Spinal Cord Series and Cases (2020)6:70
https://doi.org/10.1038/s41394-020-0317-2

ARTICLE

Combined botulinum toxin type A and electrical stimulation in individuals with C5–C6 and C6–C7 tetraplegia: a pilot study

Francesco Piccione [1] · Paolo Tonin [2] · Antonio Cerasa [2,3] · Stefano Masiero [4]

Received: 4 May 2020 / Revised: 21 July 2020 / Accepted: 21 July 2020

Abstract

Study design Single-blind pilot study.

Objectives (1) To evaluate combined BoNT-A injection of spastic antagonistic muscles and ES of wrist extensors in order to improve hand function in incomplete cervical SCI patients. (2) To identify prognostic indicators of hand improvements, as a function of motor levels of injury.

Setting Ten incomplete asymmetric SCI tetraplegics admitted to San Camillo Hospital (Venezia, Italy), who were not able to perform automatic grasping, were enrolled in the study. A better motor level (BML) C6–C7 and worse motor level (WML) C5–C6 were assigned to take into account asymmetric motor strength.

Methods Administration of 100–200 UI BoNT-A per limb into flexor carpi radialis (FCR), extensor digitorum communis (EDC), brachial biceps (BB), and pectoralis major (PM) was performed. This was in conjunction with 6 weeks of 30-min ES sessions repeated three times a day for 6 days a week in wrist extensor muscles, and 6 weeks of 30-min hand rehabilitation for 6 days a week. Assessments included wrist Range of Motion (w-RoM), Modified Ashworth Score (MAS), Functional Independence Measure motor scores (FIM motor), and Nine Hole Peg Test (NHPT).

Results Treatments produced a significant reduction in motor spasticity (MAS) and better dexterity (NHPT) in the C6–C7 BML with respect to the WML cases (p level $= 0.007$; $p = 0.01$, respectively). FIM motor scores improved more in BML (median: 20; range 20/22) than in WML (median: 10; range 8/17).

Conclusions Hand function improvement, determined by combined BONT-A and ES, was better in C6–C7 than in C5–C6 SCI patients.

Introduction

Incomplete asymmetric tetraplegia is the most common form of spinal cord injury (SCI). In this clinical condition a primary outcome of rehabilitation is to restore hand function to improve independence in activities of daily living (ADL) [1]. Hand splinting is generally used to develop tendon shortening of finger flexor muscles, combined with isometric exercises of wrist extensors in order to increase the efficacy of the grasp [2–4].

Surgical interventions, using a combination of joint fusions, tenodesis, and tendon transfer, are another option to restore key motions such as elbow flexion, wrist extension, and hand grip; however, less than 10% of individuals with tetraplegia undergo these procedures [5].

Limited access to surgery may be due to a lack of hospital units and physicians offering reconstructive surgery, or to inadequate interdisciplinary counseling to explain the risks, benefits, and outcomes of reconstructive procedures. An alternative explanation is that individuals with tetraplegia believe that surgery might hinder future innovative treatments for motor recovery [6]. Upper limb key muscle activations may be hindered by contracture or spasticity of antagonistic muscles. Consequently, botulinum toxin type A (BoNT-A) treatment has become well accepted in managing spasticity and preventing permanent shortening

✉ Francesco Piccione
francesco.piccione@ospedalesancamillo.net

1 IRCCS San Camillo Hospital, Venice, Italy

2 S. Anna Institute and Research in Advanced Neurorehabilitation, Crotone, Italy

3 Institute for Biomedical Research and Innovation (IRIB), National Research Council, Mangone (CS), Italy

4 Department of Neuroscience, Section of Rehabilitation, University of Padova, Padova, Italy

Published online: 04 August 2020

of muscles and tendons in individuals with SCI [7–9]. The effect of BoNT-A treatment becomes evident in less than 2 weeks and muscle activity generally returns to previous levels in 2 or 3 months. However, the impact of the BoNT-A on the ADL of SCI patients is uncertain and less frequently studied [7–9]. Attention has been paid to the modifications of clinical parameters, however, possible improvements in specific functional abilities have not been studied. Only one case report showed an improvement in hand function after treatment using BoNT-A in an individual with a C5–C6 SCI [10]. This lack of evidence may be related to the fact that hand deficits in persons with tetraplegia are due both to paralysis and spasticity, and that BONT-A alone may not be sufficient to counteract the muscle imbalance, weakness, and resistance to movement that happens in tetraplegia.

Alternative approaches could thus be useful, such as electrical stimulation (ES). ES helps improve grasping by exploiting the residual contractility after denervation or deafferentation of the muscles involved in arm and hand functions [11–13].

The aim of this pilot study was firstly to evaluate whether combined BoNT-A injection of spastic antagonistic muscles and ES of activatable wrist extensors, as an adjunct to motor therapy, would improve hand function in incomplete cervical SCI patients. Secondly, possible prognostic indicators of hand improvements were investigated in terms of different motor levels of injury.

Methods

Participants

Participants were enrolled among 60 consecutive SCI subjects admitted to the San Camillo IRCCS Hospital Neurorehabilitation unit (Venice, Italy) from February 2018 to March 2019. Subjects received hospital care for follow-up rehabilitative management of spasticity, pressure ulcers, bladder and bowel dysfunctions, worsening of autonomic dysreflexia, neurogenic pain, and fatigue.

The inclusion criteria of the pilot study were: (1) incomplete asymmetric C5–C6–C7 SCI tetraplegia; (2) inability to produce automatic grasping for weakly activatable wrist extensors and concomitant spasticity and/or muscular stiffness of upper limb muscles (Fig. 1); (3) previous unsuccessful rehabilitative attempts to restore hand function using hand splinting combined with isometric exercises of wrist extensors; (4) refusal to undergo of hand surgery.

Exclusion criteria: (1) the presence of intrathecal baclofen pump implant; (2) cognitive impairment influencing collaboration in rehabilitative treatment and ability to provide informed consent: cut off <30 based on the cognitive subscale of the Functional Independence Measure (FIM Cog); (3) contraindication to the use of botulinum toxin and ES [11, 14]. The enrolled patients were classified according to the International Standards for Neurological Classification of SCI and incomplete injuries were defined using the ASIA Impairment Scale (AIS) grades B, C, and D. The inclusion criteria meant that all participants had incomplete asymmetric tetraplegia; consequently, the neurological level was unsuitable, and the classification of patients was limited to motor and sensory levels (see Table 1).

In line with previous studies [1, 15], subjects were split into two groups to take into account the asymmetric motor strength: better motor level (BML) C6–C7 cases and worse motor level (WML) C5–C6 cases.

Although the treatments proposed are currently used in clinical practice, we required all participants to give written informed consent as authorized by the local ethics committee in accordance with the Helsinki Declaration.

Study design

The design was a single-blind pilot study. BoNT-A and ES treatments were made by neurologists. Evaluations were accomplished, at the beginning (T0) and the end (T1) of a 6-

Fig. 1 Pathological hand grasping in individual with SCI. Case 5 photo shows hand of an individual without ability to grasp (subject had developed flexion deformities of the proximal and distal interphalangeal joints).

Table 1 Clinical characteristics and treatments in incomplete asymmetric chronic tetraplegics patients grouped in worst and best motor level cases at the beginning and after 6 weeks training period.

Patients	Age	Sex	Etiology	Time from onset (weeks)	International Standards for Neurological Classification of SCI					Treatment data				
					AIS	Motor level		Sensory level		BONT-A injected muscles[a]	ROM wrist before/after	MAS[b] before/after	NHPT before/after	FIM before/after
						Right	Left	Right	Left					
1	**55**	**F**	**Car accident**	**24**	**C**	**C6**	**C7**	**T3**	**T3**	**EDC** (+**EDC**) *Left 150 U*	**15°/45°**	**3/1**	**0/3**	**22/42**
2	*32*	*M*	*Motorcycle accident*	*18*	*B*	*C6*	*C6*	*C8*	*T1*	*BB (+GP + SS) Right 150 U*	90°/115°	*2/1*	*0/1*	*18/32*
3	*38*	*M*	*Sport injury*	*72*	*C*	*C6*	*C7*	*T2*	*T3*	*BB (+GP + SS) Left 150 U*	95°/120°	*1/0*	*0/1*	*22/32*
4	*37*	*M*	*Motorcycle accident*	*24*	*B*	*C6*	*C6*	*T1*	*T1*	*BB (+GP + SS) Bilat 100 U*	80°/100°	*2/1*	*0/0*	*18/26*
5	*65*	*M*	*Fall*	*24*	*C*	*C6*	*C6*	*T1*	*T1*	*BB (+GP + SS) Bilat 100 U*	85°/115°	*1/0*	*0/1*	*18/28*
6	*40*	*M*	*Work accident*	*12*	*B*	*C6*	*C6*	*T1*	*T1*	*BB (+GP + SS) Bilat 100 U*	80°/105°	*2/1*	*0/0*	*18/26*
7	*32*	*M*	*Sport accident*	*120*	*B*	*C6*	*C6*	*T1*	*T1*	*BB (+GP + SS) Bilat 100 U*	80°/105°	*1/1*	*0/0*	*18/28*
8	**68**	**M**	**Fall**	**108**	**C**	**C7**	**C7**	**T3**	**T3**	**EDC** (+**EDC**) *Bilat 150 U*	**20°/55°**	**3/1**	**0/3**	**18/38**
9	*43*	*M*	*Car accident*	*12*	*C*	*C6*	*C7*	*T1*	*T2*	*BB (+GP + SS) Right 100 U*	95°/120°	*2/1*	*0/1*	*18/35*
10	**64**	**M**	**Fall**	**12**	**C**	**C7**	**C7**	**T3**	**T3**	**FCR** (+**EDC**) *Bilat 150 U*	**15°/55°**	**4/1**	**0/4**	**22/42**

Considering the key C6 motor level, we assigned three participants at best motor level (BML) C6–C7 cases 1, 8, 10 (bold text) and seven participants at worst motor level (WML) C5–C6 cases 2, 3, 4, 5, 6, 7, 9 (italic text).

[a]BONT-A Units per limb (right and/or left) in flexor carpi radialis (FCR), extensor digitorum communis (EDC), pectoralis major (PM), brachial biceps (BB).

[b]Modified Ashworth Score (MAS) in wrist flexor muscles (FRC). *ROM* range of movement, *NHPT* Nine Hole Peg Test, *FIM* Functional Independence Measure, *WML* worst motor level, *BML* best motor level.

week training period, by motor therapists blinded to the aim of the study.

Treatments

BoNT-A treatment

Following the Spasticity Study Group algorithm for dosing, administration, and treatment [14], EMG guided BoNT-A injections were performed using doses of 100–150 U per limb (1–2 sites of injections, dilutions ranging from 100 to 100 U/2 mL) into the following muscles: flexor carpi radialis (FCR), extensor digitorum communis (EDC), brachial biceps (BB), and pectoralis major (PM). FCR and EDC were injected because their spasticity hindered voluntary activity of the wrist extensors and the tendon shortening of the finger extensors. BB and PM were also treated because their uninhibited action resulted in contractures in the elbow and shoulder and therefore impeded the overall functions of the arms and hands.

All participants were BoNT-A naïve and were treated with just one application because the duration of maximal response following the botulinum toxin injection was concomitant with the 6 weeks of ES [14].

ES treatment

Participants were treated with ES applied in a bipolar arrangement, using two 30 mm diameter adhesive electrodes (anode and cathode) placed over the wrist extensor muscles in their longitudinal plane, with the cathode at the proximal end and the anode at the distal end of the muscle belly. Monophasic triangular pulses were delivered to the muscles to determine the threshold intensity (in mA) in order to elicit a clearly visible muscles contraction and joint movements while not causing the patient unnecessary discomfort. The Stimulette den2x electrostimulation device (https://schuhfriedmed.at/electrostimulation-en/) was used.

The protocol below describes the ES of the wrist flexors:

(1) Pulse amplitude: amplitude required to elicit a visible response <40 mA.
(2) Pulse shape and duration: triangular, monophasic, equal to or longer than the chronaxy of the denervated muscle >100 ms.
(3) Pulse frequency: 10–30 Hz, applied in bouts of 5–20 stimulations to each muscle involved, followed by a rest time longer than the stimulation time (on–off time ratio of no less than 1:5). The bouts of stimulation were repeated three times in each session.
(4) Treatment time: ES sessions lasted 30 min and were repeated three times a day, for 6 days a week.

ES sessions lasted 30 min and were repeated three times a day, for 6 days a week, during the 6-week training period [16].

Rehabilitative treatment

Isometric wrist extensor exercises (ME) were performed for 30 min a day, 6 days a week, for 6 weeks. Exercises were carried out using rubber bands with a sequential system of progressive resistance, followed by stretching. There were at least three repetitions for each type of band, and they were performed for a time interval that was determined by calculating 80% of the time of maximum contraction; each repetition was separated by 30 s of rest. Splinting was maintained for at least 20 h a day throughout the week to favor tendon shortening of finger flexor muscles. Subjects also followed a 6-week program of standard neurorehabilitation, consisting of 1-h sessions of stretching, passive mobilization, and general activatable muscle reinforcement plus 1-h of occupational therapy [2–4].

Clinical assessment

Changes in clinical outcome were measured using:

(1) Wrist range of movements (w-RoM): the measurement was performed by goniometry. Subjects were seated with the shoulder abducted to 90°, elbow flexed to 90°, and the wrist over the edge of a table with the forearm in pronation. Both arms of the goniometer were placed parallel to the ulnar bone, with the fulcrum over the lateral cuneiform bone and recording the angle when the subject attempted to extend the wrist. w-RoM represents the measurement of the angle of the active wrist extension with an expected range of motion from 0 to 70° [2, 4].
(2) Modified Ashworth Score (MAS) of the muscles hindering wrist extension. We measured MAS of the wrist flexor muscles (FRC) [8, 9, 14, 17].
(3) Motor items of FIM related primarily to arm and hand function (FIM motor) [18–21].
(4) Nine Hole Peg Test (NHPT) to measure manual dexterity: scores were based on the number of pegs placed in 100 s to measure effective hand function [22].

Statistical analysis

Statistical analysis was performed using the statistical package for social sciences (SPSS) for Windows (version 12.0; SPSS, Chicago IL). A nonparametric Mann–Whitney

U test was used to assess potential differences in delta scores between ML groups for all clinical variables. A two-tailed alpha level < 0.05 was employed to define significance.

Effect sizes were measured in absolute and relative terms. For relative effect sizes, we used a nonparametric effect size measure, the common language effect size (CL; [23]), which specifies the probability of a sampled observation from one group being larger than a selected observation from the other group (probability of superiority). We thus compared the FIM motor effect sizes of our two groups, BML C6–C7 cases and WML C5–C6 [23].

Results

Ten individuals with tetraplegia (9 men; median age: 41.5; range 32/68 years; median time from the onset: 24; range 12/120 weeks) met the inclusion criteria and were enrolled in the study. In this group, 30% were classified in the BML C6–C7 group (cases 1, 8, 10, Table 1, bold) and 70% in the WML C5–C6 group (cases 2, 3, 4, 5, 6, 7, 9, Table 1, italic). After the 6-week training period BML C6–C7 cases exceeded grade 4 on the wrist extensor muscles MMT test while the WML C5–C6 cases remained at grade 3 or less.

In the C6–C7 BML cases, the enhancement of w-RoM was greater (median delta value: +35°; range 30/40) than in the C5–C6 WML patients (median delta value: +25°; range 20/30), although this did not reach a significant level (*p* level = 0.09) (see Table 1). Otherwise, motor spasticity significantly decreased in the C6–C7 BML cases (MAS median delta value: −2; range −3/−2) with respect to the C5–C6 WML cases (MAS median delta value: −1; range −1/0) (*p* level = 0.007). The C6–C7 BML cases achieved an efficient automatic grasp (see participant 1 in Fig. 2), as defined by increasing values in the NHPT task (median delta values: 3; range 3/4) with respect to the C5–C6 WML cases (median delta values: 0; range 0/1) (*p* level = 0.01). Finally, with regard to the FIM motor scores, we found a significant improvement in the C6–C7 BML cases (median delta FIM motor score value: 20; range 20/22) with respect to the C5–C6 WML cases (median delta FIM motor score value: 10; range 8/17) (*p* level = 0.01), (see Table 1). The CL index, computed from the means and standard deviations of the FIM motor score, confirmed a significant difference between the relative FIM motor effect size of the two groups [23]. No BoNT-A adverse events and ES discomforts were registered during the 6-week training period.

Discussion

Our pilot study explores a nonsurgical treatment option for restoring hand function in individuals with asymmetric tetraplegia. Participants had a C5–C6 or C6–C7 motor level, had weak wrist extensors and were not able to perform automatic closure of the fingers during grasp. In our study, according to the inclusion criteria, all our enrolled patients had already undergone treatments by splinting and isometric exercises [5, 6], delivered in rehabilitative settings, without positive results, given that they had already refused the surgical treatment. Taking into account these criteria, our subjects were homogeneous and stable regarding the motor deficits and the clinical outcome. In individuals with tetraplegia, function of the hands depends not only on the extent of paralysis but also on the level of strength imbalance of the upper limb muscles due to spasticity, muscle stiffness, and shortening of the tendons, which may interfere with wrist extension and automatic grasping [2, 3].

Irrespectively of the motor level, our study shows a general clinical benefit of using BoNT-A injections in spastic antagonistic muscles combined with the reinforcement of wrist extensors with ES [7, 8, 11, 12]. In individuals with asymmetric tetraplegia, the NHPT, which measures manual dexterity and effective hand function, only improved in subjects with a more caudal injury. In line

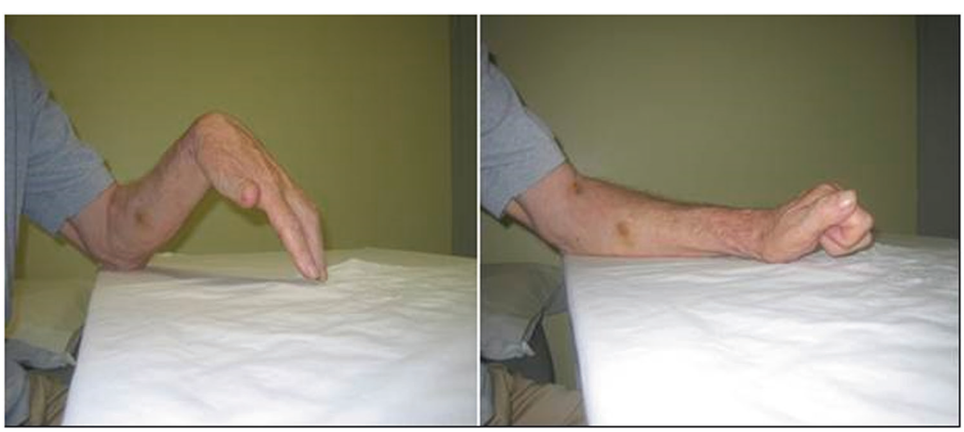

Fig. 2 Improvement of hand grasping in individual with SCI. Case 1 photo shows optimal finger grasp and side to side pinch after botulinum toxin treatment in flexor carpi radialis and extensor digitorum communis.

with Marino et al. [15], we found that composite clinical improvement of hand function was better in SCI patients with C6–C7 motor level than in C5–C6.

In BML C6–C7 subjects, automatic grasp was obtained by the improvement of the voluntary activation of the extensor carpi radialis longus and brevis muscles, which was concomitant with a reduction in spasticity of the FCR and finger extensors. In WML C5–C6 cases, the same treatments were not effective. In these subjects, resistance to wrist extension was not hindered by spasticity but by nonneural mechanisms such as shortening and changes in the mechanical properties of muscles and tendons. In these cases, BoNT-A injections had no effect [9–12]. Moreover, ES did almost nothing to restore muscle strength or reduce muscle atrophy due to denervation and disuse in the wrist.

Thus, we believe that individuals with WML C5–C6 will not benefit from combined BoNT-A injections and ES. In these subjects, reinforcement of Brachioradialis may be useful for reconstructive procedures [5, 6]. After the 6-week training period, C5–C6 WML cases remained at grade 3 or lower on the wrist extensor muscles MMT test. CL index, computed from the means and standard deviations of FIM motor score, confirmed that there was a significant difference between the relative FIM motor effect size of the two groups [23]. In treated subjects, motor level is optimal as compared to the performance of self-care and mobility tasks assessed using FIM motor scores [1, 15].

In C6–C7 subjects, the effect of BoNT-A combined with ES in restoring hand function was similar to the effect of BoNT-A combined with functional electrical stimulation (FES) in other spastic disabilities [9]. In spastic paralysis after stroke, electrical stimulation is paired with a functional task (FES) to produce forward reaching motion and to facilitate grasping [11, 16]. In individual with tetraplegia, ES has been used to improve muscle strength and to increase the range of motion of the wrist extensors in order to facilitate the use of the hand with a tenodesis effect [18–21]. The FRC and the EDC are the recommended target muscles for BoNT-A injections.

However, given that our study was with a relatively small sample size, further evaluations with larger clinical samples and the inclusion of a control group are required to confirm our preliminary evidence.

Conclusions

Based on our findings, BoNT-A injections in spastic antagonistic muscles combined with the reinforcement of wrist extensors using ES resulted in clinical improvement in individuals with asymmetric tetraplegia. Our pilot study suggests that subjects with C6–C7 levels of injury benefited most from our intervention and achieved improved hand function.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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