



Beyond speed: Gait changes after botulinum toxin injections in chronic stroke survivors (a systematic review)

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ABSTRACT

Background: The mechanisms by which spasticity reductions after botulinum toxin A (BoNT) affect gait in stroke are not well understood. We systematically reviewed the effects of BoNT on spatiotemporal, kinematic, kinetic and electromyographic (EMG) measures during gait.

Question: What are the effects of botulinum toxin on gait mechanics in stroke patients?

Methods: Systematic search using PubMed and Web of Science. We considered all studies that reported laboratory-based and instrumented gait measures as primary or secondary outcomes to determine the effects of BoNT on walking performance in stroke populations only. Selected studies were classified and analysed based on the injection sites.

Results: A total of 240 articles were identified of which 22 were selected for analysis. Overall, 91% of the studies reported spatiotemporal, 64% kinematics, 23% kinetics, 32% EMG and 23% other gait measures. All but one study found significant effects of BoNT on gait measures using instrumented assessments even when clinical measures (i.e. speed) did not significantly improve. However, the majority of the studies had a high risk of bias. Overall, BoNT improved: a) dorsiflexion during stance, propulsive forces and timing and activity of more proximal musculature with injections in the plantarflexors; b) hip, knee and ankle angles and velocities, co-ordination and energetic cost with injections in the rectus femoris; c) segmental coordination and energetic cost when several lower limb muscles were injected; and, d) elbow and trunk angles when upper limb muscles were injected.

Conclusion: Instrumented and laboratory measures of gait improve after BoNT injections in different muscle groups even in the absence of clinical changes.

1. Introduction

Spasticity is a disabling consequence after a stroke, affecting 38% of the survivors within the first year [1]. Gait impairments are common

after stroke [2] and can lead to an increased number of falls [3] reduced independence, social engagement, and quality of life [4]. One of the treatments that has shown to be efficacious and safe in reducing spasticity is intramuscular injection of Botulinum Toxin (BoNT),

Abbreviations: PT, Physiotherapy; Str, stretching; AFO, ankle-foot orthosis; FU, follow-ups; U, units; stEMG, static EMG; 10mWT, 10-meters walking test; 6mWT, 6-minutes walking test; 2mWT, 2-minutes walking test; FRT, functional reach test; MAP, motor action potential; MBI, Modified Barthel Index; BBS, Berg Balance Scale; RMI, Rivermead Mobility Index; FM, Fugl-Meyer; ES, electrostimulation; SIAS, Stroke Impairment Assessment; ABILOCO, Locomotion Ability; FAC, Functional Ambulation Categories; APS, arm position sense; EC, energy consumption; RFL, rectus femoris length; MG and LG, Medial and lateral gastrocnemius; SO, soleus; TA, tibialis anterior; TP, tibialis posterior; FDL, flexor digitorum longus; FHL, flexor hallucis longus; RF, rectus femoris; T, semitendinosus; BI, brachialis; BB, biceps; BR, brachioradialis; PM, pectoralis major; D, deltoid; ECR, extensor carpi radialis; PL, palmaris longus; FCU, flexor carpi ulnaris; FCR, radialis; FDP, flexors digitorum profundus; FDS, superficialis; FPL, flexors pollicis longus; FPB, brevis; HF, unspecified hand flexors; FF, finger-flexors; SPT, Spatiotemporal; C, Cadence; SL, Step length; StW, Step width; STR, Stride length; ST, Stance; LR, Load reception; SW, Swing; PSW, Pre-swing; SS, Single support; DS, Double support; ROM, Range of motion; DF, Dorsiflexion; KF, Knee flexion; KE, Knee extension; COI, Coactivation Index; COD, Coactivation duration; CRP, continuous relative phase; T, Torque; Tlat, trunk lateral flexion; HF, Hip flexion; KAP, Knee absorption power; KAS, Knee angular speed; AAS, Ankle angular speed; HAS, Hip angular speed; TO, toe-off; EF, elbow flexion; IMNF, instantaneous mean frequency; †, equivalent doses

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nonetheless, this effect does not always translate into improved functional outcomes such as walking [5].

BoNT effects on walking are usually assessed using gait speed, as in the 10 m walking test (10mWT). However, improved speeds can be achieved by (mal)adaptive motor strategies to propel the body forward [6,7], hence masking the mechanisms underlying the improvement. This is of great relevance when speed is used as an outcome measure in interventions aiming at restoring normal and efficient gait patterns through spasticity reduction such as BoNT. For example reviews exploring the effects of BoNT on gait speed have shown small [8], inconclusive [9] or no effects [10], possibly because speed may not be a sufficiently responsive measure [11].

By using instrumented gait analysis it is possible to obtain a better insight into the mechanisms by which, for example, a patient can walk at the same speed but more efficiently after BoNT [12]. Furthermore, due to their objectivity and reproducibility these measures can become unbiased outcome measures related to the to “body function and structures” of the International Classification of Function (ICF) [13,14]. Gait analysis measures can also become a powerful tool in determining not only the effects of BoNT but also the added benefits of BoNT-adjuvant therapies [14]. Overall, instrumented gait measures can assist in determining which muscles should be injected (and perhaps dosages), planning rehabilitation interventions and also improving clinicians’ confidence in their recommendations [12,15].

The effects of BoNT on walking after stroke will depend on the muscles compromised by spasticity and the muscles injected. Therefore, the aim of this review was to understand gait changes after BoNT injections in chronic stroke survivors, and included studies based on site of injection and indications for BoNT injections (Fig. 1).

2. Methods

The search criteria were based on those of Gupta et al. (2018) [9],

with a fifth set of terms included to constrain the results only to those referring to the effects of BoNT on “gait” OR “walking”. PubMed and Web of Science were used for the search using the terms described in Table 1. The search was last updated on the 23rd July 2018.

2.1. Inclusion and exclusion criteria

The inclusion criteria were for articles that: a) explored the effects of BoNT for spasticity in the adult stroke population; b) used objective measures of gait as primary or secondary outcome measure regardless of the BoNT site(s) of injection and dosage; c) used BoNT in conjunction with other interventions or as a single intervention.

This review excluded articles that: a) explored the use of BoNT in populations other than stroke; b) ar only reported gait speed as the outcome measure; c) case studies; d) systematic reviews, editorials, letters and expert opinions; e) did not report objective measures of gait; f) narrative articles about techniques; and g) BoNT was not administered.

2.2. Data extraction

Two reviewers (ECL and MPG) independently assessed the retrieved articles and classified them into four groups according to the injection site: a) ankle and foot muscles; b) knee extensor/flexor muscles; c) various muscles in the lower limbs; and d) various muscles in the upper limb. Articles were then classified according to the outcome measures used: a)spatiotemporal; b)electromyography; c)kinematics and/or kinetics; and d) full gait analysis (a,b and c).

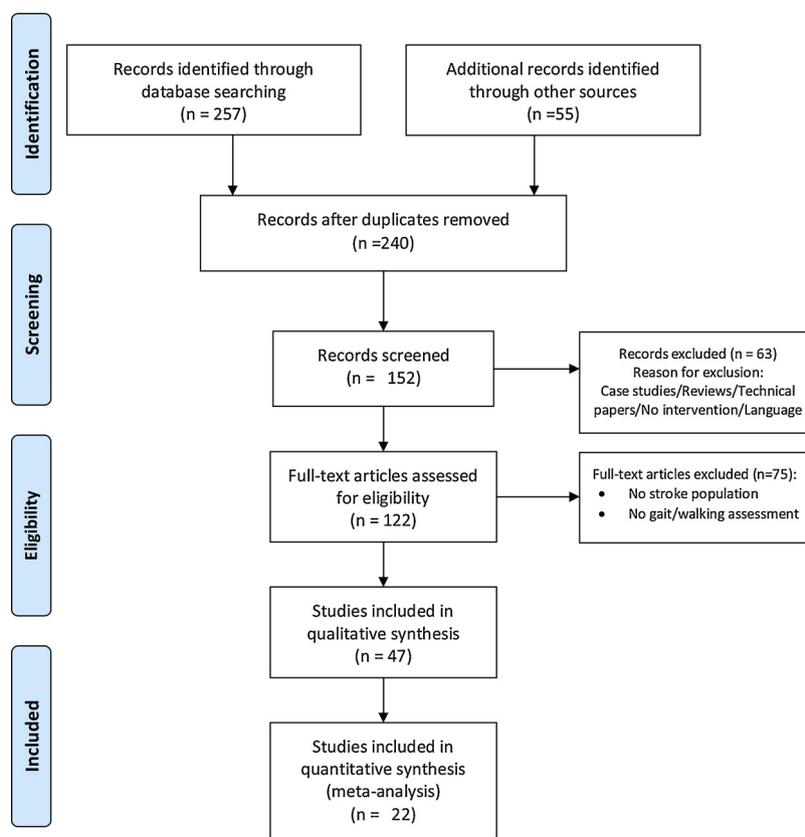


Fig. 1. PRISMA Flow Diagram: Beyond Speed: Gait Changes After Botulinum Toxin Injections in Chronic Stroke Survivors (A Systematic Review).

Table 1
Clinical, speed, gait and follow up assessments times for each of the studies included. (*) indicates the measures and timing of the significant pre-post BoNT differences.

Authors (year) + B1:M32B1:N32	Groups	Clinical Assessments	PT	Gait Speed* (m/s)		p	Gait Assessments		Significant changes	Injected Muscles and doses (U)		Toxin
				PRE	POST		types	FU (weeks)		Muscles (Units)	Total or Range	
Fujita et al. (2018) ⁴²	BoNT	FM	NO	0.57[0.20]	0.59[0.18]		SPT/EMG	2	↓SO-LR; ↓SO-PSW	MG/LG/SO/TP/ FHL/FDL	50-300	Botox
Tao et al. (2015) ³⁹	BoNT + PT	FM	YES	0.46[0.20]	0.54[0.16]	*	SPT*/ EMG*	2*		MG/LG/SO/TP/ FHL/FDL	per muscle	
	BoNT low dose	6mWT*/FM*/ MBI*/ stEMG*	YES	NA	NA	*	SPT*	4-8*	↑SL; †C; †stEMG	MG(50)/LG(50)/SO (50)/ TP(50)		Botox
Gastaldi et al. (2015) ²³	Placebo	6mWT*/FM/ MBI/ stEMG	YES	NA	NA		SPT	4-8*		Placebo		
		BBS/RMI	YES + Sic	0.36[0.59]	0.39[0.68]	*	SPT*	4-8-12*-16*	↑STr; ↓STr time; †C; ↓StW; †SS; ↓ DS	MG(77)/LG(51)/SO (77)/TP(40)/ TA(47)/FHL(55)/ FDL(55)		Xeomin
Pradon et al. (2011) ³¹	AFO inc. @3wk		AFO @3wk	0.55[0.13]	0.72[0.2]		SPT*/ KIM*/ KIN*/EMG	3*-6*	↑SL; †STr; †DF-ST; †KF-SW; † PPF-ST	MG(75)/LG(75)/SO (50)		Botox
Karadag-Saygi et al. (2010) ³⁷	BoNT + KNT	10mWT*	YES	0.65[18-.99]	0.80[18-1.2]	*	SPT*	2-4*-12*-24	↑SL	MG/LG	75-100	Botox
	BoNT + Sham	10mWT*	YES	0.59[13-1]	0.75[17-1.45]	*	SPT*	2-4*-12*-24		MG/LG	per muscle	
Novak et al. (2009) ³⁰		TAR	NA	0.50[0.24]	0.54[0.22]		SPT*/KIM*/ KIN	2*-10*	↑PF; †A-ROM; † unaffected HE	MG(58)/LG(50)/SO (100)/ TP(94)/FDL (92)		Botox
Rosseaux et al. (2008) ³³		10mWT*/FAC*/ RMI	YES	0.49	0.55		SPT	2-8-20		MLG(85)/SO(133)/ TP(50)/ TA(58)/ FDL(43)		Botox
Bartich et al. (2008) ⁴⁰	BoNT + ES + Str	MAP*	YES	NA	NA		KIM*	2*-3*-13*	↑DF	MG/LG	150-250 (50- 83) per muscle	Dysport
	BoNT + taping	MAP*	YES	NA	NA		KIM*	2*-3*-13*		MG/LG		
Pitcock et al. (2003) ³⁸	BoNT + Str	MAP*	YES	NA	NA		KIM*	2*-3*-13*		MG/LG		
	Placebo	2mWT*/RMI	38%	NA	NA	*	SPT*	4-8-13	†C	MG/LG/SO	NA	Dysport
Rosseaux et al. (2005) ³⁴	500	2mWT*/RMI	38%	NA	NA	*	SPT*	4-8-13	†C	MG/LG/SO	170†	
	1000	2mWT*/RMI	38%	NA	NA	*	SPT*	4-8-13	†C	MG/LG/SO	333†	
	1500	2mWT*/RMI	38%	NA	NA	*	SPT*	4-8-13	†C	MG/LG/SO	500†	
		10mWT*/FAC*/ RMI*	YES	0.48[0.29]	0.54[0.31]	*	SPT*	2*-8-20*	↑SL	MLG(79)/SQ(124)/ TP(48)/ TA(54)/ FHL(43)		Botox
Reiter et al. (1998) ⁴¹	BoNT	10mWT*	NO	0.24[.05]	0.28[.07]	*	SPT*	4*-12*	↑SL	MG/LG/SO/TP/ FHL/FDL	257[57] total	Botox
Hesse et al. (1996) ²⁵	BoNT + taping	10mWT*	taping	0.26[.10]	0.32[.15]	*	SPT*	4*-12*	↑SL	TP	100	
		10mWT*/RMI	NA	0.29[.19]	0.35[.21]	*	SPT*/KIM/ EMG*	4*	↑STr; ↓SO	MG/LG/SO	400 total	Botox
Roche et al. (2015) ³²			NA	0.58[.25]	0.68[.28]	*	SPT*/ KIM*/KIN	3*	↑HF; †KF; †HAS-TO; †KAS; †AAS	RF	150-200	Botox
Boudarham et al. (2013) ²¹			NA	0.61[0.23]	0.70[0.27]	*	SPT*/ KIM*/ EMG*	3*	↑SL; †C; †STr; †KF; †KAS; †RF-ST; † RF-SW; †RF-PSW; †RF(%SW); † RF (%GC); †RF/BF COD (%)	RF	164[50]	Botox
Lampire et al. (2013) ²⁹			NA	0.57[0.24]	0.70[0.28]	24	SPT*/ KIM*/ EMG/RFL*	3*	SW); †JMNf-PSW ↑KF; †KAS; † RF length; †RF length vel; †RF mean length vel	RF	200	Botox
Tok et al. (2012) ⁴⁵	BoNT	6mWT*/ 10mWT*	NO	0.32	0.43	*	SPT*/KIM*/ EC*	6*	↑KF; †K-ROM; †EC	RF	100-125	Botox
	Placebo	6mWT*/10mWT		0.35	0.35		SPT*/KIM/ EC	6				

(continued on next page)

Table 1 (continued)

Authors (year) + B1:M32B1:N32	Groups	Clinical Assessments	PT	Gait Speed* (m/s)		p	Gait Assessments		Significant changes	Injected Muscles and doses (U)		Toxin
				PRE	POST		types	FU (weeks)		Muscles (Units)	Total or Range	
Hutin et al. (2010/2011) ^{27,28}			NA	0.61[0.21]	0.74[0.26]	*	SPT*/KIM*/CRP*	3*	↑STr; ↑KF; ↑HF; ↑CRPm-SW; ↑CRP-GC/LS/SW; ↑CRPms-GC/MS/SW; ↑CRPcorr-GC/ES/MS	RF	200	NA
Stoquart et al. (2008) ³⁵		SIAS	YES				SPT*/KIM*/KIN*/EMG*/EC	6*	↑K-ROM; ↑KAS; ↓KAP-TO; ↓VL(%GC); ↓BF(%GC);	RF	200	Botox
Caty et al. and Bleyenheuft et al. (2008/2009) ^{20,22}	KF < 10deg KF > 10deg	10mWT/SIAS*/FAC/ABILOCO	YES YES	0.51[.23]	0.54[.24]		KIM*/EC*	6*	↑K-ROM; ↓Wext; ↓Wtot; ↓EC; ↑KSC both legs	RF/MG/LG/SO/ST/ FDL	300-500	Botox
Tanikawa et al. (2018) ³⁶		10mWT*	Stc	0.61[0.31]	0.70[0.31]	*	SPT*/KIM*	4*-10*	↑EF-max; ↓EF-min	RF/MG/LG/SO/ST/ FDL	300-500	Botox
Hefter et al. (2017) ²⁴	All	APS*	YES	0.34[0.25]	0.39[0.24]	*	SPT*/KIM*	3*	↓Tlat, ↓STr time; SL-unaaffected	BR/FCR/FCU/FDS/ FPL/FDP/PL	240 total	Botox
Hirsch et al. (2005) ²⁶	Free-walkers Slow (< 1.7 s/STr) Fast (> 1.7 s/STr)	APS*	YES YES YES	0.39[0.29]	0.44[0.27]	*	SPT*/KIM*	3*	↓Str-time; ↑A + K-ROM	BI/BB/BR/HF/FF	500-1000 total	Dysport
			YES	NA	NA	*	SPT*/KIM*	3*		BB/BR/FCR/FCU/ FDS/FPL/ FDP/PL/ PM/ECR/D/FPB	689[223] total	NA

3. Results

3.1. Selected studies

No studies were excluded based on the design, therefore, pre-post studies, non-randomized trials and randomized controlled trials (RCTs) were considered if measures other than speed were included. We retrieved 257 studies and identified 55 more potential studies through reference checking (Fig1. After removing duplicates, 63 studies were excluded because they were case studies or reviews, or studies exploring BoNT injection techniques or did not use BoNT. The remaining 122 studies were reviewed according to whether BoNT was applied to stroke patients and included objective gait measures. Finally, 22 studies were included, in which primary or secondary outcome measures included electromyography, forces, spatiotemporal, kinematics and kinetics measures (Table 1).

3.2. Description of the studies

3.2.1. Studies design

Three randomized double-blind [16–18] and two single-blind [19,20] trials were included. The quality of these studies, based on the PEDro score, were between 6–8 (“good”) [16,18–20] and 9 (“excellent”) [17]. One non-randomized controlled trial [21] and the other studies (n = 15) included in this review, which used pre-post or open-label designs [22–38] had a high risk of bias [39] (Table 2).

3.2.2. Demographics

Samples ranged from 8 to 234 patients (median:18) with a median age range between 15–83 years (5F:13M). The median left:right hemiparesis ratio was 8.5:6 and the median ischemic:hemorrhagic stroke type ratio was 12:11.5 (Table 2).

3.2.3. Clinical assessments

Most studies assessed spasticity using the Ashworth (or Modified) Scale. Other clinical measures included the Tardieu scale, Ely test, clonus and joint range of motion (ROM). Gait and mobility were assessed using the 10mWT, 6-minute walking test (6mWT), Fugl-Meyer (FM) and timed up and go (TUG). For all studies reporting speed, the median pre- and post-BoNT injections were 0.51 m/s (range 0.24–0.71 m/s) and 0.55 m/s (range 0.28–0.80 m/s), respectively, which represents a median change of 14% (range 4.1%–40%) (Table 1).

3.2.4. Adjuvant interventions

In 12 of the included studies patients received some form of physiotherapy [16–19,21,22,24–26,28,35–37] and in 4 studies they also received stretching [19,25,38], taping [19,20] or an ankle-foot orthosis (AFO) [33] (Table 1).

3.2.5. Toxin and doses

Most studies utilized Botox (OnabotulinumtoxinA, n = 16), 3 studies used Dysport (AbobotulinumtoxinA), 1 study used Xeomin (IncobotulinumtoxinA), and 2 did not identify the type or brand of the toxin. Detailed doses used in each study are presented in Table 1.

3.3. Effects of BoNT on gait

3.3.1. Lower leg muscles

Twelve studies investigated BoNT effects on gait after injecting: triceps surae (medial gastrocnemius, MG; lateral gastrocnemius, LG; and soleus, SO) [16–21,25,27,32,33,35,36], tibialis anterior (TA) [25,35,36], tibialis posterior (TP) [18,20,21,25,32,35,36], flexor digitorum longus (FDL) [20,21,25,32] and flexor hallucis longus (FHL) [20,21,25,36] (Table 1). These injections were mainly aimed at reducing equinovarus and doses varied widely amongst studies ranging from 100U [20] to 500U [17].

Table 2
 Description and demographics of the selected studies. BoNT: botulinum toxin; PT: Physiotherapy; Str: stretching; AFO: ankle-foot orthosis; KNT: kinesiotaping; EMG: electromyography; DLA: daily life activities; ES: electrostimulation; RF: rectus femoris; TNN: tibial nerve neurotomy; KF: knee flexion; f/m: female/male; L/R: left/right; I/H: ischaemic/haemorrhagic; TPS: time post-stroke; ROM: range of motion; Str: stride; NA: not available. [†] equivalent doses.

Authors (year)	Study type	Study aim	Groups	n	f/m	L/R	I/H	Age (mean[sd])	Age (range)	TPS months (mean [sd])	TPS (range)
Lower Leg muscles											
Fujita et al. (2018) ⁴²	Non-randomized controlled trial	Determine effects of PT after BoNT on EMG	BoNT + PT	35	4/13	6/11	6/11	57.2[10.7]	NA	75.2[51.2]	NA
Tao et al. (2015) ³⁹	Randomized double-blind placebo-controlled study	Determine if low-dose BoNT improve spasticity/gait/DLA	BoNT low dose Placebo	23	4/7	NA	6/5	58.6[10.5] 55[12] 58[14]	NA	39.8[37.7] 0.80[0.40] 0.76[0.56]	NA
Gastaldi et al. (2015) ²³	Prospective open-label study	Assess BoNT functional effects on gait		20	3/17	7/13	NA	56.1[11.36]	26-70	> 6	NA
Pradon et al. (2011) ³¹	Pre-post study	Determine effects of BoNT (and AFO)	AFO inc. @3wk	8	2/6	3/5	NA	45	33-58	74.99[35.65]	37-122
Karadag-Saygi et al. (2010) ³⁷	Randomized double-blind study	Evakuate the effects of kinesiotaping as adjunct for BoNT	BoNT + KNT	17	7/3	6/3	NA	63.8[9]	NA	35.2[29]	NA
Novak et al. (2009) ³⁰	Open-label case series	Characterize effects of BoNT on gait mechanics	BoNT + Sham	9	5/5	6/2	NA	57.3[12]	NA	39.4[30]	NA
Rosseau et al. (2008) ³³	Open-label study	Compare BoNT vs TNN for LL spasticity		45	14/31	14/20	15/19	58.1[23.84]	20-83	51.7[64.7]	4-169
Bartich et al. (2008) ⁴⁰	Single-blind randomized trial	Explore BoNT + non-pharmacological treatments for spastic foot	BoNT + ES + Str BoNT + taping BoNT + Str	23	3/5	3/5	NA	50.38[11.45]	NA	44.87[7-293]	NA
Pittock et al. (2003) ³⁸	Double-blind randomized placebo-controlled study	Assess BoNT in post-stroke calf spasticity	Placebo 170† 333† 500†	234	18/37	30/25	34/18/x	55.9[11.4] 56.4[12.8] 54.8[13.6] 54.7[10.2] 51.7[11]	NA	43.2[60] 33.6[37.2] 37.2[40.8] 46.8[45.6] 43.6[52.6]	NA 3.6-350.4 2.4-213.6 2.4-214.8 2.4-180 6-246
Rosseau et al. (2005) ³⁴	Open-label study	Predict functional results after BoNT		47	23/24	22/25	24/23	51.7[11]	28-74		
Reiter et al. (1998) ⁴¹	Single-blind RCT	Compare BoNT vs selective TP-BoNT and taping	BoNT + taping	18	7/11	10/8	NA	54.7[13.5] 57.2[15.7]	28-70	23.6[11.4] 29.3[20.7]	10-72
Hesse et al. (1996) ²⁵	Pre-post study	Investigate effects of BoNT on PF activity		12	2/10	9/3	12/0	56	25-76	22.3	11.4-48
Roche et al. (2015) ³²	Prospective observational study	Determine if changes in fast gait predict BoNT effects		22	5/17	10/12	12/10	53.73[12.11]	34-75	140.2[95.8]	24-527.9
UpperLeg Muscles											
Boudarham et al. (2013) ²¹	Pre-post study	Determine effects of RF-BoNT on EMG and gait mechanics		14	3/11	12/2	NA	54[12]	40-75	86[38]	24-156
Lampire et al. (2013) ²⁹	Pre-post study	Quantify effects of BoNT on RF length and velocity during gait		10	2/8	6/4	NA	39.6[9.5]	33-52	91.8[122.2]	6-432
Tok et al. (2012) ⁴⁵	Non-randomized placebo-controlled trial	Compare RF-BoNT with placebo on gait	BoNT Placebo	15	7/8	6/9	12/3	53.86[14.74] 59.00[8.11]	NA	14.59[7.15] 13.41[7.02]	NA
Hutin et al. (2010/2011) ^{27,28}	Pre-post study	Effects of RF-BoNT in intersegmental coordination / mechanisms		14	3/11	8/6	6/7	41[14]	26-66	71.9[108]	6-432
Stoquart et al. (2008) ³⁵	Pre-post study	Effects of RF-BoNT on gait swing knee-flexion		19	NA	NA	NA	53[15]	23-78	52[56]	7-241
Caty et al. and Bleyenheuft et al. (2008/2009) ^{20,22}	Pre-post study	Effects of BoNT on activity, QoL, participation / kinematic segmental coordination	KF < 10deg KF > 10deg	20	5/15	NA	NA	52.3[16.1]	23-81	45.9[32.9]	7-118
Tanikawa et al. (2018) ³⁶	Pre-post study	Evaluate effects of BoNT on gait flexed-elbow		20	5/15	10/10	7/13	51	15-76	65.99	5.26-179.51
Heffer et al. (2017) ²⁴	Pre-post study	Determine effects on BoNT on upper trunk posture during gait	All	11	5/6	5/6	NA	69.91[19.18]	47-78	114.64[73.14]	68-304
Hirsch et al. (2005) ²⁶	Open-label pilot study	Determine association between UL-BoNT and knee/ankle ROM	Free-walkers Slow (< 1.7 s/Str) Fast (> 1.7 s/Str)	13	6/7	7/6	NA	58.61[9.46]	41-72	53.08[68.37]	1-244

Following ankle plantarflexor injections, significant improvements in speed [16–18,20,21,25,27,33,36], cadence [18,21,25], step length [16,18,33,35], stride length [21,25,27], step width [25], asymmetry index [21], double support [21] and single support times [25] were found. Only four studies reported kinematic and found increased ankle dorsiflexion during stance [19,32,33], plantarflexion before toe-off and ROM [32]. One study found no significant kinematic changes pre/post BoNT [27]. Only two studies reported kinetics and focused on the plantarflexion moment [33] and ankle and hip power and positive work [32]. Whereas Pradon et al. found a significant increase in the peak plantarflexor moment [33], Novak et al. found no differences in ankle power (and work) post BoNT [32].

Four studies reported MG [18,21], LG [18], SO [21,27], TA [21,27], rectus femoris (RF) [21] and biceps femoris (BF) [21] EMG gait measures. Fujita et al. found a significant increase in BF activity in early-stance, decrease in TA activity during mid-stance and increase during late-stance, and decrease of SO, MG and RF activation during swing [21]. Hesse et al. also reported significant reductions of SO around heel-contact [27].

3.3.2. Upper leg muscles

Six studies focused on RF BoNT using doses between 100U [40] to 200U [29–31,34,37] for the treatment of stiff knee. These studies found significant improvements in speed [23,29–31,34], cadence [23], step [23] and stride length [29,30]. The same studies have also reported significant improvements in kinematics: increased peak knee [23,30,31,34,37,40] and hip [23,30,34] angle at swing and hip [34], knee [23,29,34,37] and ankle [34] angular velocity at toe-off, and knee ROM [37].

Measures of lower limb coordination using the continuous relative phase (CRP) [29,30] between the shank and thigh show a reduced CRP root-mean square (CRP_{RMS}) in mid-stance, CRP reversals (CRP_R) for the whole gait cycle (GC), in late-stance and in swing [29,30], and increased CRP_{RMS} in swing. Furthermore, a greater correlation between the CRP for paretic and control limbs was found. These results indicate a greater, “more stable” and symmetric lower limb coordination [29,30].

Significant RF [23] VL and ST [37] EMG reduction throughout the GC and RF-BF coactivation duration during swing [23] may also contribute to a more energetically efficient gait. Boudarham et al. found a significant decrease of RF instantaneous EMG mean frequency during push-off, which may indicate a “preferential activation of slow type-I fibers after BoNT” [23].

Only one study reported physiotherapy delivered as an adjuvant intervention [37] and in 4 studies this information was not available [23,29–31,34]. However, Tok’s study in which no intervention other than RF BoNT was delivered, significant improvements in knee kinematics and energy efficiency were still observed [40].

3.3.3. Several lower limb muscles

One study, and another comprising a secondary analysis, injected BoNT in several lower limb muscles [22,24]. This study used treadmill walking to determine lower limb kinematics, mechanical work as well as energy cost using VO₂/CO₂ measures [24]. Patients were classified by their baseline knee flexion amplitude during walking (> 10° and < 10°). BoNT injected into knee flexors/extensors and ankle plantarflexors (range 300–500U) significantly improved knee flexion amplitude, especially in the most affected group (< 10°). A significantly improved kinematic coordination (hip, knee and ankle) in the paretic limb and normal values in the unaffected side were found in the secondary analysis [22]. This study also found a decreased energy consumption [37,40], possibly explained by a reduction in the total lower limb mechanical work [24]. These results were also reflected in the 10mWT where patients walked significantly faster after BoNT [24].

3.3.4. Upper limb muscles

Three studies reported spatiotemporal and kinematic measures after BoNT for the treatment of the spastic arm [26,28,38]. However, doses and injections sites, which included shoulder [28], arm [26,28] and forearm [26,28,38] muscles, differed considerably amongst studies (Table 1). All studies reported significant increases in gait speed [26,28,38]. When classified by stride time (1.7 s/stride cut-off), Hirsch et al. found a significant increase in knee and ankle ROM of the paretic leg in the slow but not in the fast striders [28]. Tanikawa et al. and Hefter et al. found significant reductions in elbow flexion [26] and trunk lateral deviation [38] during gait, respectively. Unassisted patients walked significantly faster with reduced pre-swing time and increased non-affected leg step length after arm/forearm BoNT injections [26].

4. Discussion

The aim of this review was to understand gait changes after botulinum toxin injections in chronic stroke survivors. Although different types of gait analysis (e.g. kinematics) can be performed to determine changes, most studies only report speed as the main outcome measure [8,10]. Despite its relevance for daily life, speed does not provide information about the mechanisms underlying improvements in gait patterns after BoNT, hence, it is probably not the optimal measure to consider for clinical decision-making.

Only 5 studies [16,29–33] reported mean speed increases above the minimal detectable change (MDC) (0.13–0.18 m/s) [41] and only one [33] reported a mean increase above the minimal clinically important difference (MCID) (0.18–0.19 m/s) [42] for stroke populations. Despite this, most studies in this review showed that instrumented and laboratory measures of gait significantly improved after BoNT. This may reflect the fact that clinical measures (e.g. 10mWT) may not be responsive [11] and that more objective and sensitive measures of gait should be employed [5] to determine the effects of spasticity treatment with BoNT. This was also noted by Tanikawa et al. who found spasticity reductions associated with upper limb BoNT lasted for a shorter periods when assessed during walking compared to static conditions [38].

In adults, speed increments result in longer strides, longer single support and shorter double support [43]. Similarly, increased speed in stroke has been associated with improvement in spatiotemporal measures after BoNT not only in lower limb [16,18,21,23,25,27,29,30,33] but also after injections in upper limb muscles [26]. These positive changes reflect a more efficient gait pattern but may also indicate an improvement in balance control during walking that may potentially lead to a decreased risk of falling.

Joint kinematic changes were observed in some of the studies that also reported significant reductions in spasticity or passive ROM [19,22–24,26,32,34,37,38,40]. This suggests that improvements in non-functional tests may also translate into walking changes and lower limb coordination [22,29,30]. However, this does not necessarily indicate that a joint has recovered its functionality, since these changes may not be coupled to increases in the forces exerted by the same joints to move the body forward [32,34].

Compared to gait patterns in healthy adults [44], stroke survivors compensate for deficits in ankle motion by increasing activity in hip flexors in order to achieve a faster speed [6]. After BoNT in the lower leg muscles, Pradon et al. found an increased peak plantarflexor moment [33], however, Novak et al. found no significant differences in ankle power (and work) [32]. Since ankle power is more strongly associated with speed than the peak moment [44], this may explain the lack of significant differences in speed in Novak’s study. Interestingly, the latter study did not report adjuvant interventions, and more muscles and higher doses were injected compared to other studies [33]. These factors may have resulted in weakening of the distal musculature essential for the push-off at the end of stance. Determining the effects of BoNT on distal musculature may have implications beyond propulsion

as it has been shown that decreased push-off may also affect dynamic stability [45].

At the knee, power absorption (eccentric activation) significantly increased after BoNT in RF [37], which may indicate an increased elongation of RF for potential transfer of elastic energy from the knee to hip to move the leg forward during swing [46]. This is in line with a study by Lampire et al. that found an increased and rapid RF elongation during late-stance and early-swing after BoNT [31]. Furthermore, energy expenditure was also found to decrease after RF BoNT [37,40], which again indicates a more efficient walking pattern.

A crucial factor to consider when determining the effects of BoNT on walking performance is physiotherapy as an adjuvant intervention [14]. However, in 23% of the studies included in this review we were not able to retrieve information on whether physiotherapy was delivered and in one study it was reported that only 38% of patients received a single physiotherapy session [17]. In a recent study it was found that BoNT in lower leg muscles followed by high intensity physiotherapy was more effective than BoNT alone in improving SPT and EMG gait measures. These changes led to a greater knee stability at the beginning of the gait cycle due to increased BF/RF and reduced SO/MG coactivation during swing, which reduces the risk of falls by slipping or tripping [21]. Interestingly, the study by Tok et al. study did not include any adjuvant therapy after RF BoNT and yet significant improvements in most gait measures were observed [40]. Although this may indicate that gait improves regardless of other interventions, there is strong evidence to support adjuvant interventions, e.g. physiotherapy, to enhance BoNT effects [14].

It is noteworthy that only 2 of the selected studies utilized a placebo group to determine BoNT effects in gait. Compared to placebo, Pittock et al. (2003) found no significant effects on BoNT on the 2-minutes walking test (2mWT) and cadence (calf muscles injections) [17], whereas Tok et al (2012) found significant improvements, compared to placebo, in knee kinematics when injecting the RF [40]. Others studies have also reported greater improvements in gait for the BoNT compared the placebo group (plantarflexor musculature) [47–49] when using subjective outcome measures (e.g. Physicians Rating Scale). Since the functional effects of BoNT on gait have not yet fully described, further studies using placebo groups should also consider objective measures of gait such as those provided by gait analysis.

Finally, it has been proposed that the effects of BoNT on muscle spasticity have an effect in the way how the nervous system processes sensory information and executes motor commands by eliciting neuroplastic changes [22,50]. However, it is most likely that these changes cannot be detected using current clinical tools [5,11]. In this regard, instrumented assessments, e.g. using wearable inertial systems, may be more sensitive to determine these changes [51].

4.1. Limitations

Since our primary focus was stroke, studies including other populations (i.e. traumatic brain injury) were not considered. Five RCTs included in this review were scored as “good” or “excellent” using the PEDro scale, however, the other studies had a high risk of bias due to non-randomisation or lack of a control group. Only one of the high quality studies used kinematics, while the other four used counting of steps during walking to determine cadence and step length. A reason for this may be that instrumented and/or laboratory-based assessments may not be available in clinical settings or that associated time and costs involved are too high. Inertial measurement systems can partly substitute for laboratory measures in busy clinical settings, hence, facilitating the use of objective and sensitive measures to better determine the effects of BoNT on spasticity and gait rehabilitation [51], however, no studies using these systems were retrieved. This may be due to their implementation may still be in the early stages.

5. Conclusions

This review found that even when speed changes after BoNT injections are not significant, improvements in spatiotemporal, kinematic, kinetic and electromyographic measures occurred. Although several factors can affect the results of BoNT injection such as muscle(s) selection, dosage, demographics, brain damage characteristics and adjuvant interventions, all studies reported gait improvements, mostly significant, for up to 20 weeks post-injection.

BoNT injected in the lower leg muscles, increased dorsiflexion during stance and propulsive forces and activity of more proximal musculature explain most of the gait changes. RF BoNT resulted in significant improvements in hip, knee and ankle angles and velocities, lower limb coordination and reduced energetic cost of walking. Multiple lower limb muscles improved segmental coordination and reduced energy costs, whereas injections in the upper limb muscles improved elbow and trunk angles.

Determining the effects of BoNT beyond gait speed changes can assist in the clinical decision-making process. Future studies should further explore the mechanisms underlying BoNT-related changes to identify the most suitable variables that determine the efficacy of BoNT options.

Competing interests

The authors declare that they have no competing interests.

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