physical therapies (including exercise) are often proposed as adjunct treatments. However, the actual effectiveness of exercise in ICD is unclear. The aim of the current work is to assess the potential effectiveness of the Sensorimotor Perceptive Rehabilitation Integrated (SPRInt) exercise program as adjunct therapy for ICD.

Methods Fifteen ICD patients received BoNT injections in the neck muscles and, 12 weeks later, received BoNT a second time and SPRInt started. SPRInt consists in 18 exercise sessions in which augmented feedback of movement (including visual and acoustic feedback) is extensively used. Dystonia burden was measured by the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Patients were evaluated immediately before, 6 and 12 weeks after each BoNT injection.

Results Six weeks after the first BoNT injection (i.e., at BoNT peak effect), TWSTRS total score was better than baseline and remained improved at 12 weeks. TWSTRS disability domain slightly improved 6 weeks after the first BoNT injection, but after 6 more weeks returned to its baseline level. Disability improved more at SPRInt end (i.e., 6 weeks after the second BoNT injection), being even lower than after toxin alone. With a single-subject analysis, 4/10 patients who did not improve disability after BoNT improved after SPRInt plus BoNT.

Conclusions SPRInt plus BoNT can be more effective than BoNT alone in improving cervical dystonia patients' difficulties in the activities of daily living.

Trial registration www.ClinicalTrials.gov, identifier NCT03247868 (https://register.clinicaltrials.gov).

Keywords Cervical dystonia · Botulinum toxins · Type A · Exercise · Physical therapy modalities · Neurofeedback · Rehabilitation

Introduction

Idiopathic cervical dystonia (ICD) is an adult-onset, focal dystonia characterized by involuntary contractions of neck muscles, which leads to abnormal head postures and movements [1]. ICD non-motor burden is high, with patients complaining pain, anxiety, and poor self-efficacy [2]. Eventually, ICD has a negative impact on the activities of daily living causing reduced quality of life [3].

Good quality evidence supports botulinum neurotoxin (BoNT) as the first-line treatment in ICD [4, 5]. Nevertheless, up to one patient out of three is not satisfied with this

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10072-019-04061-5) contains supplementary material, which is available to authorized users.

✉ Antonio Caronni
acaronni@dongnocchi.it

[1] U. O. di Recupero e Rieducazione Funzionale, I.R.C.C.S. Fondazione Don Carlo Gnocchi Onlus, via Alfonso Capecelatro 66, 20148 Milan, Italy

[2] U. O. di Medicina riabilitativa e neuroriabilitazione, Ospedale Niguarda, Milan, Italy

conventional treatment [6] and can look for non-pharmacological treatments.

Physiotherapy is often proposed as a useful tool in addition to BoNT [7]. A variety of different physiotherapic interventions have been tested in ICD, such as passive stretching and electromyographic feedback [8], relaxation [9], and taping [10]. However, the actual effectiveness of physiotherapy in ICD is unclear [7] and studies in which non-farmacological interventions are added to BoNT are warranted [11].

It is well accepted that randomized studies, including randomized controlled trials (RCT) and randomized crossover trials, offer the highest quality of evidence about the effectiveness of interventions [12]. Therefore, uncertainty about the effectiveness of physiotherapy in ICD points out the need for well-conducted randomized studies. Indeed only a few RCT studies were able to demonstrate the increased efficacy of combined BoNT and physiotherapy in comparison with BoNT alone [7, 13]. However, costs of a RCT can be high and simpler experimental designs (such as observational studies) are a reasonable first step in treatment effectiveness evaluation [14].

The *Sensorimotor Perceptive Rehabilitation Integrated* (SPRInt) program is an exercise program strongly based on movement-augmented feedback. SPRInt was specifically developed as an adjunct therapy for ICD patients, to be added to the customary BoNT injection. There is solid theoretical basis for the therapeutic effectiveness of augmented movement feedback in patients affected by movement disorders [15], in particular in cervical dystonia [16]. As an example, impaired feedback and impaired feedback processing were proposed as a pathophysiological explanation in ICD [17]. Alternatively, abnormal neck postures could be associated with abnormal sensory inflow and thus to poor proprioception and poor motor coordination [18]. In addition, previous reports showed positive results with the application of augmented feedback in different dystonia types [8, 19].

In the current observational study, we describe a series of ICD patients who were treated at first with BoNT alone and then with BoNT and SPRInt. The aim of the study is twofold. First, we want to evaluate the safety of SPRInt as an adjunct treatment for ICD. Second, we want to provide preliminary result on the potential effectiveness of exercise using augmented movement feedback as an adjunct therapy for ICD.

Methods

From March 2016 to May 2017, 15 consecutive ICD patients were recruited. Patients attended the botulinum toxin outpatient clinic of the IRCCS Fondazione Don Gnocchi Onlus—Santa Maria Nascente in Milano (Italia). Of the 15 recruited participants, one dropped out after the first BoNT injection for working problems. Fourteen participants completing all time points were included in the final analysis.

The study was approved by the local Ethic Committee and recorded at ClinicalTrials.gov (NCT03247868). Each participant gave his/her written consent to take part in the study.

Kempen's checklist for reporting case series was followed [14].

Participants

Patients affected by ICD were included in the study according to the following criteria: (1) age between 18 and 80 years and (2) disease duration ≥ 1 year.

Patients were excluded in the case of (1) neck skeletal abnormalities (e.g., cervical stenosis), (2) cervical myelopathy or significant cervical radiculopathy based on clinical signs, (3) a major neurological disorder in addition to ICD (e.g., stroke), (4) BoNT injection less than 3 months prior to the study enrollment.

Well-accepted criteria [1] were used for the ICD diagnosis, which was made by a neurologist (Ann.C.) with more than 10 years' experience in ICD.

For diagnostic purposes, all patients had morphologic neck examination (X-ray or magnetic resonance of the cervical spine if needed to exclude other causes of pain or postural cervical spine abnormalities).

Study design

The study was articulated into two phases, each of 3 months duration (Fig. 1).

Patients received the standard treatment (i.e., BoNT injections alone) during the first phase and the experimental intervention (i.e., BoNT followed by SPRInt, BoNT + SPRInt) during the second phase.

Participants were evaluated at five time points (from T0 to T4). At T0 (i.e., baseline), patients were evaluated just before receiving the BoNT treatment. The T1 follow up visit was scheduled 6 weeks after T0. At T2 (i.e., 12 weeks after T0) patients were evaluated and received the second BoNT injection. Contextually patients started the SPRInt program. Similarly to the first phase, during the second phase, patients were evaluated 6 weeks (T3) and 12 weeks (T4) after the injection. At T4, BoNT injections were also offered, in accordance with the patient's needs.

It is important to stress that at T2 (i.e., when the pharmacological effect of the first BoNT injection is expected to wear off) the need for a new BoNT injection was evaluated for each patient and if this was considered not appropriate, the patient could drop out from the study.

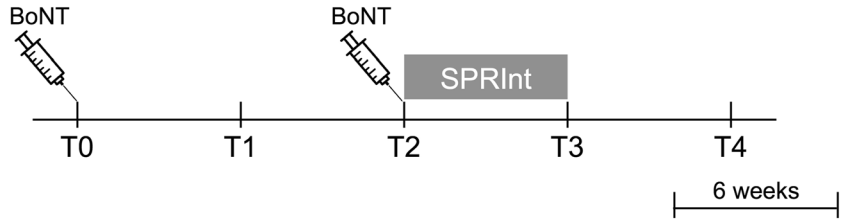

Fig. 1 Study design. Patients received the first botulinum toxin injection at T0. At T2, patients received the second toxin administration and started the SPRInt program. T1, toxin peak effect; T3, toxin peak effect and SPRInt peak effect (i.e., SPRInt end)

Interventions

Each participant had a poly-EMG study of neck muscles, which substantiated the ICD diagnosis and was helpful in choosing the dystonic muscles. BoNT injections were guided by ultrasound used in conjunction with monopolar needle EMG. An experienced neurologist (Ann.C.) chose the muscles to be treated and made the injections at both time points following a published algorithm [20]. Total BoNT dosage was kept into the labeled approved Food and Drug Administration indications [21]. The abobotulinumtoxin dosage was converted into incobotulinumtoxin equivalent units according to Scaglione and colleagues [22] (conversion ratio abobotulinumtoxin/incobotulinumtoxin = 3/1).

The SPRInt program consists of exercises with augmented movement feedback, specifically designed for people with ICD. The exercise program consisted of 18 one to one sessions (45 min/session, three sessions/week) lead by a physiotherapist who was directly involved in the SPRInt program design. Full details on SPRInt are given in the Supplementary Materials 1 and 2.

Outcome measures

Patients were evaluated with a battery of tests and questionnaires at each time point of the longitudinal study.

The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS [23, 24]) is a common outcome measure in clinical trials assessing treatments effectiveness in ICD [25]. The TWSTRS consists of three different domains (severity, disability, and pain), which are often used as distinct scales [26]. The TWSTRS severity domain measures "how bad" ICD is, thus measuring the impairment severity. More specifically, ICD postures in the different direction of the space, their severity and duration (e.g., the amount in degrees of torticollis) are collected with a standardized clinical examination and scored. The disability domain measures how hard it is to complete daily activities, such as driving, watching television, and reading, because of ICD. Finally, the pain domain quantifies some aspects of pain such as severity and duration. In all domains, high scores indicate a severe disease, poor daily activities (high disability), and hard pain.

Anxiety, depression, and health-related quality of life were also measured (Supplementary Materials 1).

Data analysis and statistics

Two complementary analyses were performed: a *whole-sample* analysis and a *single-subject* analysis. Given that all outcomes are measured on ordinal scales, non-parametric statistics were chosen for both analysis types.

In the whole-sample analysis, median and interquartile range (IQR) were chosen as central tendency and variability indices, respectively. This analysis primarily looked for meaningful changes of the TWSTRS total and/or domain scores in the five time points. Friedman rank sum test followed by the Wilcoxon signed-rank test was used to evaluate differences among the five time points: the Friedman test was used for checking the overall time effect and the Wilcoxon test was used to compare two sessions at a time. Wilcoxon tests were set so that to respond to the following a priori questions:

1. At BoNT peak effect, are TWSTRS scores (i.e., ICD severity and ICD-related disability and pain) significantly different from baseline (T1 vs T0)?
2. At BoNT peak effect and SPRInt end, are TWSTRS scores significantly different from baseline (T3 vs T2)?
3. At treatment end, do TWSTRS scores return to their pre-treatment status (T2 vs T0; T4 vs T2)?
4. At BoNT peak effect, are TWSTRS scores significantly different when patients are treated with BoNT + SPRInt compared to when they are treated with BoNT alone (T3 vs T1)?
5. At treatment end, are TWSTRS scores significantly different when patients are treated with BoNT + SPRInt compared to when they are treated with BoNT alone (T4 vs T2)?
6. At the end of the study, do TWSTRS scores return to their pre-treatment value (T4 vs T0)?

Note that the T4 vs T2 comparison is used both in question 3 and 5. Because of multiple comparisons, the customary significance level (0.05) was corrected according to Holm-Bonferroni [27].

Prompted by the whole-sample analysis results, we run a single-subject analysis to evaluate for each patient if the score of the TWSTRS disability domain was significantly different in the different time points. More specifically, we were interested in identifying those patients who improved their disability domain score at T1 with respect to T0 (i.e., BoNT responders) and those who improved at T3 with respect to T2 (i.e., BoNT + SPRInt responders).

Details on the single-subject analysis applied here can be found elsewhere [28]. Briefly, the McNemar test was used to check if the disability domain score was significantly different in two time points (i.e., T1 vs T0 and T3 vs T2). Polytomous items, such as those making up the TWSTRS, can be considered made of ordered dichotomous (i.e., affirmed/denied) items [29, 30]. In this respect, item's score (i.e., the number of passed category thresholds) represents the number of problems collected from the patient. With this approach, the McNemar test is used to evaluate if the number of patient's problems enclosed in the TWSTRS disability domain is significantly different between two evaluations.

R 3.3.0 [31] was used for figures and statistics.

Results

Table 1 reports demographic and clinical information for each of the 14 ICD patients who completed the study. One of the 15 enrolled patients dropped out after T2 for a personal reason (he could not attend physiotherapy sessions because of his new job). None of the 15 patients rejected the second BoNT injection, nor was this considered clinically not appropriate.

No adverse effect was recorded.

Whole-sample analysis

Figure 2 shows the time course of the TWSTRS total score and TWSTRS domain scores, before and after treatments.

The Friedman test showed that the TWSTRS total score was significantly different at the various time points (Friedman $\chi^2 = 25.99$, d.f. = 4, $p < 0.001$). At T1 (i.e., at BoNT peak effect), TWSTRS total score was significantly reduced compared to T0 ($p = 0.002$). At T2 (i.e., when the BoNT effect is expected to wear off), TWSTRS total score was still smaller than T0 ($p = 0.017$). At T3 (i.e., at SPRInt end and at the peak of the second BoNT injection), TWSTRS total score was smaller than T2 ($p = 0.004$). No significant difference was observed between T4 and T2 TWSTRS total score, while at T4 the TWSTRS total score was still significantly smaller compared to T0 ($p = 0.023$). To note, T3 TWSTRS total score was smaller than T1 TWSTRS total score ($p = 0.024$). These findings suggest that BoNT improves ICD (T1 vs T0) and that 3 months after treatment the improvement is still present (T2 vs T0). The SPRInt program in association with a second BoNT administration further improves the TWSTRS total score (T3 vs T2). Moreover, after BoNT + SPRInt, patients' TWSTRS total score is significantly better than after BoNT alone.

Table 1 Patients demographics and clinical data. Median and IQR (in brackets) are given for counts and ratio measures (last row). *Inco* incobotulinumtoxinA, *Abo* abobotulinumtoxinA. For toxin dose, median and IQR are calculated after converting the Abodosage into Incoequivalent units (conversion ratio Abo/Inco = 3/1)

					T0		T2	
ID	Sex	Age (years)	Disease duration (years)	BoNT type	Number of sites	BoNT dose (units)	Number of sites	BoNT dose (units)
1	F	49	7	Inco	4	90	2	50
2	M	69	14	Abo	6	950	5	700
3	M	79	27	Inco	4	190	6	180
4	F	48	7	Inco	6	190	5	155
5	M	54	10	Abo	8	1000	7	750
6	F	49	5	Abo	4	800	5	800
7	F	73	3	Inco	6	150	5	135
8	M	42	7	Abo	7	750	6	750
9	M	53	4	Inco	8	300	6	300
10	M	46	12	Abo	6	750	4	300
11	F	46	2	Inco	4	100	5	125
12	M	37	2	Inco	6	200	6	200
13	F	43	2	Inco	3	120	5	180
14	F	44	1	Inco	4	100	4	100
	F = 7	48.5 (9.3)	6 (7)	Inco = 9	6 (2)	195.0 (135.3)	5 (1)	180.0 (118.3)

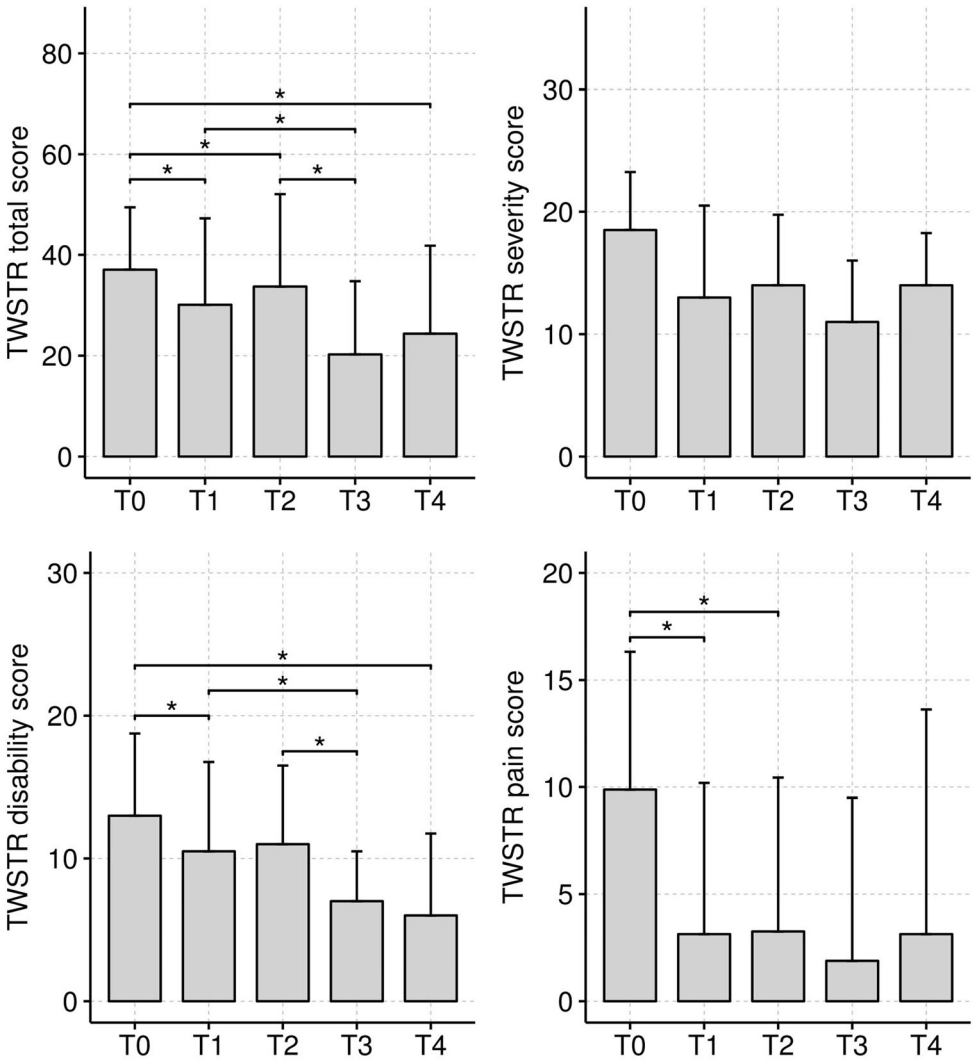

Fig. 2 Time course of the TWSTRS total score and TWSTRS domains scores. Median (bar height) and IQR (whisker length) are reported. *Y* axis is scaled from test minimum to maximum score. Stars mark a significant difference between two time points. None of the planned comparisons (see the methods) were significant for the TWSTRS severity score. Numeric values are given in Supplementary Materials 1

The Friedman test also showed that the TWSTRS severity (Friedman $\chi^2 = 19.44$, d.f. = 4, $p = 0.004$), disability (Friedman $\chi^2 = 26.66$, d.f. = 4, $p < 0.001$), and pain (Friedman $\chi^2 = 17.29$, d.f. = 4, $p = 0.008$) scores changed in the different time points.

TWSTRS disability score was significantly reduced at T1 compared to T0 ($p = 0.049$), but no difference was observed between T2 and T0 ($p = 0.089$). At T3, TWSTRS disability was not only reduced compared to T2 ($p = 0.015$), but also reduced compared to T1 ($p = 0.041$). No difference was observed between T4 and T2 disability, but at T4 the disability score was still smaller than T0 ($p = 0.041$).

From Fig. 2, it is immediately apparent the different time course of the pain domain score compared to that of the disability and severity domains. Pain score drops immediately after the first BoNT injection (T0 vs T1, $p = 0.019$) and remains low throughout the duration of the study (e.g., T0 vs T2, $p = 0.038$).

Finally, even if the Friedman test was significant for the severity domain score too, no difference was found in the a priori planned comparisons.

After treatments, no modification was found for quality of life, depression, and anxiety (Supplementary Materials 1).

Single-subject analysis

The whole-sample analysis suggests that patients' disability benefits the most from the association of BoNT and SPRInt. The aim of the single-subject analysis was to investigate this aspect in greater detail.

The McNemar's test on the disability domain score showed that disability significantly improved after BoNT in 4 patients (T1 vs T0; $p \leq 0.025$) and that BoNT in association to SPRInt significantly improved disability in 5 patients (T3 vs T2; $p \leq 0.046$; see Supplementary Materials 1 for the full results of the single subject analysis). It is remarkable that only one patient improved his disability score both after BoNT alone ($p =$

0.014) and BoNT + SPRInt ($p = 0.025$). In fact, 3 of the 4 patients who improved after BoNT did not respond to BoNT + SPRInt and, similarly, 4 of the 5 patients who improved after BoNT in association to SPRInt did not respond to BoNT alone. From another point of view, 4 of the 10 patients who did not respond to BoNT alone showed a significant disability reduction after BoNT + SPRInt. Finally, 6 patients did not significantly improve with any of the treatments.

Discussion

The current observational study shows that exercise with augmented movement feedback in addition to BoNT could be an effective treatment for ICD patients, particularly improving their difficulties in the activities of daily living. These results highlight as well that disability measures, such as the score of the TWSTRS disability domain, are responsive to exercise in ICD. On this basis, disability measures (rather than impairment measures) should be preferred as main outcomes in clinical trials evaluating exercise effectiveness in ICD.

BoNT injections are the first-line treatment for ICD, effectively correcting abnormal neck posture, reducing pain and improving the activities of daily living [5, 32–34]. BoNT is well tolerated and safe and BoNT adverse events are usually transient and mild/moderate [21]. However, BoNT dose-dependent adverse reactions have been reported [35] and it has been shown that high doses of BoNT and short reinjection intervals could potentially increase the risk to develop neutralizing antibodies, eventually leading to clinical non-responsiveness [21]. On the other hand, many ICD patients feel the need for close injections (i.e., earlier than the 12 weeks of the customary treatment schedule) and would prefer treatments that last longer [36, 37].

In view of all that, any adjunct therapy able to increase BoNT effect size and duration would be valuable. Exercise and physiotherapy are often suggested as an adjunct therapy in ICD. As an example, a cross-sectional study reported that about half of the ICD patients had physiotherapy at some point of their disease and that they felt the need for more physiotherapy [38]. However, there is no clear evidence of physiotherapy effectiveness in ICD [11].

A number of factors make the path toward evidence complicated. For example, different studies evaluated different exercise programs (e.g., ranging from active exercise to relaxation [8, 9]). In addition, physiotherapy could be effective in a sub-group of selected patients (e.g., more disabled people) and the outcome measures used to assess drugs' effectiveness (e.g., impairment-centered measures) could be not appropriate to assess rehabilitation effectiveness, which would prefer disability and participation level measures. In view of these issues, exploratory studies (as the current study) before technically more demanding trials are appropriate [14].

In the current work, we report that ICD overall severity (i.e., the TWSTRS total score) is improved both after BoNT injections alone (i.e., T1) and after BoNT in association with the SPRInt exercise program (i.e., T3). At T3, the TWSTRS total score was reduced compared to T1, suggesting that the BoNT and SPRInt association could be more beneficial than BoNT alone. However, this conclusion is weakened by the fact that at T2 (i.e., 12 weeks after the first BoNT administration, when the BoNT effect should have worn off), the TWSTRS total score was still better than T0. Therefore, we cannot exclude that the further improvement observed after the BoNT and SPRInt association (T3 vs T1) is favored by the second BoNT administration adding on the tail of the first one rather than by the genuine association of BoNT and exercise.

With this regard, the analysis of the different TWSTRS domains scores is helpful. This analysis showed that BoNT alone had little effect on the TWSTRS disability score (T0 vs T1), which actually wore off after 12 weeks (T2 vs T0). On the contrary, the association of BoNT and SPRInt substantially improved disability (T3 vs T2), with patients reaching a disability level significantly better than those reached after BoNT alone (T3 vs T1).

The positive effect of the combined treatment on disability is further confirmed by the single-subject analysis, which showed that about half of patients whose disability did not respond to BoNT alone, actually improved after BoNT + SPRInt. The single-subject analysis could give some clues for the appropriate prescription of exercise as an adjunct therapy in ICD. In fact, this analysis showed that it is unlikely that patients who already improve their disability after BoNT alone improve further after BoNT + SPRInt. On the other hand, patients getting better after BoNT + SPRInt are more likely those who did not respond optimally to BoNT alone. If these preliminary results are confirmed, it can be proposed that proper responders to BoNT have no additional benefit from the addition of neck exercises. On the contrary, the association of BoNT and exercise seems actually indicated in those ICD patients who poorly respond to BoNT alone.

Our study has some obvious limitations. The sample size is small (thus increasing the chance of a type II error), but it should be noted that ICD is a rare disease [39]. It can be argued that patients received their second BoNT injection too early given that, after the first injection, the TWSTRS total score has not returned to its baseline levels. In other words, it is not possible to exclude a *carryover effect*. However, the injection schedule used here is strongly supported by current guidelines and it is in line with the view that BoNT should be scheduled so that to minimize the "off period" [40]. A cross-over study, in which patients are randomly allocated to receive treatments in the order BoNT and then BoNT + SPRInt or BoNT + SPRInt and then BoNT alone, seems thus an appropriate continuation of the current work. It should also be

pointed out that, at our knowledge, there is no published paper reporting the process of translation and adaptation of the Italian version of the TWSTRS. Despite this, TWSTRS is widely used in the clinic and has been used as well in previous works [24]. To note, the TWSTRS is rather simple and so we are confident that the Italian version performs similarly to the original one.

The current work shows that exercise can be an effective and safe adjunct therapy in ICD, although additional studies (such as randomized, controlled trials) are needed before these results can be generalized for broader clinical use.

Acknowledgements We are particularly grateful to the patient who agreed to appear in the video attached as supplementary materials.

Funding support This research was supported by the financial contribution of Italian Ministry of Health-Ricerca Corrente.

Compliance with ethical standards

Ethical aspects of the study were reviewed and approved by the local ethic committee (Comitato Etico "IRCCS Fondazione Don Carlo Gnocchi", Comitato Etico Centrale IRCCS Regione Lombardia) and the study has been recorded at ClinicalTrials.gov (NCT03247868). Each participant gave his/her written consent to take part in the study. The patient who agreed to appear in the video attached to the current work as Supplementary Materials 2 gave her written consent to publication.

Competing interests The other authors declare that they have no conflicts of interest. Alessandro Crippa created the feedback system used in the study (Leonardo, produced by Chinesport).

References

1. Albanese A, Bhatia K, Bressman SB, DeLong MR, Fahn S, Fung VSC, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK (2013) Phenomenology and classification of dystonia: a consensus update. Mov Disord 28:863–873
2. Zetterberg L, Lindmark B, Söderlund A, Åsenlöf P (2012) Self-perceived non-motor aspects of cervical dystonia and their association with disability. J Rehabil Med 44:950–954
3. Ben-Shlomo Y, Camfield L, Warner T (2002) What are the determinants of quality of life in people with cervical dystonia? J Neurol Neurosurg Psychiatry 72:608–614
4. Simpson DM, Hallett M, Ashman EJ et al (2016) Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 86:1818–1826
5. Castelao M, Marques RE, Duarte GS, et al (2017) Botulinum toxin type A therapy for cervical dystonia. Cochrane Libr
6. Comella C, Bhatia K (2015) An international survey of patients with cervical dystonia. J Neurol 262:837–848
7. De Pauw J, der Velden K, Meirte J et al (2014) The effectiveness of physiotherapy for cervical dystonia: a systematic literature review. J Neurol 261:1857–1865
8. Smania N, Corato E, Tinazzi M et al (2003) The effect of two different rehabilitation treatments in cervical dystonia: preliminary results in four patients. Funct Neurol 18:219–226
9. Boyce MJ, Canning CG, Mahant N, Morris J, Latimer J, Fung VSC (2013) Active exercise for individuals with cervical dystonia: a pilot randomized controlled trial. Clin Rehabil 27:226–235
10. Pelosin E, Avanzino L, Marchese R, Stramesi P, Bilanci M, Trompetto C, Abbruzzese G (2013) Kinesiotaping reduces pain and modulates sensory function in patients with focal dystonia: a randomized crossover pilot study. Neurorehabil Neural Repair 27:722–731
11. Delnooz CCS, Horstink MWIM, Tijssen MA, van de Warrenburg BPC (2009) Paramedical treatment in primary dystonia: a systematic review. Mov Disord Off J Mov Disord Soc 24:2187–2198
12. Hill N, Frappier-Davignon L, Morrison B (1979) The periodic health examination. Can Med Assoc J 121:1193–1254
13. Tassorelli C, Mancini F, Balloni L, Pacchetti C, Sandrini G, Nappi G, Martignoni E (2006) Botulinum toxin and neuromotor rehabilitation: an integrated approach to idiopathic cervical dystonia. Mov Disord Off J Mov Disord Soc 21:2240–2243
14. Kempen JH (2011) Appropriate use and reporting of uncontrolled case series in the medical literature. Am J Ophthalmol 151:7–10
15. Korein J, Brudny J, Grynbaum B et al (1976) Sensory feedback therapy of spasmodic torticollis and dystonia: results in treatment of 55 patients. Adv Neurol 14:375
16. Marsden CD (1976) The problem of adult-onset idiopathic torsion dystonia and other isolated dyskinesias in adult life (including blepharospasm, oromandibular dystonia, dystonic writer's cramp, and torticollis, or axial dystonia). Adv Neurol 14:259–276
17. Shaikh AG, Zee DS, Crawford JD, Jinnah HA (2016) Cervical dystonia: a neural integrator disorder. Brain 139:2590–2599
18. De Pauw J, Mercelis R, Hallemans A et al (2017) Cervical sensorimotor control in idiopathic cervical dystonia: a cross-sectional study. Brain Behav 7:e00735
19. Young SJ, van Doornik J, Sanger TD (2011) Visual feedback reduces co-contraction in children with dystonia. J Child Neurol 26:37–43
20. Anna Castagna AA (2018) Management of cervical dystonia with botulinum neurotoxins and EMG/ultrasound guidance. Neurol Clin Pract 029785a
21. Wissel J (2018) Towards flexible and tailored botulinum neurotoxin dosing regimens for focal dystonia and spasticity–insights from recent studies. Toxicon 147:100–106
22. Scaglione F (2016) Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. Toxins (Basel) 8:65
23. Consky ES, Basinski A, Belle L et al (1990) The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS): assessment of validity and inter-rater reliability. Neurology 40:445
24. Lalli S, Piacentini S, Franzini A, Panzacchi A, Cerami C, Messina G, Ferré F, Perani D, Albanese A (2012) Epidural premotor cortical stimulation in primary focal dystonia: clinical and 18F-fluoro deoxyglucose positron emission tomography open study. Mov Disord 27:533–538
25. Jen M-H, Kurth H, Iheanacho I, Dinet J, Gabriel S, Wasiak R, Jost WH (2014) Assessing the burden of illness from cervical dystonia using the Toronto Western Spasmodic Torticollis Rating Scale scores and health utility: a meta-analysis of baseline patient-level clinical trial data. J Med Econ 17:803–809
26. Jankovic J (1994) Therapy with botulinum toxin. Marcel Dekker
27. Holm S (1979) A simple sequentially rejective multiple test procedure. Scand J Stat 65–70
28. Caronni A, Sciumè L (2017) Is my patient actually getting better? Application of the McNemar test for demonstrating the change at a single subject level. Disabil Rehabil 39:1341–1347
29. Andrich D (1978) A rating formulation for ordered response categories. Psychometrika 43:561–573
30. Masters GN (1982) A rasch model for partial credit scoring. Psychometrika 47:149–174. https://doi.org/10.1007/BF02296272

31. R Core Team (2017) R: a language and environment for statistical computing
32. Simpson DM, Blitzer A, Brashear A et al (2008) Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review) Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 70:1699–1706
33. Esquenazi A, Novak I, Sheean G, Singer BJ, Ward AB (2010) International consensus statement for the use of botulinum toxin treatment in adults and children with neurological impairments–introduction. Eur J Neurol 17:1–8
34. Marques RE, Duarte GS, Rodrigues FB, et al (2016) Botulinum toxin type B for cervical dystonia. Cochrane Libr
35. Yiannakopoulou E (2015) Serious and long-term adverse events associated with the therapeutic and cosmetic use of botulinum toxin. Pharmacology 95:65–69
36. Jankovic J, Truong D, Patel AT, Brashear A, Evatt M, Rubio RG, Oh CK, Snyder D, Shears G, Comella C (2018) Injectable DaxibotulinumtoxinA in cervical dystonia: a phase 2 dose-escalation multicenter study. Mov Disord Clin Pract 5:273–282
37. Jankovic J, Truong D, Patel A, et al (2018) Outcomes of week-24 completers and subjects who had follow-up beyond week 24 after a single treatment of DaxibotulinumtoxinA for injection (RT002): results of a phase 2, open-label (level II), dose escalating study in isolated cervical dystonia (P5. 037)
38. Zetterberg L, Aquilonius S-M, Lindmark B (2009) Impact of dystonia on quality of life and health in a Swedish population. Acta Neurol Scand 119:376–382
39. Defazio G, Esposito M, Abbruzzese G, Scaglione CL, Fabbrini G, Ferrazzano G, Peluso S, Pellicciari R, Gigante AF, Cossu G, Arca R, Avanzino L, Bono F, Mazza MR, Bertolasi L, Bacchin R, Eleopra R, Lettieri C, Morgante F, Altavista MC, Polidori L, Liguori R, Misceo S, Squintani G, Tinazzi M, Ceravolo R, Unti E, Magistrelli L, Coletti Moja M, Modugno N, Petracca M, Tambasco N, Cotelli MS, Aguggia M, Pisani A, Romano M, Zibetti M, Bentivoglio AR, Albanese A, Girlanda P, Berardelli A (2017) The Italian Dystonia Registry: rationale, design and preliminary findings. Neurol Sci 38:819–825
40. Poliziani M, Koch M, Liu X (2016) Striving for more good days: patient perspectives on botulinum toxin for the treatment of cervical dystonia. Patient Prefer Adherence 10:1601