Do gait parameters improve after botulinum toxin injections in post stroke patients? A prospective study

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ABSTRACT

The intramuscular injection of botulinum toxin is one of the most efficient ways to treat localized spasticity in patients suffering from Central Nervous System lesions like stroke, cerebral palsy and multiple sclerosis. The gait analysis based on kinetics and kinematics is a recognized way of measurement of the effect of intramuscular injection of botulinum toxin in spastic patients suffering from chronic stroke. The aim of this study is to provide evidence of the beneficial effect of botulinum toxin on characteristics of gait pattern on patients suffering from chronic stroke. So, thirteen patients with spasticity due to chronic stroke were included in the protocol and were treated by botulinum toxin injections in the lower extremity. All patients were evaluated before the injection as well as one month after the botulinum injection on a foot pressure sensitive walkway with a power plate and by the readings of seven inertial measurements units which recorded spatio-temporal specific parameters during walking, and the spasticity was measured according to modified Ashworth Scale. While all spatio-temporal parameters of motion analysis and balance improved for most of the patients after botulinum toxin injection, only one parameter, the normal to hemiplegic step length, reached statistical significant improvement ($p < 0.03$). Moreover the modified Ashworth score was statistically improved post injection ($p < 0.001$). In conclusion the use of botulinum toxin injections is beneficial in post stroke patients as this is depicted in gait parameters improvement which accompanies the spasticity reduction.

1. Introduction

Stroke is a major cause of long-term disability in adults(Dunne et al., 2012; Feigin et al., 2009). Among poststroke patients, about 25 % of them are capable of performing the Activities of Daily Living (ADL) and to participate in the community, along with the healthy population (Dobkin, 2005; Pimentel et al., 2014). As one would expect, the quality of life is higher in post stroke patients who acquire better functionality than in those who remain in low functionality (Pimentel et al., 2014; Samsa and Matchar, 2004). On the other hand more than two thirds of stroke survivors develop impaired motor function and post stroke spasticity(Datta Gupta et al., 2019). Approximately 20 %–40 % of stroke survivors will develop spasticity, the severity of which depends on and is influenced by various factors, such as the level of paralysis, the degree of neuropathic and/or nociceptive pain as well as the time since the onset of the unpleasant sensation(Thilmann et al., 1991; Wein et al., 2018;

Wissel et al., 2010). Spasticity arises as a consequence of the loss of myotatic reflex inhibition that results from an upper motor neuron lesion(Pimentel et al., 2014). Moderate to severe focal muscle over-activity, especially with associated muscle contractions, can limit functional ability and have a profound impact on independence and quality of life(Brainin et al., 2011; Dunne et al., 2012). In particular, spasticity that develops in the lower extremities of hemiparetic patients is a major problem, as it can reduce their functional ability and gait rehabilitation(Mancini et al., 2005).

Botulinum toxin type A (BoNT-A) is a neurotoxin that acts peripherally to motor end plate, blocking neuromuscular transmission and producing a focal, temporal chemical denervation, whose efficacy in reducing neuromuscular overactivity is well known(Blasi et al., 1993; Mancini et al., 2005). Intramuscular injections of BoNT-A are used to target one or more of the positive signs of upper motor neuron syndrome, reducing spasticity of specific muscle groups(Tao et al., 2015;

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Ward, 2008). The peak clinical benefit of BoNT-A is seen within 4–8 weeks after the injection and treatment effects generally wane at about 12 weeks(Dunne et al., 2012; Gracies et al., 2007). A large number of studies, randomized-controlled trials and meta-analysis, have reported the success of BoNT-A in improving disability and post-stroke pain in patients suffering from stroke. In particular BoNT-A presents unquestionable advantages as the absence of serious side effects and optimal tolerance by patients, the lack of sensory effects and the ability to target specific muscle groups, so allowing harmful spasticity to be selectively reduced in one area while preserving potentially useful spasticity in another(Davis and Barnes, 2000; Kaji et al., 2010; Miscio et al., 2004; Pierson et al., 1996).

Stroke has a wide range of symptoms in its clinical presentation. It goes from flaccid paralysis to increased muscle tone and spasticity (Esquenazi et al., 2015). Equinovarus foot posture is the most frequent abnormal limb posture seen in those with hemiparetic gait. In post-stroke patients with lower-limb spasticity, spastic equinus foot represents a prolonged abnormal lower-limb posture and affects gait, standing and transfer(Ferreira et al., 2013; Tao et al., 2015). More specifically, the foot and ankle are inverted and pointed downwards into plantar flexion. As a result the foot positioning on the ground is poor, with three main components, equinus, varus and clawing of the toes. (Rousseaux et al., 2005). The muscles that can potentially contribute to the equinovarus deformity include the gastrocnemius, soleus, tibialis posterior, extrinsic toe flexors, extensor hallucis longus in combination with the lack of activation of the peroneus longus(Cioni et al., 2006; Esquenazi et al., 2015). In addition, adult patients with hemiplegia often present with lower limb spasticity, on more central muscles like the knee extensors and the hip adductors.

Various hemiplegic gait patterns are observed as a result of an upper motor neuron lesion that affects the lower extremities. The most common clinical presentation is the one that the deficit in ankle dorsiflexion during the swing phase forces the patient in order to advance the limb to attempt a global circumduction. Afterwards, during the stance phase, the equinovarus foot deformity is responsible for poor plantar support. In severe cases there is loss of heel strike during the initiation of gait and the spasticity of the biarticular gastrocnemius leads to a genu recurvatum(Rousseaux et al., 2005).

The aim of this study is to provide evidence of the beneficial effect of intramuscular BoNT-A injections on characteristics of gait pattern on patients suffering from upper motor neuron lesion with equinovarus deformity, particularly with regards to spatio-temporal parameters. Specifically, both stride and step length (hemiplegic to normal and normal to hemiplegic) will be calculated before and after BoNT-A injection.

2. Material and methods

2.1. Patients

This is a prospective single-blind pre- and post-intervention study of 14 chronic stroke patients suffering from spastic hemiparesis documented by CT scan, who received BoNT-A injection for lower extremity spasticity and were examined with gait analysis. All patients that fulfilled the inclusion criteria were enrolled in the study in a sequential way. Initially 14 patients started the study, but there was one drop out due to serious health complications which were not due to BoNT-A. The clinical research was carried out at the premises of the S. Niarchos Rehabilitation Center, in University Hospital of Ioannina, Greece and was conducted over a period of 18 months (September 2018–March 2020).

Inclusion criteria: Age from 18 to 75 years, patients had to be able to walk either freely or while wearing a splint or by the use of a crutch, level of spasticity ≥1+ on the Modified Ashworth Scale (MAS), post-stroke period at least 6 months and none surgical operation on the lower extremities.

Exclusion criteria: Patients with dementia or aphasias, history of previous injection of BoNT-A the last six months, fixed joint posture (contraction), hospitalization and pregnancy.

This study was approved by the local ethics committee and all subjects provided written informed consent prior to participation.

2.2. Gait analysis

Gait analysis in patients was performed using two systems. The first system receives and integrates data from seven Inertial Measurements Units IMU (Rehagait Pro, Hasomed) placed in specific anatomical points of interest on the lower extremities of the patient (at the ankle joints, at the calves, at the thighs and one at the theoretical body center of mass). The second system is a pressure sensitive walkway (Win-Track, Medicapteurs). Both systems record spatio-temporal specific parameters during walking and standing. Fig. 1 shows the parameters calculated by the Rehagait Analyzer system and Table 1 shows the parameters calculated from the Win-Track walkway. Also mean velocity for each walking trial was calculated with the RehaGait Analyzer system.

2.3. Methods

2.3.1. Treatment procedure

The same botulinum toxin – type A of 100 U per vial (BOTOX, Allergan) were injected to all patients. The total injected dose of BoNT-A was 250 U to each patient. Specifically, 75 U were injected to the lateral head and 75 U to the medial head of gastrocnemius, 50 U were injected to the soleus and 50 U to the posterior tibialis, with a dilution of 2 mL/ 100 U. For the above muscles, one up to three local points for injection has been selected. Both solution preparation and injection were performed by the same physician with EMG guidance throughout the research (AP), while a second physician was responsible for the physical examination of the patients (GIV). A second group of physicians (blinded to the time of botox injection) was responsible for the gait analysis (DNV and DD) in a different place (gait analysis lab).

2.3.2. Clinical protocol

Post-stroke patients were evaluated before the BoNT-A injection as well as 1 month after the injection. Before gait analysis, a clinical examination was conducted, in order to determine the spasticity according to modified Ashworth Scale.

For statistical reasons the modified Ashworth scale was changed to 0–5 grades (instead of 0, 1, 1+, 2, 3, 4).

Each patient had to be evaluated by both gait analysis systems at the same date and time. The seven IMU sensors of the RehaGait Analyzer were fasten at the specific anatomical places of the lower body as described. Then the patient had to walk, in self-chosen speed, across a walkway covering at least 15 m. The procedure was repeated 4 times, with short intervals between the repetitions if the patient felt fatigue or dizziness. During examination, patients wear their own shoes and could carry their walking aids.

At a second stage the patients were evaluated with dynamic and postural analysis, at the pressure sensitive walkway. With bare feet they were placed in the middle of the walkway and had to remain still for 10 s with their eyes open/closed. Finally, they made 6 continuous passages on the dynamic plate in self-chosen speed (Figs. 2 and 3).

All gait analysis and clinical examination procedures were carried out by the same researchers (DNV, DD) and under the same conditions.

2.4. Statistical analysis

For the statistical analysis was used IBM SPSS Statistics v.23 software. All of our data sets were tested for normality with Kolmogorov-Smirnov test. With the exception of Ashworth scale data all other variables were found not to follow the normal distribution. We used Wilcoxon's Matched-Pairs Signed-Ranks to test the statistical significance of
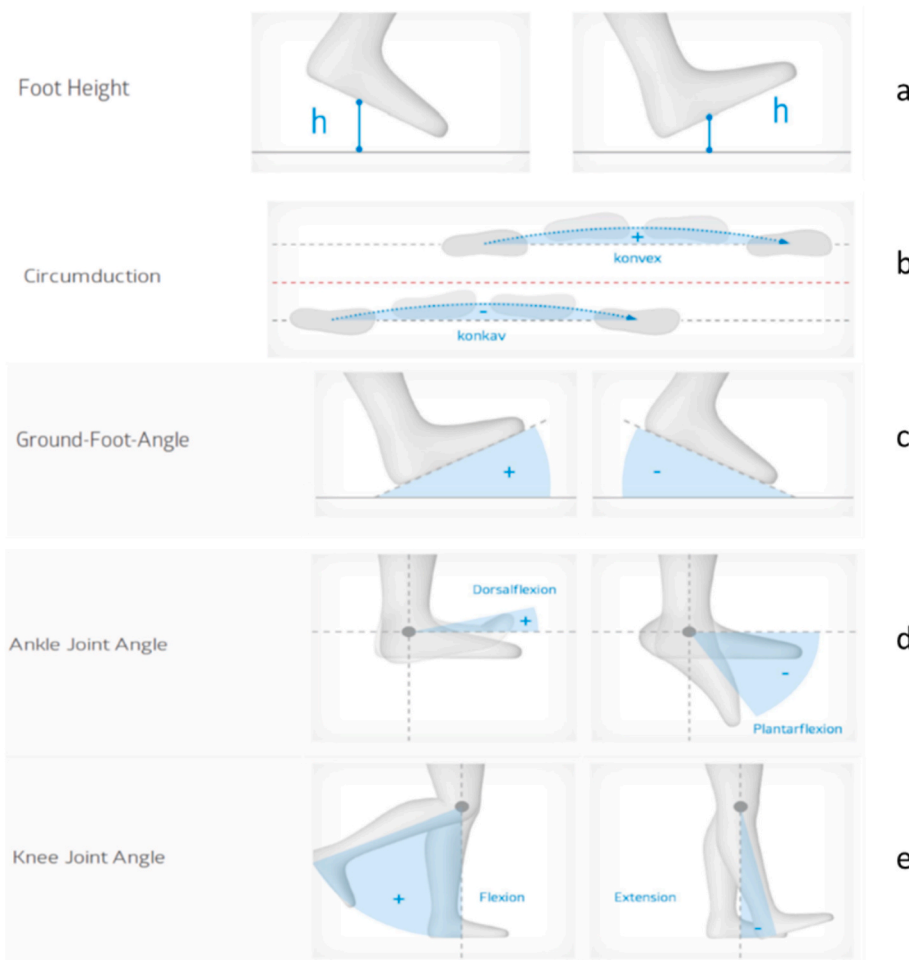
Fig. 1. Parameters recorded by the RehaGait© system. Foot Height (a) Indicates the maximum distance between the floor and the sole of the foot in the swing phase. Circumduction (b) the distance between an imaginary straight line of a foot and the point of maximum actual deflection of this foot during the swing phase is indicated. Heel strike angle (c) = positive angle between ground and foot at the moment of the foot contact (initial contact) Toe off angle (c) = negative angle between floor and foot at the moment of toe-off (toe-off) Ankle Joint Angle (d) Specifies the extent of movement in the upper ankle in the sagittal plane Knee Joint Angle (e) Specifies the extent of movement in the knee joint in the sagittal plane. Taken from RehaGait© Analyzer User Manual.

Table 1
Parameters from the Win-Track walkway.

Win-Track, Medicapteurs
Area (foot contact area)
A-P Deviation of COP
L-L Deviation of COP
Time stance
N– H Step Length
H–N Step Length
Angle of hemiplegic foot (angle between the line of the foot and the line of the walkway)
P max
P avg
A-P: anteroposterior, L-L: laterolateral, N: normal, H: hemiplegic, P: pressure, COP: center of pressure

the observed differences (paired *t*-test for Ashworth scale) with significance level $p < 0.05$. Post hoc power analysis was carried out using the Gpower 3.1.

3. Results

Thirteen chronic stroke patients with spastic hemiparesis who received BoNT-A injection for lower extremity spasticity did finally complete in the study (there was one drop out patient due to serious health complications which were not due to BoNT-A).

Table 2 shows the demographic and anthropometric characteristics of the 13 patients.

Most of our patients were overweight or obese, but this BMI value remained the same throughout the study.

No adverse event was observed for the one month follow-up after the BoNT-A injection.

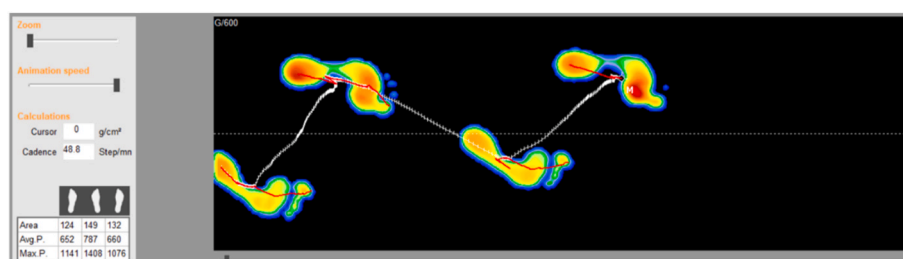Ashworth scale scores of the 13 patients, before and 1 month after

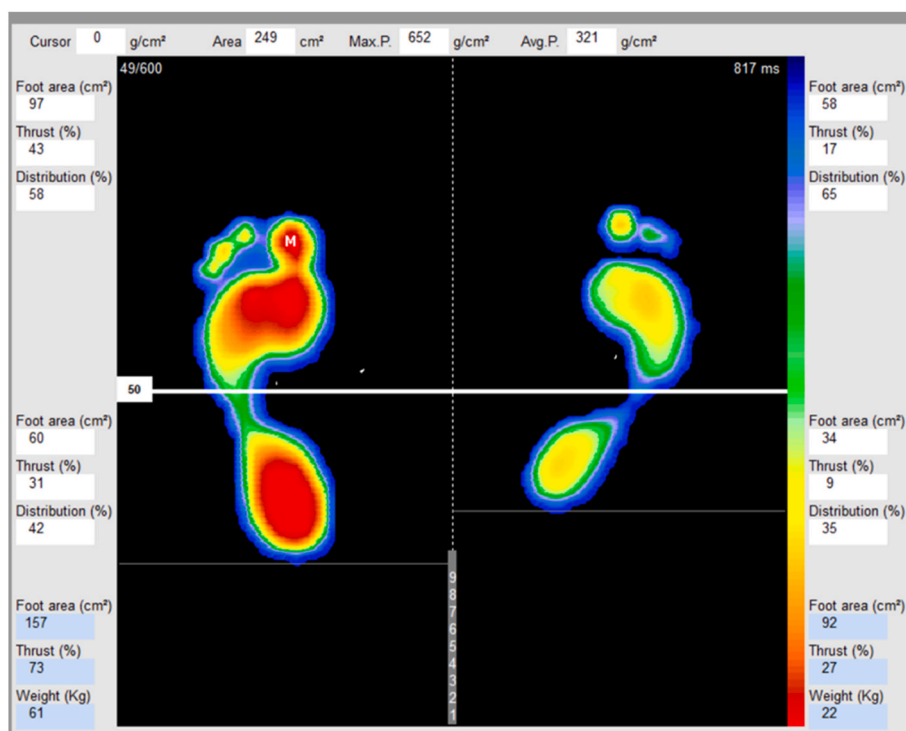**Fig. 2.** Dynamic analysis with Win-Track, Medicapteurs.

Fig. 3. Postural analysis with Win-Track, Medicapteurs.

Table 2
Anthropometric and demographic characteristics of the 13 patients.

Hemiplegia (side)	Age (Years)	PostStroke Months	Sex	Height (cm)	Weight (kg)	BMI
R	50	50	M	175	91	29.71
R	37	23	M	182	85	25.66
L	54	18	M	172	91	30.76
R	50	22	M	172	102	34.48
R	70	26	M	162	67	25.53
L	73	55	F	160	78	30.47
L	49	32	M	169	104	36.41
R	55	46	M	159	82	32.44
R	67	30	F	160	63	24.61
L	43	6	M	179	84	26.22
R	72	8	F	155	73	30.39
R	72	7	M	170	82	28.37
L	52	6	F	154	66	27.83

Table 3
Ashworth scale score before and 1 month after BoNT-A injection. In parenthesis the modified Ashworth scale was changed to 0–5 grades for statistical reasons.

Patient	Hemiplegia Side	Spasticity B	Spasticity A	Botox IU
1st	R	3 (4)	2 (3)	250
2nd	R	3 (4)	1+ (2)	250
3rd	L	4 (5)	3 (4)	250
4th	R	3 (4)	2 (3)	250
5th	R	4 (5)	2 (3)	250
6th	L	3 (4)	3 (4)	250
7th	L	3 (4)	2 (3)	250
8th	R	3 (4)	2 (3)	250
9th	R	3 (4)	1+ (2)	250
10th	L	3 (4)	2 (3)	250
11th	R	3 (4)	2 (3)	250
12th	R	3 (4)	2 (3)	250
13th	L	3 (4)	2 (3)	250

BoNT-A injections (Table 3), shows a statistically significant mean value difference (p < 0.001, Table 4). For statistical reasons the modified Ashworth scale was changed to 0–5 grades. Post hoc power analysis showed power exceeding 0.9 for the primary outcome regarding MAS measurements before and after BoNT-A.

Comparison of the parameters calculated from the IMU system (RehaGait), between normal and hemiplegic lower extremity before BoNT-A injection showed statistically significant differences for the parameters Max Ankle angle (p = 0.033), Max Knee angle (p = 0.006), Max foot height (p = 0.008) and Max circumduction (p = 0.013), (Table 5). Respectively after BoNT-A injection (Table 6) statistically significant differences were observed for the parameters Min Ankle angle (p = 0.006), Max Ankle angle (p = 0.039), Max Knee angle (p = 0.007), Max foot height (p = 0.004) and Max circumduction (p = 0.033). No statistical significant result occurred, comparing the parameters of the hemiplegic lower extremity before and after BoNT-A injection (Table 7).

Mean gait velocity was compared before and after BoNT-A injection, with no statistical significant difference (z = −0.353, p = 0.724).

Statistical analysis, before and after injection, of the gait parameters calculated from the pressure sensitive walkway are shown in Table 8. Significant statistical differences were observed comparing the foot contact area between hemiplegic and normal foot both before (p = 0.002) and after (p = 0.001) injection. Normal to hemiplegic step length before vs. after injection also shows statistical significant difference (p = 0.03).

Table 4
Paired *t*-test for the Ashworth scale score before and after BoNT-A. The modified Ashworth scale was changed to 0–5 grades for statistical reasons.

Paired *t*-test. Ashworth scale score before and after BoNT-A.		
	Spasticity Before	Spasticity After
Mean	4.1538	3
Standard Deviation	0.1410	0.3333
N	13	13
P	**<0.001**	

Table 5
Normal vs Hemiplegic (N/H) before BoNT-A injection, statistically significant parameters from IMU system.

IMU Normal vs Hemiplegic (N/H) before BoNT-A injection Wilcoxon's Matched-Pairs Signed-Ranks					
Variable	N/H	mean	SD (±)	Z	p-value (<0.05)
Max Ankle angle	N	30.445	31.107	−2.132	**0.033**
	H	10.370	12.281		
Max knee angle	N	30.739	9.166	−2.76	**0.006**
	H	19.524	6.329		
Max foot height	N	0.116	0.029	−2.656	**0.008**
	H	0.066	0.029		
Max circumduction	N	0.015	0.008	−2.494	**0.013**
	H	0.031	0.017		

Table 6
Normal vs Hemiplegic (N/H) after botulinum injection, statistically significant parameters from IMU system.

IMU Normal vs Hemiplegic (N/H) after BoNT-A injection Wilcoxon's Matched-Pairs Signed-Ranks					
Variable	N/H	mean	SD (±)	Z	p-value (<0.05)
Min Ankle angle	N	−20.441	17.365	−2.76	**0.006**
	H	−8.481	4.422		
Max Ankle angle	N	37.695	35.423	−2.062	**0.039**
	H	12.042	11.561		
Max Knee angle	N	31.963	10.834	−2.691	**0.007**
	H	17.954	7.486		
Max foot height	N	0.117	0.029	−2.848	**0.004**
	H	0.069	0.032		
Max circumduction	N	0.0155	0.011	−2.138	**0.033**
	H	0.0277	0.014		

Table 7
Hemiplegic Before vs After BoNT-A injection, parameters from IMU system.

IMU Hemiplegic Before vs After BoNT-A injection Wilcoxon's Matched-Pairs Signed-Ranks		
	Z	p-value
Min Ankle angle	−0.035	0.972
Max Ankle angle	−0.454	0.65
Min knee angle	−0.594	0.552
Max knee angle	−0.804	0.422
Heel Strike angle	−1.223	0.221
Toe Off angle	−0.175	0.861
Max foot height	−0.624	0.532
Max circumduction	−0.66	0.509

Table 8
Hemiplegic Before vs After BoNT-A injection, parameters from pressure walkway.

Win Track					
Hemiplegic Before vs After BoNT-A injection Wilcoxon's Matched-Pairs Signed-Ranks					
Variables	N	Mean	Std. Deviation	Z	p-value (<0,05)
Area H, B vs A	B/13	89,231	35,9795	−0.14	0.889
	A/13	91,923	34,3334		
A-P Deviation B vs A	B/12	1,9708	1,07438	−0.445	0.656
	A/12	1,7167	0,61987		
L-L Deviation B vs A	B/12	2,4458	1,30671	−0.8	0.424
	A/12	2,1955	0,98170		
Time Stance B vs A	B/13	1547,692	632,1248	−1.573	0.116
	A/13	1219,538	626,1216		
Angle Foot B vs A	B/13	14,777	14,4138	−0.628	0.53
	A/13	13,0269	12,82654		
P max B vs A	B/13	686,923	126,1804	−0.175	0.861
	A/13	5006,154	15564,0648		
P avg B vs A	B/13	373,692	80,5089	−0.196	0.844
	A/13	372,923	83,3476		
H–N_step_Length_B vs A	B/12	235,5583	119,27666	−1.1	0.271
	A/12	260,5792	168,66938		
N–H_step_Length_B vs A	B/13	261,8077	88,23900	−2.167	**0.03**
	A/13	320,0769	106,16297		

Figs. 4 and 5, shows the development of two random patients before and after BoNT-A injection . Figures are generated from RehaGait Analyzer software comparing the measured parameters between different tests of the same patient. The recorded value of its parameter is normalized to the reference median value and gets a score (0–1). On the horizontal axis are the different testing sessions for each patient. Score points between different sessions are linked to a regression line. Positive slope of this line indicates an improvement of the specific parameter. Negative slope of this line indicates deterioration.

4. Discussion

This is a prospective pre- and post-intervention study of 13 chronic stroke patients who received BoNT-A injection for lower extremity spasticity and were examined by gait analysis. Our data supports the hypothesis that BoNT-A injection improved spasticity. However, only the improvement in the normal to hemiplegic step length reached statistical significance. The rest of the spatiotemporal gait parameters were also ameliorated, but without the improvement reaching statistical significance.

In our study we used two systems of gait analysis, a 1.61 m dynamic plate of 12288 sensors and seven IMUs (Inertial Measurements Units), which are relatively economical and accurate gait systems that can be used without the need for the cost and installation of a 3D gait analysis. We examined both the stance and the swing phase of gait cycle of both normal and hemiplegic leg, while, it is the first known study that shows a statistically significant improvement in step length between the normal and hemiplegic foot.

Spasticity and strength are commonly assessed with the use of ordinal scales [Ashworth scale, Tardieu scale for spasticity and Medical Research Council Scale (MRC) for strength]. Although the inter- and intra-rater reliability of these scales is good enough, some limitations exist because spasticity and strength are measured subjectively by the examiner. The low sensitivity of these scales results in a majority of patients being assigned intermediate scores, which is a problem when data are used for longitudinal or cross sectional evaluations. Therefore, it is necessary to use other more specific tools in order to adjudicate the positive impact of BoNT-A on spasticity and strength(Ben-Shabat et al., 2013; Blackburn et al., 2002; Gregson et al., 1999, 2000; Hameau et al., 2014; Li et al., 2014; Reiter et al., 1998). Gait analysis is a relatively modern examination, where hemiparetic patients can be evaluated in various kinematic and kinetic parameters. In our study a combination of kinetic and kinematic gait parameters were measured before and one month after BoNT-A injection using IMUs and a dynamic plate. The measurements were registered when patients could walk comfortably and without special aid. This agrees with the literature studying gait parameters of stroke patients as they measure gait at a comfortable
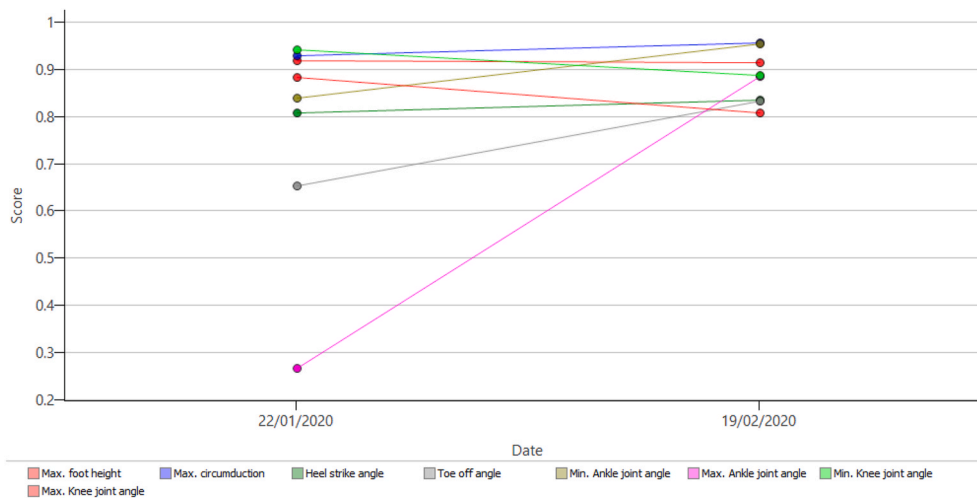
Fig. 4. Graphical development of patient A before and after BoNT-A injection according the measured parameters.
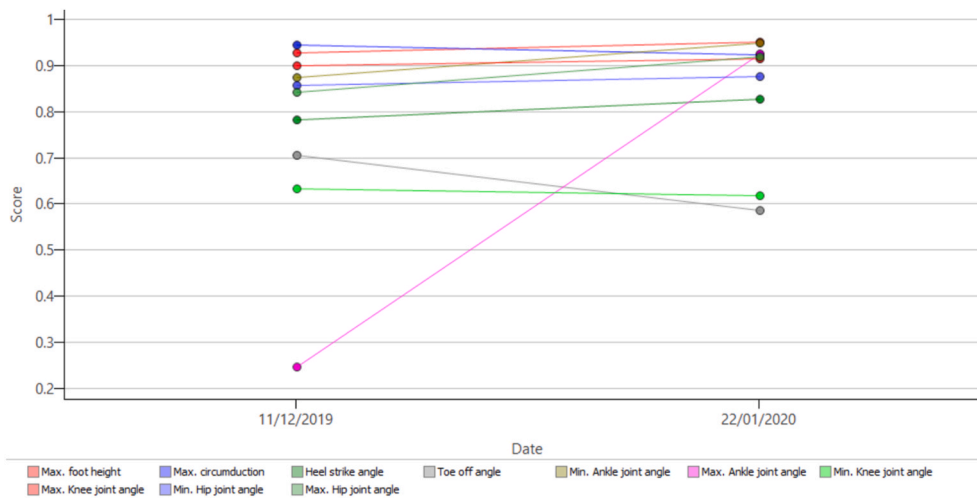

Fig. 5. Graphical development of patient B before and after BoNT-A injection according the measured parameters.

speed(Tilson et al., 2010).

Many studies of stroke patients following BoNT-A injections have repeatedly shown a reduction of spasticity on lower leg muscles, but with different results. This effect was attributed to an improvement in active and passive ankle dorsiflexion, eversion and toe clawing(Ben--Shabat et al., 2013; Cioni et al., 2006). In our study measuring spasticity with MAS the ankle and foot increased tone was significantly reduced in one month post injection.

In a prospective study (Gastaldi et al., 2015), 20 chronic post-stroke patients suffering from equinovarus foot deformity were injected with 200–400 U of BoNT-A. Gait analysis was performed before the injection and monthly for the next four months. It was concluded that some spatio-temporal parameters as gait speed and stride length had a statistically significant improvement. Similarly (Esquenazi et al., 2015), studied the effect of BoNT-A in 42 patients with hemiplegia due to CNS damage (stroke, brain injury, CP) on gait. Statistically significant results were found in gait speed and cadence, with no statistically significant effect found on stride. However, the results show that a marginally non statistically significant result (p = 0.06) appears in the table showing the step length in unaffected leg, but this is not underlined by the authors. In our study 13 post stroke patients were examined, where we had a statistically significant result only in normal to hemiplegic step length among the measured gait parameters. Another study (Pittock et al., 2003), which used the European botulinum toxin (Dysport), showed a statistically significant reduction in spasticity but no statistically significant results in gait parameters were found. Our results are quite similar with those of other researchers (Pimentel et al., 2014). One study (Dunne et al., 2012) used simpler technology (i.e. video recordings) showed statistically significant results in gait. Similar to a study (Fujita et al., 2019) where the study group was patients with BoNT-A infusion monotherapy and patients with BoNT-A and physiotherapy and the same with other studies (Kaji et al., 2010); (Carda et al., 2011) (Rous-seaux et al., 2005). Another study (Tao et al., 2015) presents the examination of 23 patients immediately after stroke (4–6 weeks), where the treatment group showed statistically significant results in speed, cadence and step length as in MAS. In our study, patients received the injections at least 6 months post-stroke. Furthermore, we considered that the addition of a placebo arm in our study would have been unethical. We applied the same model like in other studies (Oh et al., 2018) (Wein et al., 2018) who converted the MAS units into absolute numbers, so that statistically the comparison can be made (MAS 1+ was recorded 2, 2 was recorded 3 etc). The same model was applied in our study and other studies as well. Regarding the number of BoNT-A units (250 U) injected into the muscles below the knee in the hemiplegic leg, our study is in accordance with most studies (Mancini et al., 2005).

The characteristics of gait asymmetry in stroke patients are the decrement in single leg support of the hemiparetic side, while in the unaffected side there is prolongation of single leg support. Finally the

double support time is also increased(Olney and Richards, 1996). Furthermore, ankle dorsiflexion is decreased during stance and swing phases, while knee hyperextension in the stance phase is observed in almost all patients (although excessive knee flexion is seen in some patients). In our study knee and ankle range of motion were increased but did not reach statistically significance. This comes in agreement with other studies. In most patients we observed an improvement in some parameters, where each patient demonstrated fluctuations, so that overall no statistically significant results were obtained. Only the normal to hemiplegic step length reached statistical significant increase after BoNT-A injection ($p < 0.03$). This finding indicates that the swing phase of hemiplegic leg gained in distance due to better knee extension and ankle dorsiflexion. We preferred to examine separately the step length from the hemiplegic to normal side and the step from normal side to hemiplegic instead of examining only the stride length or only the affected side step length. This way the performance of the affected leg was depicted both in the stance and swing phase of the gait cycle.

Studies using kinetic data and dynamic plate have shown increased lateral plantar support and reduced foot area of hemiplegic side. Gastrocnemius spasticity results to abnormal force transfer from hind-foot to forefoot with limited rollover and reduced or absent push-off in terminal stance(Mayer, 2002). Our study demonstrated improved hemiplegic foot area following BoNT-A injections.

Three systematic reviews and meta-analysis and one systematic review with no meta-analysis were found in the literature regarding the effect of botulinum toxin on gait of post-stroke patients. Gupta et al. reported that in their systematic review they could not proceed with meta-analysis, because of the different measurements for different gait parameters, the small sample size with a large confidence interval and the lack of power calculations in some studies(Gupta et al., 2018). The results of Foleys' meta-analysis found that the BTA treatment was associated with a rather small yet significant treatment effect on the 10 MWT(Foley et al., 2010), while Wu et al. reported that although gait speed increased, there was no statistically significant difference between the BTA- and placebo groups(Wu et al., 2016). Baker and Pereira concluded that BTA may improve active outcomes in the upper limb but further evidence would be needed, on the other hand no conclusion was made for the lower limb(Baker and Pereira, 2016). In our study we found statistically significant differences only in spasticity and in the normal to hemiplegic step length (swing phase of hemiplegic leg of the gait cycle). So it seems that although the spasticity decreases statistically significantly, we do not observe similar results in gait parameters.

Several authors have recently reported that in post-stroke patients, due to spasticity in the lower extremity, we observe three deformities of the foot: equinus, varus and clawing of the toes(Rousseaux et al., 2005). However, the most common muscles injected were medial and lateral gastrocnemius, soleus and tibialis posterior. Injection into other muscle groups, especially those that cause clawing of the toes, such as Flexor Digitorium Longus, Extrinsic Toe Flexors, and also Extensor Hallucis Longus are adding for spasticity of foot (Esquenazi et al., 2015). In our study we chose to inject the above common muscles (gastrocnemius, soleus and posterior tibialis), without involving the toe muscles. Maybe, future studies for spastic foot have to add the muscles that cause toe deformities, to the BoNT-A injections.

Currently only few studies have examined the correlation between spasticity and function (i.e. balance or fall risk). Ikai et al.(2006) reported that individual's balance influences include the ranges of motion of upper and lower limbs and the plantar contact area. Hara et al. showed that the Functional Reach Test (FRT) (which reflects static balance and evaluates the patient fall risk) of patients who had BoNT-A injections improved statistically significantly difference ($p < 0.05$) at both discharge, and 3-month follow-up when compared with admission (Hara et al., 2017). A systematic review (Phadke et al., 2014) concluded that patients with lower spasticity had a lower risk of falls and balance impairments. However, only one study in this review measured the correlation between spasticity and balance impairments and found a non

significant correlation(Pang and Eng, 2008). Although there is a trend regarding the positive outcome of BoNT-A in balance, future studies are needed in order to draw a firm conclusion regarding the influence of BoNT-A to function.

The major limitations of our study are the short period of follow up (only one month) and the small sample of thirteen patients. Yet many of the previous mentioned studies have shown that in one month after BoNT-A, the beneficial effect is shown in the majority of the cases. Concerning the small sample of patients the power analysis for the primary outcome showed that it is above 0.9 regarding the MAS measurements before and after BoNT-A and 0.68 for the normal to hemiplegic step length. Still, low power, equal to 0.18, due to sample size restrictions was achieved to detect differences in the hemiplegic to normal step length. In addition, due to coronavirus pandemic, other candidate for inclusion patients were not able to participate. On the other hand the separate measurement of step length between the two sides (hemiplegic and normal) and the inclusion of patients in the phase of chronic post stroke (older than 6 months) are the strongest points of the design of our study.

In conclusion BoNT-A injections to post stroke patients benefited both gait parameters and spasticity. Further studies with longer follow up period and targeted patient subgroups should be done in order to reach definite conclusions regarding the proper methodology of BoNT-A use against spasticity of the stroke patients.

Ethical Statement

Hereby, I Dimitrios N. Varvarousis consciously assure that for the manuscript "Do gait parameters improve after botulinum toxin injections in post stroke patients? A prospective study" the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.
8) All procedures performed in studies involving human or animal participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

I agree with the above statements and declare that this submission follows the policies as outlined in the Guide for Authors and in the Ethical Statement.

Date: 9/2/2021.

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Credit author statement

Dimitrios N. Varvarousis: Conceptualization; Formal analysis; Investigation; Project administration; Methodology; Visualization; Writing – original draft. **Dimitrios G. Dimopoulos:** Formal analysis; Software; Project administration; Writing – review & editing. **George I.**

Vasileiadis: Conceptualization; Resources; Investigation; Writing – review. **Ioannis Manolis:** Resources; Visualization; Writing – original draft; **Avraam Ploumis:** Conceptualization; Formal analysis, Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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