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Original Research Article

Effects of 3 Cycles of Increasing Botulinum Toxin Doses on Functional Parameters of Post-stroke Spastic Gait: A Prospective Cohort Study

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Abstract

Background: Single botulinum toxin type A (BT-A) injections reduce spasticity, but the effects of repeated injections on walking activities remain unclear.

Objectives: To demonstrate cumulative effectiveness of progressively higher doses of BT-A on walking activities (primary outcome) and spasticity reduction.

Methods: 32 individuals with lower-limb spasticity impairing gait post-stroke were included in this prospective cohort study. Participants received 3 injections of increasing doses of Inco BT-A (400–600–800 U) in both upper and lower limbs and were followed for 7 months. Activity evaluations included the 10 MWT, 6MWT, TUG, and a timed stairs test (TST). Spasticity was assessed using the Modified Ashworth (MAS) and Modified Tardieu (MTS) scales.

Results: Activities remained stable after the 1st injection but improved after the 2nd and 3rd cycles on the 6MWT (+0.07 and +0.12 m/s, respectively, $p < 0.05$) and TST (−13.7 s and −14.8 s, respectively, $p < 0.05$). Spasticity significantly reduced after each injection cycle, with greater reductions after the 2nd and 3rd cycles.

Conclusions: Repeated, progressively higher doses of Inco BT-A in lower-limb spasticity post-stroke improved walking activities and reduced spasticity, more so after successive cycles and higher doses. This could suggest cumulative effects, better effects due to higher doses, or both. This supports the use of progressively higher doses to thoroughly treat spasticity patterns.

clinicaltrials.gov : NCT04544280.

Keywords

(MeSH terms): muscle spasticity, botulinum toxins type A, stroke, spastic gait, rehabilitation, lower limb

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Introduction

Spasticity is frequently responsible for gait impairment after stroke, impacting victims' quality of life (Barnes et al., 2017; Baude et al., 2019). Spasticity is an umbrella term for a common clinical phenomenon including increased joint resistance to passive stretch, which has neural and non-neural origins (Baude et al., 2019; Li et al., 2021; van den Noort et al., 2017). Botulinum toxin type A (BT-A) injections are one of the first line recommended treatments to manage spasticity after stroke (Suputtitada et al., 2024). In order to adequately treat spasticity patterns, a considerable number of muscles must be injected with recommended doses (Ashford et al., 2018). When spasticity is widespread (i.e., in the case of upper and lower limb involvement), maximal labeled doses of BT-A can represent a limit to optimal treatment (McAllister et al., 2019).

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Evidence supports the effectiveness of a single BT-A injection cycle in reducing lower-limb spasticity, but its impact on activities and participation is less clear (Bollens et al., 2013; Caty, Detrembleur et al., 2008; Cotinat et al., 2023; Hutin et al., 2010; Robertson et al., 2009). A meta-analysis showed a slight improvement in walking speed following BT-A treatment, although repeated injections may be necessary for significant gains (Foley et al., 2010). Studies on multiple BT-A injection cycles are limited and have mainly used currently labeled doses (Esquenazi et al., 2021; Hara et al., 2018; McAllister et al., 2019; Pittock et al., 2003). Higher doses have been shown to be safe and benefits in activities and quality of life are emerging, but further research is needed to confirm these findings (Esquenazi et al., 2021; Gracies et al., 2017; Santamato et al., 2017; Wissel et al., 2017).

This study aimed to evaluate the effects of three successive cycles of progressively higher BT-A doses on walking activities in individuals with widespread post-stroke spasticity. A pragmatic approach was used to mimick clinical practice, thereby allowing to better address diverse spasticity patterns. Our primary hypothesis was that walking activities (International Classification of Functioning, disability and health -ICF model) would be further improved after the third cycle versus the first (WHO, 2007). Our secondary hypothesis was that spasticity (body structure and functions -ICF) would be reduced after each injection cycle, but more importantly after the third. Thus, our primary outcome was walking activities and our secondary outcome the clinical assessment of spasticity.

Materials and Methods

This pragmatic, prospective, non-randomized, dose-titration, multicentre cohort study followed the STROBE checklist for cohort studies (Elm et al., 2007). The protocol was registered on clinicaltrials.gov (NCT04544280) and approved by the local ethics committee. All participants provided written informed consent.

Participants

Participants were recruited from the Physical Medicine and Rehabilitation Departments of Cliniques universitaires Saint-Luc and Centre Hospitalier Universitaire de Namur site Godinne (Belgium), from the in and outpatient clinic. Participants were adults (>18 years old) with stroke for more than 3 months, responsible of lower limb spasticity, including the plantar flexors (MAS $\geq$1) and resulting in gait impairment objectified by the clinical assessment. Participants presented gait impairments that were attributed to spasticity on the visual clinical examination (e.g., pes equinus and stiff knee gait). Additionally, they had widespread spasticity, affecting multiple limb segments on the lower limb, including the potential involvement of the upper limb. This presentation met the criteria for focal chemical denervation by BT-A injections of up to 800 U of Inco BT-A, as determined by the investigators (experienced physicians in PM&R). Additionally, participants had the ability to understand simple instructions.

Participants were excluded if they had other neurological or orthopaedic ongoing illnesses interfering with the studied lower limb's function and if they were ineligible for BT-A injections (BT-A injections in the previous 3 months or underlying neuromuscular disease).

Study Design

The study design is shown in Figure 1. Participants received 3 cycles of progressively higher doses of incoBoNT-A at 3 months intervals (50 U/ml in normal saline).

1. Visit 1 [V1]: 400 U into the lower limb only or the lower and upper limb
2. Visit 3 [V3] : 600 U into the lower limb only or the lower and upper limb
3. visit 5 [V5] : 800 U into the lower and upper limb. If a dose of 800 U was not clinically indicated, participants exceptionally received a dose $\geq$600 U on the third cycle.

Muscle and Dose Selection

At screening, the authors (GS, CS, and TD—physicians in Physical Medicine & Rehabilitation with 8–20 years of experience in spasticity management) selected the target muscles and doses for the first injection cycle (400 U of inco BT-A). Muscle selection was based pragmatically on participants' needs and guided by clinical gait evaluation. The primary impairment targeted was pes equinus or equinovarus foot, focusing on the ankle plantar flexors (gastrocnemius and soleus), with at least one of these muscles injected in each cycle.

Doses were first allocated to the spastic lower limb muscles. If additional doses were available and indicated, they were administered to spastic upper limb muscles. The total dosage for the lower limb was systematically increased with each cycle, although the dose per muscle was not necessarily increased. More muscles were injected to address various spasticity patterns effectively, prioritizing relevance as assessed by the physicians.

Visits and Evaluations

Participants were evaluated immediately before and one month after each injection cycle, resulting in a total of six

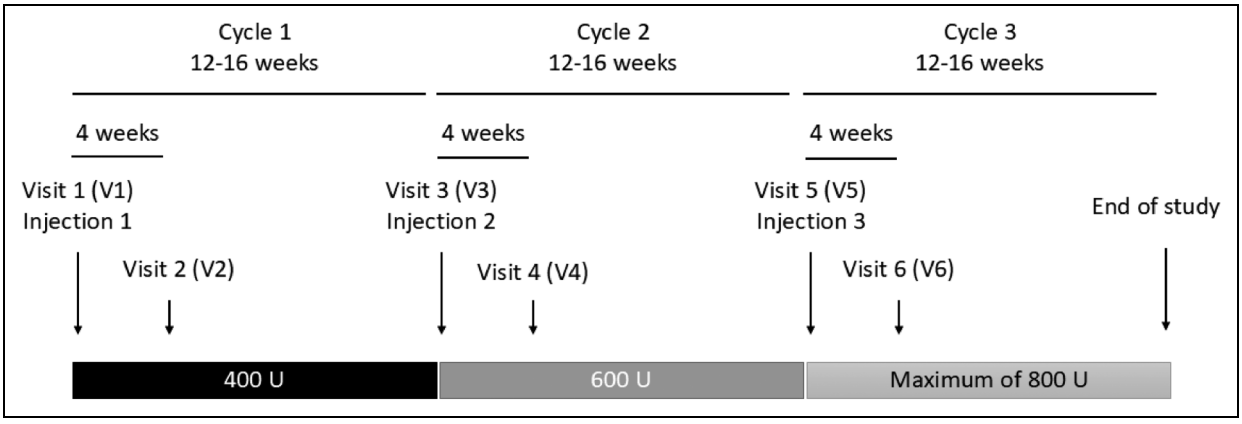


Figure 1. Study design.

evaluations (six visits). If participants were ineligible for re-injection at the pre-injection visits (V3 at 3 months and V5 at 6 months) due to insufficient spasticity, injections were postponed. Participants were re-evaluated every 2 weeks until they became eligible, with a maximum of three postponements. If eligibility was not achieved within this limit, participants were excluded from the study.

Evaluations followed the ICF model (Pohl et al., 2020). Mobility (ICF activities domain) was assessed through : the 10 meters walk test (10 MWT) (Perera et al., 2006), the 6 min walk test (6MWT) (Eng et al., 2004), the Timed Up and Go test (TUG) (Flansbjer et al., 2005) and the ABILOCO questionnaire (Caty, Arnould et al., 2008). The 10 MWT measures walking speed while the 6MWT assesses walking distance (walking capacity) (*Rehabilitation Measures*, n.d.). Walking capacity, as defined by the ICF, is the ability to perform walking activities (Organization, 2001), whereas walking performance refers to actual walking activities in home or community settings (Selves et al., 2020). Climbing activities with the timed stairs test (TST), measuring the time to climb up and down two flights of 7 steps (20 cm high) (Flansbjer et al., 2005; *ICF Browser*, n.d.; *Rehabilitation Measures*, n.d.; Zaino et al., 2004). Upper limb function with the Box and block test (BBT) (Chen et al., 2009) and the ABILHAND questionnaire (Penta et al., 2001).

Impairments were evaluated through clinical assessments. Spasticity in the plantar flexor muscles (knee flexed and extended), knee extensor muscles, ankle invertor muscles, and elbow, wrist, and finger flexor muscles was assessed using the MAS and Tardieu scales. Passive joint range of motion (ROM) was measured with a hand goniometer, and motor control was assessed with the Fugl-Meyer test (adaptive version) (Hou et al., 2012). Quality of life (QoL) was evaluated using the French version of the Short-Form Health Survey (SF-36), with higher scores indicating better health status (Anderson et al., 1996; *Rehabilitation Measures*, n.d.).

Changes in antispastic medication, physical/occupational therapy or any other rehabilitation treatment (i.e., orthotic devices or splinting/casting), were not permitted from 2 weeks prior to screening and throughout the study. Ongoing medication and rehabilitation treatments were recorded at each visit. Adverse events (AE) were recorded at each visit after the first injection cycle. Participants were actively questioned about AEs and were prompted to report any medical event.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics version 26 (Armonk, New York) and Sigmaplot 13.0 (Systat, Chicago, Illinois). Normality was verified. To achieve 80% power with a mean difference on the 10mWT greater than the MDC (0.06 m/s) (*Rehabilitation Measures*, n.d.) at a 5% significance level, a sample size of 30 stroke individuals was required. The calculation used Cohen's a priori method and the G.Power 3 program (Cohen, 1988; Faul et al., 2007). We hypothesized a progressively better effect with each subsequent injection cycle. Results at 1 month post-injection (V2, V4, V6) were compared to baseline (V1).

The effects of treatment on continuous variables were assessed using one-way repeated-measures analysis of variance (One-way RM-ANOVA). Ordinal data were analyzed with RM-ANOVA on ranks (non-parametric test). Chi-squared tests compared the distributions of qualitative variables. Statistical significance was set at 5% ($p < 0.05$). The study followed an intention-to-treat approach, analyzing all participants and replacing missing data with the group's mean value at that time.

Results

Thirty-two participants were included between September 2018 and October 2021. The flow chart is presented in

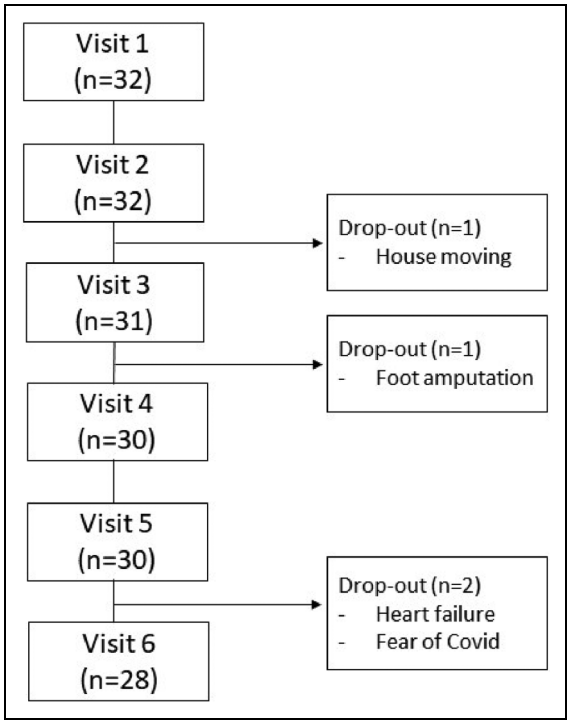


Figure 2. Study flow chart.

Figure 2. Six participants received less than 800 U in the 3rd cycle (600–770 U) based on clinical assessment. Median dosages (min-max) injected into the lower limb were: first cycle 350 U (250–400 U), second cycle 470 U (260–600 U), and third cycle 600 U (400–800 U). Injections were postponed by 2 weeks for two participants in the 2nd cycle and two participants in the 3rd cycle. Four participants dropped out due to reasons unrelated to the study (moving, foot amputation, heart failure, and fear of COVID-19). Three serious adverse events were recorded, none attributed to the study drug (foot amputation due to type 2 diabetes, heart failure, health worsening). No participant was excluded due to insufficient spasticity before re-injection. All participants received rehabilitation sessions throughout the study, with total duration ranging from 30 to 90 min per week. These remained constant throughout the study. Characteristics of the participants are detailed in Table 1. Females comprised a minority (n = 11; 34.4%), with a mean age of 54.5 years (12.4) and a mean BMI of 25.2 kg/m^2(4.4). Left hemiparesis was most common (n = 19; 59%), a third had a hemorrhagic stroke (n = 12; 37.5%), and the mean time since stroke was 26.8 months (32.8). Thirteen participants were naive to BT-A treatment (40.6%), and four were on antispastic drugs. Oral drugs and rehabilitation treatments remained stable throughout the study. No BT-A naive effect was observed.

Results on functional parameters at visits 1, 2, 4, and 6 are presented in Table 2.

Table 1. Participants Characteristics.

	Participants (n = 32)
Gender, male/female, n	21/11
Age, years	54.5 (12.4)
BMI	25.2 (4.4)
Affected side of the body, left/right, n	19/13
Type of stroke, hemorrhagic/ischemic, n	12/20
Time since stroke, months	26.8 (32.8)
Time since previous BT-A injection at inclusion, months	7.1 (3.0)
BT-A naïve, n (%)	13 (40.6)
FMA-UE (%)	50.0 (30.9)
FMA-LE (%)	64.8 (27.4)

Abbreviation: BMI = Body Mass Index. BT-A : botulinum neurotoxin A. FMA-LE = Fugl Meyer Assessment Lower Extremity. FMA-UE = Fugl Meyer Assessment Upper Extremity. Results are presented as mean (SD).

Locomotion Activities

Results are presented in Figure 3. Walking speed (10MWT) remained stable after the 1st injection cycle but improved significantly after the 2nd cycle (visit 4) compared to baseline (0.12 m/s; p = 0.03). Scores remained stable at visit 6, following the 3rd injection cycle. Walking distance (6MWT), was stable after the 1st injection cycle but increased significantly after the 2nd and 3rd cycles compared to baseline (+27 m; p = 0.03 and +43.8 m; p = 0.03, respectively). TUG scores remained stable throughout all visits. TST scores were stable after the 1st injection cycle but improved significantly after the 2nd and 3rd cycles compared to baseline (−13.7 s; p = 0.005 and −14.8 s; p = 0.009, respectively). The improvement was significantly greater after the 3rd injection than after the 2nd (p = 0.015). Results on the ABILOCO questionnaire remained stable throughout the study (p = 0.61).

Upper Limb Function

Results of the BBT and ABILHAND questionnaire remained stable throughout the study (p = 0.34, p = 0.39).

Quality of Life

Scores of the SF-36 questionnaire showed no significant changes throughout the study (p = 0.06–0.55).

Body Function and Structure

Results of the clinical evaluations (MAS, MTS, ROM, FMA-UE and FMA-LE) are presented in Table 2 and Figure 4.

Table 2. Functional Parameters at Visit 1, 2, 4 and 6.

	Visit 1	Visit 2	Visit 4	Visit 6	p-Value
Locomotion activities					
10 MWT (m/sec)	0.74 (0.30)	0.81 (0.34)	0.86 (0.34)[a]	0.84 (0.32)	0.02
6MWT (m)	292.1 (141.5)	302.5 (148.3)	319.1 (154.2)[a]	335.9 (154.2)[a]	0.01
TUG (sec)	19.0 (9.4)	18.1 (8.4)	17.0 (8.7)	16.2 (9.2)	0.02
TST (sec)	59.4 (38.1)	58.5 (40.7)	45.7 (25.3)[a/b]	44.6 (24.9)[a/b]	<0.001
Abiloco (log)	4.0 (2.1)	3.6 (2.1)	3.6 (2.3)	3.7 (2.6)	0.61
Upper limb activities					
BBT (blocks)	10.2 (17.0)	8.3 (14.0)	11.0 (18.9)	12.5 (19.1)	0.34
Abilhand (log)	0.38 (1.85)	0.18 (1.90)	0.79 (2.15)	0.73 (2.38)	0.39
Activity limitation					
Activlim (log)	2.03 (1.12)	1.78 (1.49)	2.67 (1.95)	2.32 (2.23)	0.07
Quality of life					
SF36-total score (/800)	459.1 (146.5)	437.7 (154.2)	510.0 (175.6)	464.8 (181.0)	p (0.06–0.55)
Body function & structure					
MAS knee extensor	1.7 (1.3)	1.0 (1.1) [a]	1.2 (1.2)	1.0 (1.1)[a]	<0.001
MAS plantar flexors-KE	2.5 (1.2)	1.3 (1.3)[a]	1.7 (1.6)[a]	0.9 (0.9)[a/c]	<0.001
MTS-V2 plantar flexors-KE	2.0 (1.0)	1.2 (1.1)[a]	1.2 (1.1)[a]	0.8 (0.7)[a]	<0.001
MTS-V3 plantar flexors-KE	2.4 (1.0)	1.6 (1.3)[a]	1.6 (1.3)[a]	1.0 (1.0) [a/b/c]	<0.001
MAS plantar flexors-KF	2.5 (1.2)	1.2 (1.3)[a]	1.5 (1.3)[a]	0.9 (0.9)[a]	<0.001
MTS-V2 plantar flexors-KF	2.1 (1.1)	1.3 (1.2)[a]	1.3 (1.2)[a]	0.8 (0.7)[a]	<0.001
MTS-V3 plantar flexors-KF	2.6 (1.0)	1.8 (1.3)[a]	1.9 (1.3)[a]	1.2 (1.2)[a/b/c]	<0.001
MAS ankle inversors	1.3 (1.5)	0.5 (1.1)[a]	0.5 (0.9)[a]	0.6 (0.8)	0.01
MAS elbow flexors	1.7 (1.4)	1.4 (1.3)	1.2 (1.3)	1.4 (1.2)	0.005
MAS wrist flexors	1.7 (1.3)	0.7 (0.8) [a]	1.2 (1.1)	1.2 (1.3)	<0.001
MAS finger flexors	2.5 (1.2)	1.3 (1.2)[a]	1.4 (1.3) [a]	1.6 (1.4)[a]	<0.001

Abbreviation: 10 m WT : 10 meters walk test; 6MWT : 6 min walk test; FMA-UE : Fugl Meyer Assessment Upper Extremity; FMA-LE : Fugl Meyer Assessment Lower Extremity; MAS: modified Ashworth scale, MTS = modified Tardieu scale; KE = knee extended; KF = knee flexed; TST : timed stairs test; TUGT : timed up and go test; a : significant difference compared to visit 1; b : significant difference compared to visit 2; c : significant difference compared to visit 4. Results are presented as mean (SD).

Knee extensor spasticity, assessed with the MAS, improved after the 1st injection (−0.7, $p < 0.001$), remained stable after the 2nd injection ($p = 0.09$), and improved after the 3rd injection cycle (−0.7, $p = 0.005$).

Plantar flexor spasticity, knee-extended, evaluated with MAS and MTS, improved after each injection cycle compared to baseline (V2: MAS : −1.2, $p < 0.001$, MTS-V2 : −0.8, $p = 0.001$, MTS-V3 −0.8, $p = 0.01$; V4: MAS : −0.8, $p = 0.008$, MTS-V2 : −0.8, $p = 0.003$, MTS-V3 : −0.8, $p = 0.003$; V6: MAS : −1.6, $p < 0.001$, MTS-V2 : −1.2, $p = 0.001$, MTS-V3 : −1.4, $p = 0.001$).

A more pronounced decrease was observed after the 3rd injection (V6) compared to the 1st injection (V2) (MAS: −0.8; $p = 0.02$, MTS-V3 : −0.6; $p = 0.04$). Additionally, the reduction in spasticity was also significantly greater after the 3rd injection (V6) compared to the 2nd injection with the MTS-V3 (−0.6; $p = 0.02$).

Similarly, plantar flexor spasticity, knee-flexed significantly decreased (MAS and MTS, $p < 0.001$, respectively) after each injection cycle (V2, V4, and V6; $p < 0.001$). Moreover, the reduction in spasticity was significantly greater after the 3rd injection (V6) compared to the 1st injection (V2) and 2nd injection (V4) as evaluated with MTS-V3 (−0.6; $p = 0.01$, −0.7; $p = 0.003$).

Spasticity of ankle invertor muscles significantly decreased after the 1st and 2nd injection cycles (V2: $p = 0.03$, V4: $p = 0.02$). Elbow flexor spasticity remained stable throughout the study. A reduction in spasticity of wrist flexor muscles was observed after the 1st injection ($p < 0.001$). Finally, finger flexor spasticity decreased after each injection cycle (V2, V4, and V6; $p < 0.001$).

Results on FMA-UE and FMA-LE remained stable throughout the study ($p = 0.21$).

Discussion

Activities: Functional Parameters of Gait

To our knowledge, this is the first pragmatic cohort study to treat both upper and lower limb spasticity in stroke patients using progressively higher doses of Inco BT-A. This approach allowed treatment of more muscles and better management of diverse spasticity patterns, mirroring typical clinical practice, where initial lower doses are increased gradually for a safer and more comprehensive management of spasticity (Ashford et al., 2018). Performance in walking activities (ICF) remained stable after the 1st injection cycle and improved following the

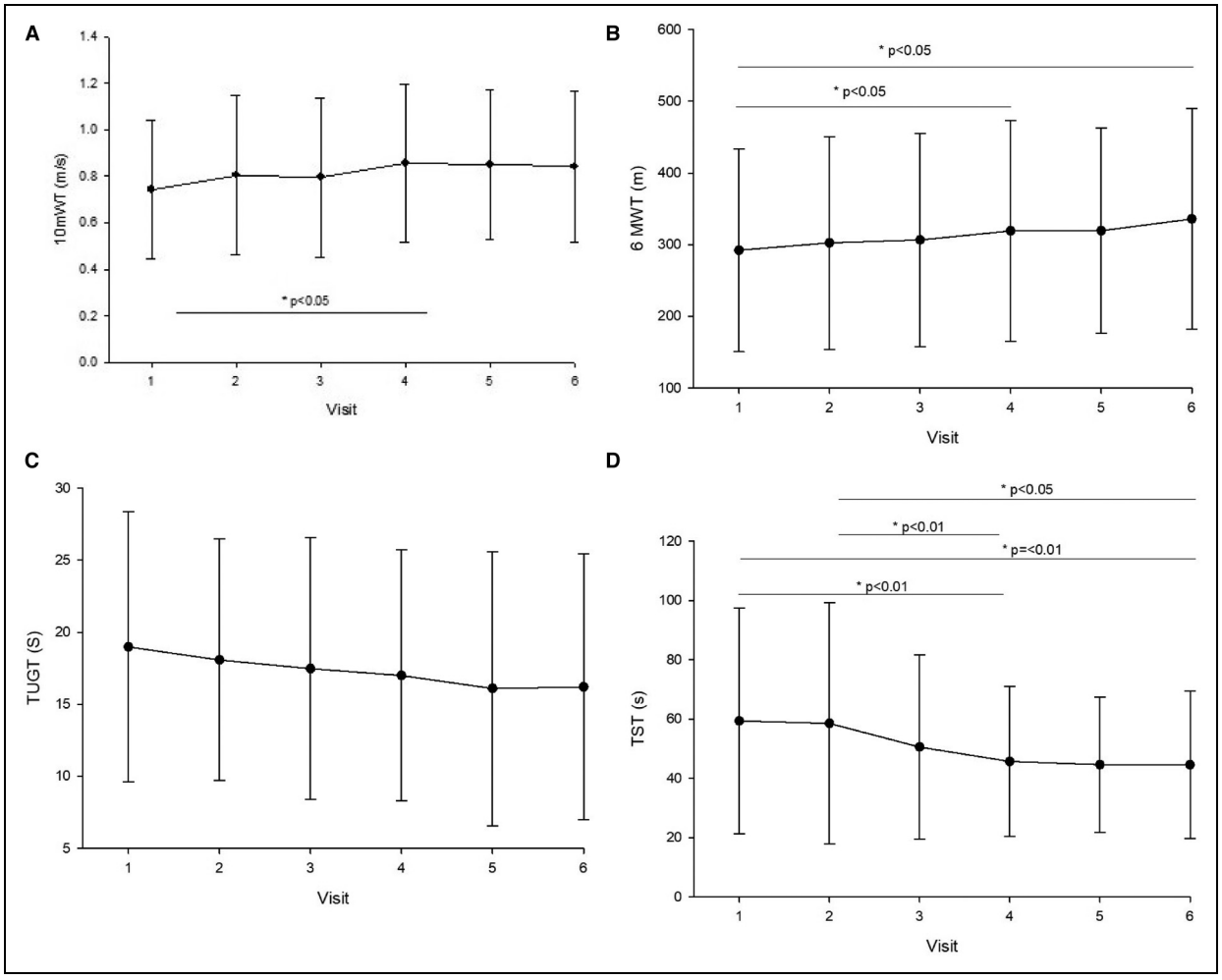


Figure 3. Functional parameters at each visit. Part A represents the 10 meters walk test (10 m WT), part B the 6 min walk test (6MWT); part C the Timed Up and Go test (TUGT); part D the timed stairs test (TST).

2nd and 3rd cycles (6MWT, 10MWT and TST). Focusing solely on one injection cycle would not have shown significant functional effects. However, by studying three consecutive cycles with progressively higher doses, we were able to observe improvements in walking activities. This suggests that treating more spasticity patterns with appropriate doses in individuals with widespread spasticity yields better functional outcomes. Reductions in spasticity on the MAS and MTS were observed after each injection cycle, with greater reductions in plantar flexor muscles following the 3rd injection cycle compared to the 2nd.

Studies examining a single BT-A injection for equinovarus foot post-stroke showed conflicting results on walking speed, the most commonly used walking activity outcome measure (Cotinat et al., 2023; Foley et al., 2010). Foley et al.'s (2010) systematic review and meta-analysis reported a modest increase in walking speed (0.04 m/s) after one BT-A cycle for equinovarus foot, though with a small effect size (Hedge's $g = 0.193$) and no clinical significance (MCID = 0.16 m/s) (Foley et al., 2010; *Rehabilitation Measures*, n.d.). A more recent systematic review by Lizama et al. (2019), concluded that there were no improvements on walking speed with BT-A for lower limb spasticity and that improvements were only present on other spatiotemporal parameters of gait (Lizama et al., 2019). Recent studies on spastic equinovarus foot and stiff knee gait post-stroke have also shown conflicting results regarding walking speed, with some reporting stability and others minor increases (up to 0.13 m/s, below the MCID of 0.16 m/s) (Caty, Detrembleur et al., 2008; Cotinat et al., 2023; Hutin et al., 2010; *Rehabilitation Measures*, n.d.; Robertson et al., 2009). Robertson et al. found no change in the TST following a single 200 U injection of Ona-BT-A in the rectus femoris ($n = 10$) (Robertson et al., 2009). Consistent with these findings, our study did not observe improvements in walking activities after the initial 400U injection. Participants to our study exhibited widespread spasticity, where the total dosage of the first cycle (average 335 U on lower limbs) was insufficient to address all spasticity

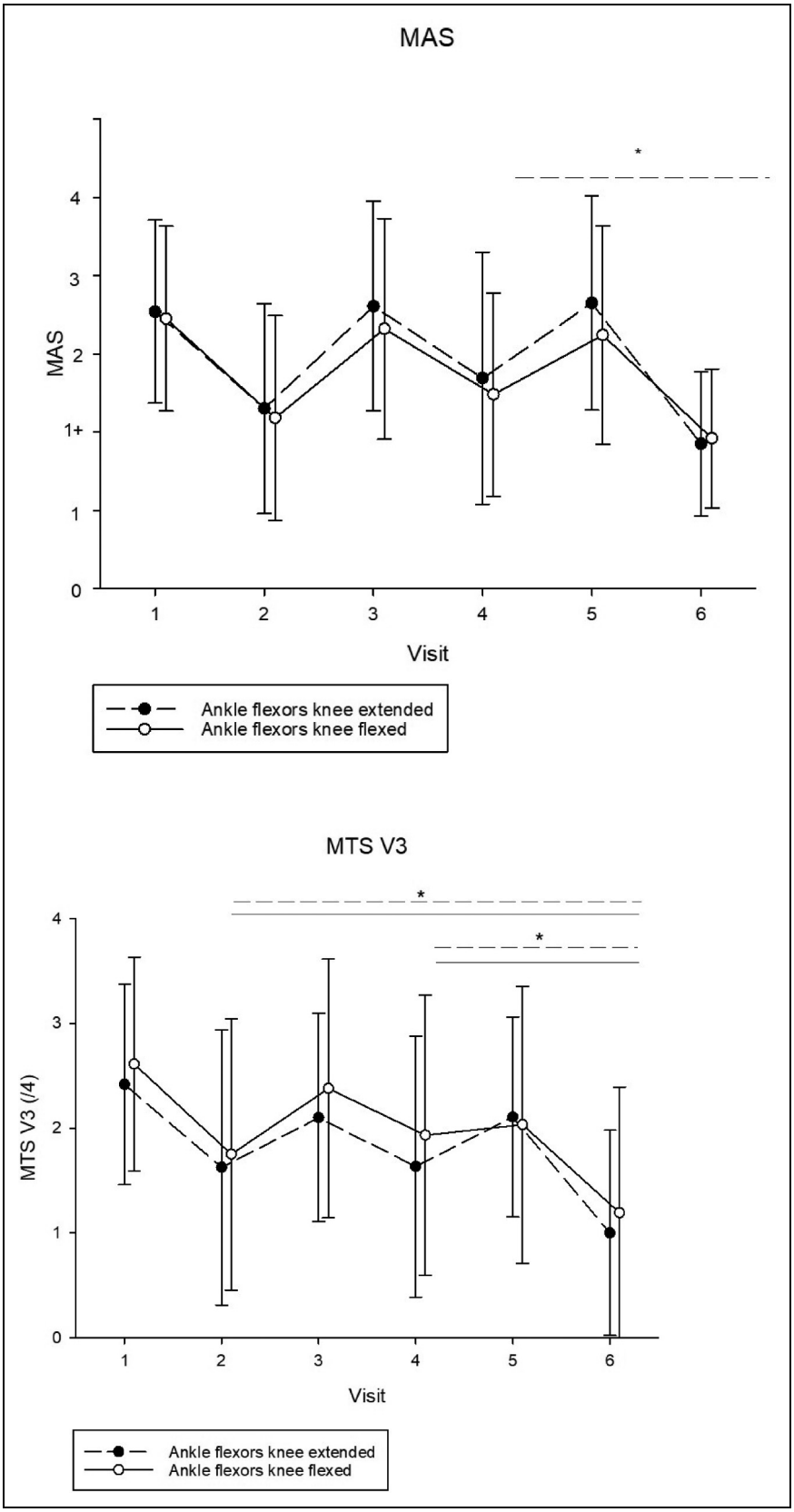


Figure 4. Spasticity evaluation at each visit (body function and structures). MAS : modified Ashworth scale. MTS : modified Tardieu scale. * significant results ($p < 0.05$). Not every significant result is shown in the figure. V1-V2, V1-V4 and V1-V6 were significant for all evaluations.

patterns across upper and lower limbs. To date, only four studies have investigated the effects of repeated BT-A injections for lower limb spasticity post-stroke. Esquenazi et al., in a secondary analysis of a large multicenter study (n = 352), administered 1000–1500 U of Abo BT-A up to four injection cycles, reporting improvements in comfortable walking speed (0.07 to 0.09 m/s) on the 10 MWT after each cycle, comparable to our findings on the 6MWT and 10 MWT after the 2nd cycle, and on the 6MWT after the 3rd cycle (+0.07 m/s) (Esquenazi et al., 2021). Similar improvements were observed in our study on the TST, which assesses mobility, endurance, and walking capacity, with more significant improvements noted after the 3rd injection compared to the 2nd ($p = 0.015$). To our knowledge, no studies have tested the effects of repeated BT-A injections on stair negotiation time, a critical factor for community ambulation (Perry et al., 1995).

McAllister et al. observed improvements in the 10 MWT of 0.03 to 0.09 m/s in stroke survivors with upper and lower limb spasticity (n = 127) after up to 4 injection cycles of 1000–1500 U of Abo-BT-A (McAllister et al., 2019). They demonstrated that treating both upper and lower limb spasticity with the same total doses did not hinder improvements. Participants were randomized into two groups: one receiving treatment for lower limb only and the other for both upper and lower limbs. Our findings are consistent with theirs; improvements in walking speed after the 2nd and 3rd cycles in the 6MWT and TST were +27 m and +44 m, and −13.7 s and −14.8 s, respectively. This supports the notion that optimal treatment of upper and lower limb spasticity in people with stroke may enhance walking speed, along with improving upper limb function, provided sufficient BT-A doses are administered to fully address their spasticity patterns. Similarly, a systematic review on gait changes post-BT-A injections for stroke-related spasticity noted that treating upper limb spasticity improved post-stroke walking capacity (Lizama et al., 2019). Hara et al. retrospectively evaluated repeated injection cycles for lower limb spasticity in stroke patients (n = 34) and reported speed improvements of 0.06 to 0.16 m/s (Hara et al., 2018), comparable to those observed in our study, which were notably greater after the 3rd cycle. However, caution is needed in interpreting Hara et al.'s results due to their retrospective methodology.

In our study, participants walked an additional 27 and 44 meters at the 6MWT (walking endurance) after the 2nd and 3rd cycles, respectively, surpassing the MCID for the 6MWT (14–34 m) and the MDC in chronic stroke (36.6 m) (Bohannon & Crouch, 2017; Flansbjer et al., 2005). Mean walking distance during the 6MWT at baseline and after the 1st injection cycles (292 m and 303 m, respectively) exceeded the cutoff for most limited community ambulators (225.2 m), though not for unlimited community ambulators (312.2 m) (Fulk et al., 2017; Perry et al., 1995; *Rehabilitation Measures*, n.d.). Following the 2nd and 3rd injection cycles, mean walking distances increased to 319 m and 336 m, respectively, surpassing the threshold for unlimited community ambulation, a crucial factor in enhancing quality of life (Selves et al., 2020). Detailed analysis of our data revealed that 41% of participants achieved unlimited community ambulation at baseline, rising to 63% by the end of the study (V6). These findings align with Esquenazi et al., who reported that participants transitioned from limited to unlimited community ambulation with improved walking speed following repeated injection cycles (Esquenazi et al., 2021). However, in their study, doses remained constant throughout the four cycles. Our results also align with findings on upper limb spasticity, where significant improvements typically occur after 3 to 5 injection cycles before reaching a plateau (Gracies et al., 2021).

We argue that the improvements in walking endurance observed in our study stem from both repeated injections and higher doses of BoNT-A, enabling treatment of more muscles and addressing a broader range of spasticity patterns in a pragmatic manner, potentially yielding cumulative benefits. However, the study design does not allow to determine whether the results were due to cumulative effects, to increased doses or both. Following the initial injection cycle with lower doses (400 U), no changes in walking speed or endurance were observed, consistent with results seen after single-cycle treatments (Bollens et al., 2013; Caty, Detrembleur et al., 2008; Cotinat et al., 2023; Robertson et al., 2009). This suggests that participants may require time to adjust to reduced spasticity and undergo rehabilitation, influenced in part by the time-consuming processes of brain plasticity (Esquenazi et al., 2021). Future studies should distinguish between the effects of repeated injections and higher doses of BoNT-A.

Body Structures and Body Functions: Spasticity

Reductions in spasticity after BT-A have been well-documented. This study not only demonstrated spasticity reduction after each injection cycle but also showed enhanced effects with progressively higher doses of BT-A. Specifically, reductions in spasticity in the plantar flexor muscle group were more pronounced after the 3rd injection compared to the 1st and 2nd injections, with decreases of −0.8, −0.8, and −1.4 mean points on the MTS-V3 after each injection cycle in the plantar flexor muscles knee extended, and −0.8, −0.7, and −1.4 mean points knee flexed. These findings are consistent with those reported by Wissel et al., who administered increasing doses of Inco BT-A up to 800 U (Wissel et al., 2017). While their study primarily focused on safety, they observed a rising percentage of participants with ≥1 point reduction on the MAS over successive cycles. Some researchers suggest that repeated BT-A injections progressively diminish motor unit recruitment, thereby reducing responses to rapid stretch (spasticity) and co-contractions (Gracies et al., 2017).

These results indicate that improvements in impairments (body structure and function-ICF) precede improvements in activities (ICF), necessitating at least 2 injection cycles. This delay may stem from the time required for motor patterns essential to activity performance to rewire (Cotinat et al., 2023; Dai et al., 2021; Esquenazi et al., 2021).

Limitations

A slightly higher incidence of right hemiplegia compared to left hemiplegia is observed (Hernández et al., 2003). However, in our cohort, the opposite distribution was present, which appears to be a result of random variation. Importantly, there is no evidence to suggest a different incidence of spasticity based on the laterality of the lesion (Lee et al., 2019). Therefore, we do not anticipate that this variation would significantly influence the outcomes of our study.

This study presents some limitations. First, the authors chose a pragmatic approach, allowing an adjustment of the treatment to the patients' individual needs. Consecutively, no control group was used, participants serving as their own controls. In rehabilitation research, RCTs may not capture the high variability among subjects with the same condition, making cohort studies valuable for allowing participants to act as their own controls (Kalincik et al., 2023). Second, no changes were observed on QOL, likely due to the diverse domains of the SF-36 questionnaire and varied participant responses to QOL questionnaires. This is consistent with other studies showing QOL stability (Bollens et al., 2013; Caty, Detrembleur et al., 2008). Bollens et al. and Caty et al. also found no significant QOL changes, suggesting the SF-36 may not be sensitive enough for people with stroke. Lastly, no long-term assessment beyond 12 weeks post-injection was conducted, which limits understanding of the sustained effects of the treatment.

Conclusions

This study provides evidence that repeated injections of progressively higher doses of BT-A in the lower and upper limbs of people with spasticity after stroke improves walking activities including endurance and stair negotiation, which may enhance community ambulation. Greater reductions in spasticity were observed after three injection cycles, suggesting cumulative effects. These findings support the clinical management of post-stroke spasticity and recommend using progressively higher doses of BT-A to optimally address widespread spasticity.

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Statements and Declarations

Ethics Committee

This study was approved by the Comité Hospitalo-Facultaire UCLouvain-Saint Luc (403) (approval no. 2018-002499-42) on August 29th, 2018.
The trial was registered in clinicaltrials.gov (NCT04544280).

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Additional Material

Injected muscles
Lower limb
Rectus femoris
Vastus medialis
Semitendinosus/semimembranosus
Gastrocnemii caput mediale/laterale
Soleus
Tibialis posterior
Flexor digitorum longus
Flexor digitorum brevis
Flexor hallucis longus
Upper limb
Pectoralis major
Biceps brachii
Brachialis
Coracobrachialis
Flexor carpi ulnaris
Flexor carpi radialis
Pronator teres
Flexor digitorum superficialis
Flexor digitorum profundus
Flexor pollicis longus
Interossei dorsales
Adductor pollicis

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