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Original article

Botuloscope: 1-year follow-up of upper limb post-stroke spasticity treated with botulinum toxin

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ABSTRACT

Background: Botuloscope is a cohort study supported by a French public grant and aiming to evaluate a 1-year treatment of the post-stroke spastic upper limb with botulinum toxin type A (BoNT-A) in terms of individual satisfaction with respect to personalized goals and quality of life.
Methods: This was an open-label prospective, multicentric study (11 French centres) that followed 330 adults [mean (SD) age 53.7 (13.7) years] over 1 year; participants had ranked 5 therapeutic goals at inclusion [mean (SD) 5.1 (7.3) years post-stroke], had severe hemiparesis [median motricity index (MI) 40 (Q1–Q3 24 to 60)], and were assessed at inclusion (M0) and at month 3 (M3) and M12. Outcome criteria were: spasticity, range of motion, pain [visual analog scale (VAS)], motor function [Modified Ashworth Scale (MAS)] and activities (MI; Frenchay Arm Test), and overall satisfaction with the achievement of each goal (VAS) and quality of life (Reintegration to Normal Life Index). Criteria at M0 and M12 were compared. Adverse effects were also collected, as were medication changes.
Results: The primary goal was comfort and activities for 63% of participants and motor function for 36%. Participants underwent a mean of 2.4 injection sessions, 19% causing adverse effects. The greatest spasticity attenuation occurred with wrist flexors (median decrease in MAS −2 [Q1–Q3; −2 to −1], $P < 10^{-3}$). Fewer individuals took oral anti-spastic drugs (56% at M12 vs 50% at M0; $P < 10^{-2}$). Range of motion increased by 16°, on average (13 to 19; $P < 10^{-3}$) for wrist extension. Pain prevalence decreases at rest (29% at M0 vs. 19% at M12; $P < 10^{-4}$) and during mobilization (64% vs. 43%; $P < 10^{-4}$), and fewer participants took analgesics (25% vs. 17%; $P < 10^{-3}$). Satisfaction was high for the goals "hand hygiene" and "pain release" and moderate for "improvement in upper limb function". However, function was more improved for participants who selected this goal as the first priority than others ($P < 10^{-2}$). Overall, 22% had the goal "improving gait and balance", which was reasonably achieved at M12. Quality of life improved markedly [median 8 (4 to 11) vs. 6 (3 to 10); $P < 10^{-4}$]. Prevalence of complete dissatisfaction with the first objective was 10% to 15%.
Conclusion: This is the first long-term follow-up of BoNT-A treatment for upper limb spasticity involving a large cohort independent of industry. Quality of life was improved by treating upper limb spasticity with BoNT-A, even at 5 years post-stroke. Personalizing objectives of the treatment amplified its efficacy. BoNT-A was a powerful analgesic when pain was spasticity-related. Treating the spastic upper limb also improved balance and gait abilities.

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1. Introduction

Spasticity is a disabling complication of stroke, whose local treatment by injections of botulinum toxin type A (BoNT-A) has become the reference treatment, although the improvement remains to be clarified [1–5]. Despite abundant literature about the spastic upper limb, evidence is still lacking regarding possible the beneficial effect of BoNT-A on function and activities [6]. Most studies were post-marketing open-label studies or randomized controlled trials of limited sample size (< 50 for 13/22 RCTs) analyzing the effects of a single-injection session of BoNT-A on predetermined muscles. Only 7 multicentric randomized double-blind clinical trials analysed the effect of a single injection of BoNT-A set on wrist and finger flexors [7–13].

In clinical practice for a given patient, therapeutic objectives and targeted muscles vary by the clinical exam and responses to previous injections. Hence, pragmatic trials and open-label studies with repeated sessions of injection represent interesting methods of research [1], underused so far in spasticity. However, among about 50 open-label studies published regarding treating spasticity with BoNT-A, only 4 followed a large sample size over several cycles of injection [14–17]. None was independent of the pharmaceutical industry. Many major issues indirectly linked with spasticity such as pain, patients satisfaction, or quality of life have almost never been investigated in the literature, particularly in the long term.

The Botuloscope study is the first open-label study completely independent of the pharmaceutical industry. Its main objective was to evaluate the clinical benefit of treating spasticity after stroke with BoNT-A injections as part of routine clinical practice. It investigated the effect of several cycles of BoNT-A injections on the post-stroke upper limb in several hundreds of patients followed over 1 year, with regular and detailed assessments of impairment, activities and indirect participation of quality of life.

2. Methods

2.1. Study design

Botuloscope was a multicentric observational study funded by the French health ministry performed in 11 rehabilitation departments in France from January 2004 to December 2006. This was a pragmatic open prospective cohort study with a 1-year follow-up (visits at inclusion, at 1 and 3 months, then at 1 year; M0, M1, M3, M12, respectively) by expert teams in spasticity management. Participants were eligible if they were ≥ 18 years old, could give their consent, and, in accordance with the clinical judgment of the practitioner, required BoNT-A treatment for post-stroke upper limb spasticity. Individuals with associated muscular disease or receiving curare, amino glycoside antibiotics, amino-quinolones, or cyclosporine were excluded. According to French law, the local ethics committee approved the study. All participants provided written informed consent before inclusion. At the time of the study, observational studies were not yet systematically declared on a WHO-compliant registry.

The study was designed to monitor the achievement of therapeutic goals, an approach found relevant in spasticity [8,16]. Before the first injection set, participants were instructed to rank 5 therapeutic goals among a list determined by the panel of principal investigators of all centers. They could add another therapeutic goal if desired. This ranking was made with the physician's help, taking into account both patient expectations and improvement prediction by the clinician. Therapeutic goals were classified as comfort and activities, motor function, and reduction in oral drug use (detailed in results).

On the basis of clinical examination and individual therapeutic goals, physicians freely determined target muscles, number of injection sites, the formulation (onabotulinumtoxin A or abobotulinumtoxin A) and the appropriate dose. Then physicians were free to propose and perform a second and a third injection set depending on the clinical results of the previous one (at least 4 months later) and on patients' expectations and wishes.

2.2. Collected data

Relevant data were collected on participant demographics, disease description, stroke, and process of care before the inclusion. All participants underwent a clinical assessment before the first BoNT-A injection set, then at M1 and M3 and finally at M12 after the first injection set.

Assessment was performed by a physiotherapist or an occupational therapist who did not take part in the injections. Muscle tone was assessed by the Modified Ashworth Scale (MAS) [18], with scores ranging from 0 (no increase in muscle tone) to 4 (limb segments rigid in flexion or extension), on shoulder abductor muscle groups and flexor muscle groups of the elbow, wrist and fingers. Passive range of motion (pROM) was assessed at the slowest possible speed with a manual goniometer with participant arms mobilized in relation to the movement of joint segments. At M0 and M12, participants were asked about pain at rest as well as when the upper limb was mobilized. Pain was quantified on a visual analog scale (VAS, 0–10). Upper limb motor function was assessed by the motricity index (MI) [19,20]. Upper limb activities were assessed by the Frenchay Arm Test (FAT) [21], scored as pass (= 1) or fail (= 0), with 1 point considered the minimum clinically important difference (MCID) [22].

Individual satisfaction (i.e., perception of achievement for each goal) was assessed at each visit by using a VAS ranging from 0 (no change) to 10 (total achievement of the goal). Quality of life was evaluated by the Reintegration to Normal Life Index (RNLI) [23] twice: at M0 and M12. Each of the 11 questions was scored from 0 (no problem with item) to 2 (total disagreement with item) given a total score ranging from 0 (best quality of life) to 22 (worst quality of life).

Safety data collected concerned target muscles, doses, injection techniques, and adverse effects systematically sought by a structured interview with the physician who used a short question list dealing with local and general effects.

2.3. Statistical analysis

All statistical analyses were performed by using SAS v9.1 (SAS Inst., Cary, NC). Participants who withdrew or were lost to follow-up were excluded from the analysis. Continuous data are expressed as mean (SD) and median (Q1–Q3) for ordinal data and categorical data as number (%). Because indications for injections and pattern of muscle injected were freely determined by the physician and could vary from one cycle to the other, comparisons between pre- and 1-, 3-, and 12-month post-BoNT-A injection data involved the McNemar test for paired categorical data (MAS) and the Wilcoxon signed rank test for paired continuous data (pROM). MI and FAT results were analysed with the Friedman test. Statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

3. Results

Over a 2-year period, 395 individuals were included: 65 (16%) did not complete the 1-year follow-up: 34 were lost to follow-up (9%), 15 (4%) decided to withdraw, 9 (2%) stopped the study for medical reasons unrelated to the protocol, and 7 died (2%). In total,

Table 1
Baseline patient characteristics ($n = 330$).

Male	197 (60%)
Age (years), mean (SD), range	53.7 (13.7), 17–83
Type of stroke[a]	
Ischaemic	232 (71%)
Haemorrhagic	97 (29%)
Duration since the stroke (years), mean (SD), range	5.1 (7.3), 0.5–48.6
Side of paresis[a]	
Left	182 (55%)
Right	147 (45%)
Aphasia[b]	99 (30%)
Apraxia[b]	21 (6%)
Neglect[b]	70 (21%)
Medical history	
Anti-spastic treatment	224 (68%)
Ongoing treatment at inclusion	184/224 (82%)
Physiotherapy	304 (92%)
Occupational therapy	64 (19%)
Previous botulinum toxin injection	149 (45%)

[a] $n = 1$ missing data.
[b] According to the clinical opinion of physicians.

330 individuals completed the study and were followed for 1 year (83%). Their main clinical characteristics are in Table 1: mean (SD) age 53.7 (13.7) years, 60% males, chronic hemiparesia (left 55%), and inclusion at a mean of 5.1 (7.3) years after stroke (71% with ischaemic stroke). The spasticity was severe, with most participants showing difficulties in mobilizing joints: at M0, the median MAS score was 4 (3 to 5) for shoulder abductors, 4 (3 to 4) for elbow flexors and wrist flexors and3 (2 to 4) for forearm supinators. The upper limb function and related activities were relatively poor: median MI score 40 (24 to 60), with 75% of participants unable to perform any of the 5 tasks of the FAT at M0 [median score 0 (0 to 1)]. At M0, most participants were receiving oral treatment for spasticity (68%) and regular physiotherapy (92%); 45% had previously received BoNT-A injections.

Selected therapeutic goals are presented in Table 2. The primary goal was improving comfort and activities in daily life for 63% of participants, whereas improving function was the primary goal for 36%. Most individuals selected several therapeutic goals. As expected, getting the member position less uncomfortable, improving comfort, permitting easier dressing, and improving hand hygiene were frequent well-being goals, regardless of their priority. Of note, one third of participants selected decreasing pain as the therapeutic goal. Functional therapeutic goals for upper limb injections concerned prehension (49%) and also surprisingly balance and gait (24%).

The number of injection sessions during the year of treatment was 804, with an average of 2.4 injection sets per individual. Almost all individuals were injected several times during the year: 3 injections (55%) or 2 injections (33%). Procedures for achieving injections and targeted muscles are summarized in Table 3. The most frequently injected muscles were flexors of elbow, wrist and fingers and forearm pronators. The mean number of muscles injected per procedure was 5.5, most often with a guidance by electrostimulation, without analgesia. Both formulations were equally injected, with the following mean doses: abobotulinumtoxin A 875 units (SD 318; maximum dose 1000 units) and onabotulinumtoxin A 214 units (SD 92; maximum dose 400 units).

Adverse effects were reported for 150/804 (19%) injection sessions: 8% were related to the injection technique (pain or small haematoma at injection sites), 8% muscle pain or transitory fever, and 6% fatigue and muscle weakness. Their occurrence was not related to brand name or dose. All these adverse effects were minor, easily controlled by symptomatic treatment and never required hospitalization. No case of botulism-like symptoms of diplopia or dysphagia was reported.

The effect of injections on impairment is presented in Fig. 1. After the first injection session until the end of follow-up, spasticity was reduced on the MAS between M0 and M1 by a median of 2 points for wrist flexors (-2 to -1; $P < 10^{-3}$) and 1 point for elbow flexor (-2 to 0; $P < 10^{-3}$), forearm muscles (-2 to -1; $P < 10^{-3}$) and shoulder abduction (-1 to 0; $P < 10^{-3}$) (Fig. 1A). In parallel, pROM was increased by 16° (13 to 19; $P < 10^{-3}$) in wrist extension, 12° (9 to 15; $P < 10^{-3}$) in shoulder abduction, 3° (1 to 6; $P < 10^{-3}$) in elbow extension, and 8° (5 to 12; $P < 10^{-3}$) in forearm supination (Fig. 1B). The prevalence of pain at rest decreased from 29% at M0 [97/330; median VAS 4.6 (3 to 6)] to 19% at M12 [63/330; 4.1 (3 to 6); $P < 10^{-4}$]. The prevalence of pain when the physician mobilized the upper limb decreased from 64% at M0 [211/330; median VAS 5 (3.5 to 7)] to 43% at M12 [143/330, 5 (3.8 to 7); $P < 10^{-4}$].

Upper limb function and activities were improved. MI and FAT scores were significantly better ($P < 10^{-4}$) at M1, M3, and M12 than at M0 but with small and non-clinically relevant differences: median gain of 0 points and mean 0.2 points on a 5-point scale for the FAT (MCID = 1) and mean gain of 4 points on a 100-point scale for the MI (MCID = 12). These small improvements in the whole cohort masked strong improvements in each individual. Fig. 2 shows much greater improvements in motor function (mean MI

Table 2
Therapeutic objectives chosen among a list determined by the panel of investigators ($n = 330$). The priority ranking was made with the physician, taking into account both patient and clinician expectations. The first column shows the number of patients who chose the objective whatever its ranking.

	Not sorted $n = 330$	Sorted by decreasing priority				
		1st $n = 330$	2nd $n = 314$	3rd $n = 267$	4th $n = 192$	5th $n = 99$
Motor function						
Improve upper limb function	163 (49%)	99 (30%)	27 (9%)	20 (7%)	14 (7%)	3 (3%)
Improve gait and balance	78 (24%)	19 (6%)	25 (8%)	17 (6%)	11 (6%)	6 (6%)
Comfort and activities						
Getting the member position less uncomfortable	198 (60%)	60 (18%)	56 (18%)	49 (18%)	14 (7%)	19 (19%)
Improve comfort	190 (58%)	38 (12%)	64 (20%)	39 (15%)	32 (17%)	17 (17%)
Permit easier dressing	170 (52%)	34 (10%)	54 (17%)	52 (19%)	25 (13%)	5 (5%)
Improve hand hygiene	148 (45%)	33 (10%)	40 (13%)	33 (12%)	30 (16%)	12 (12%)
Decrease pain	105 (32%)	30 (9%)	21 (7%)	26 (10%)	23 (12%)	5 (5%)
Improve aesthetic style	76 (23%)	8 (2%)	10 (3%)	15 (6%)	26 (14%)	17 (17%)
Improve sleep	17 (5%)	1 (0.3%)	1 (0.3%)	6 (2%)	2 (1%)	7 (7%)
Decrease spasm	25 (8%)	6 (2%)	8 (3%)	3 (1%)	6 (3%)	2 (2%)
Daily care and management						
Decrease in oral treatment	10 (3%)	0 (0%)	2 (1%)	4 (1%)	1 (0.5%)	3 (3%)
Others	24 (7%)	2 (0.6%)	6 (2%)	3 (1%)	8 (4%)	3 (3%)

Table 3
Characteristics of the 804 sessions of botulinum toxin type A (BoNT-A) injections: procedure and targeted muscles.

Injected muscles	
Flexor digitorum superficialis	645 (80%)
Flexor digitorum profundus	501 (62%)
Biceps brachialis	435 (54%)
Flexor carpi radialis	421 (52%)
Brachialis	340 (42%)
Flexor policis longus	318 (40%)
Pectoralis major	277 (34%)
Palmaris longus	271 (34%)
Pronator teres	265 (33%)
Brachioradialis	245 (30%)
Flexor carpi ulnaris	193 (24%)
Pronator quadratus	38 (5%)
Deltoideus	28 (3%)
Sub-scapularis	15 (2%)
Other	290 (36%)
Number of muscles injected per session, mean (SD)	5.5 (2.4)
Number of injections per muscle, mean (SD)	1.8 (0.6)
Injection guidance[a]	
EMG stimulation	744 (93%)
EMG detection	167 (21%)
Drug injected	
Number of sessions with onabotulinumtoxin A	405 (50%)
Injected dose (units) of onabotulinumtoxin A, mean (SD)	214 (92)
Number of sessions with abobotulinumtoxin A	399 (50%)
Injected dose (units) of abobotulinumtoxin A, mean (SD)	875 (318)
Analgesic protocol[b]	87 (10%)
Nitrous oxide	76 (87%)
Anxiolytic or analgesic	3 (3%)
Analgesic cream (lidocaine patch)	2 (2%)

EMG: electromyography.
[a] At the time of the study, ultrasonography guidance was not used.
[b] $n = 5$ missing data.

gain 7 points) and activities (median FAT gain 2 points) for individuals who chose "improve upper limb function" as the first goal than others, over the MCID [1] for the FAT ($P < 10^{-2}$).

Individual satisfaction corroborated these findings (Table 4). Globally, participants were satisfied after the first injection, and their satisfaction lasted during the whole year of treatment. The goal that was best achieved after the first BoNT-A session was "improving hand hygiene" [median VAS 6.0 (3.4 to 7.3)]. The goal "decrease pain" had the highest Q3 at M1, M3, and M12, which indicates that 25% of participants perceived a very strong pain release (VAS $\geq$ 7.6 at M1 and M3, VAS $\geq$ 8 at M12). Pain release was also the best-achieved goal at the end of the 1-year follow-up. Conversely, the goal least achieved during the whole year was "improving upper limb function": It had the lowest median (3.0) and also the lowest Q1 at M1 (0.8), M3 (1.0), and M12 (0.0), which indicates the deception of some participants who expected a functional improvement of the upper limb. Even unexpected goals such as improving gait and balance by treating upper limb spasticity met objectives in terms of satisfaction. Participants who had prioritized this objective felt that their gait and balance abilities were improved 1 year later [median VAS 5.4 (3.5 to 7.0)]. Depending on the evaluation period, 10% to 15% of participants reported no improvement in any goals they had first selected.

The median RNLI score significantly decreased from 8 (4 to 11) to 6 (3 to 10) during the year of treatment ($P < 10^{-4}$), which indicates substantial improvement in quality of life.

These positive results were associated with a reduced number of participants taking oral anti-spastic drugs — 56% at M0 vs. 50% at M12 ($P < 10^{-2}$) — as well as reduced number taking oral analgesic drugs: 25% at M0 vs. 17% at M12 ($P < 10^{-3}$).

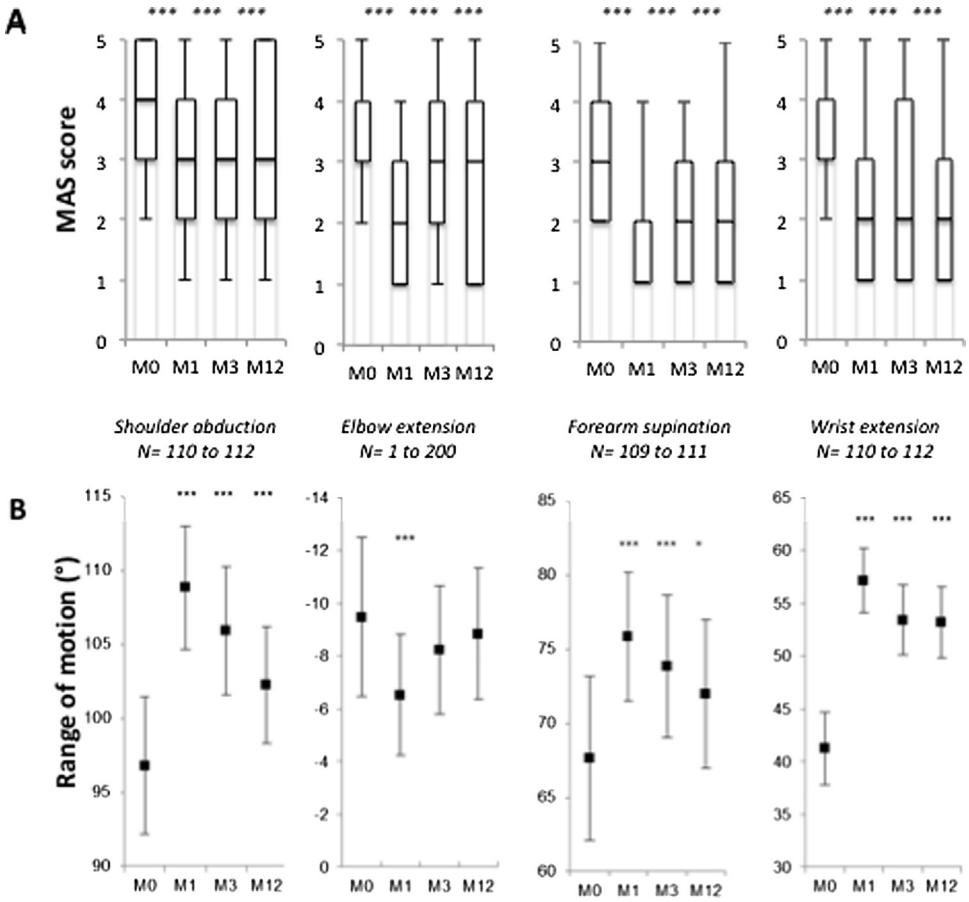

Fig. 1. Spasticity impairments at baseline (M0) and at 1, 3 and 12 months (M1, M3, M12) after inclusion. A: Modified Ashworth Score (median [Q1–Q3]); B: passive range of motion (mean [95% CI]). CI: confidence interval.

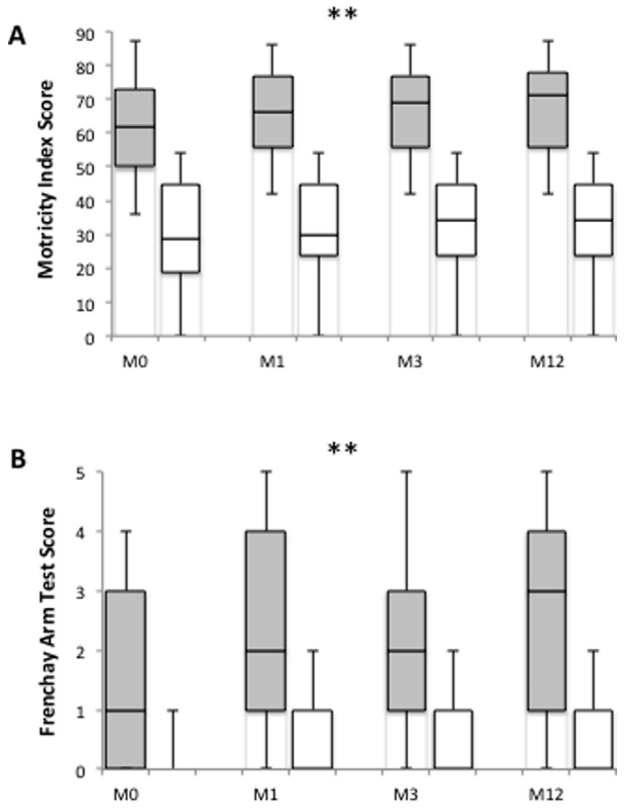

Fig. 2. Time course of Frenchay Arm Test. A: and motricity index; B: comparison between patients with "improve upper limb function" as the first objective of treatment ($n = 99$, grey) with others: a first objective of treatment in "comfort and activities" category or "improve gait and posture" ($n = 231$, white box). Horizontal line is median, box edges are Q1 and Q3 and whiskers are range. There is a significant difference between groups at month 0 (M0) ($P < 10^{-4}$). The improvement in Frenchay Arm Test score and motricity index is significantly greater with "improving upper limb function" as a first objective as compared with the other objectives ($P < 10^{-2}$).

4. Discussion

4.1. Previous open-label cohorts

Botulinum toxin is now a first-line post-stroke spasticity treatment. The literature is abundant, but few studies reach high-quality standards. Recent systematic reviews on post-stroke upper limb spasticity [1–4] highlight the weakness of publications dedicated to BoNT-A treatment. Among 22 randomized controlled trials identified, 19 analyzed the effects of a single session of BoNT-A injection; 12 trials included fewer than 50 patients. Only 7 [7–13] met the highest international quality standards (i.e., multicentric randomized double-blind trial). Among these latter trials, 2 had a reasonable sample size (> 100 individuals) [8,13], and only 1 had a large sample size (> 200) [12].

In total, 51 open-label cohorts were retrieved from international databases: 43 had a small sample size (< 50 individuals). Only 4 open-label studies followed large sample sizes of 279 [14], 333 [15], 456 [16] and 757 individuals [17], over several cycles of injections. Most studies were funded by the pharmaceutical industry. BoNT-A injections appeared to be effective for reducing muscle tone, improving passive upper limb mobilization and nursing [8] but failed to show any efficacy on active upper limb function [13,15,24,25].

The Botuloscope cohort was comparable to other cohorts of individuals with post-stroke spasticity in terms of stroke characteristics [12,15,26,27] with pronounced motor impairments and very limited upper limb function. BoNT-A injection patterns followed the usual distribution described for upper limb post-stroke spasticity [14,28,29], mainly targeting flexor muscles (elbow, wrist, fingers), with great variability in dose and number of injections among individuals. This is one of the major interests of open-label studies to monitor the wide range of use of BoNT-A, in line with the diversity of therapeutic goals and real-life practices.

Botuloscope is the first open-label study that is independent of the pharmaceutical industry and recruited a large sample of individuals (330 followed over 1 year), which advocates for the generalizability of our results. The study confirms that BoNT-A injections reduce muscular overactivity and improve pROM, which facilitates nursing care and makes life less uncomfortable. It strengthens the relevance of modern concepts in spasticity treatment, pointing out the variety of objectives, to be defined by consensus between the patient and physician [26,30]. Overall, Botuloscope reveals that motor function is strongly improved in individuals for whom this was the primary objective. In these individuals as in others, Botuloscope also reveals enhanced quality of life after 1 year of BoNT-A treatment. Botuloscope also stresses the high prevalence of pain in spastic patients, leading to expectations that BoNT-A injections alleviate pain.

Although spasticity was attenuated and pROM enhanced, gains were clinically limited and very close to the reliability and MCID of these measures (1 point for the MAS [31], 11° for shoulder abduction pROM [32], 7° for elbow extension pROM and 8° for forearm supination pROM [33]): 1 point on the MAS and 5–10° for joint mobility. This weak improvement questions the part injections play in global improvement including quality of life [34]. The functions and activity-related gain were similarly limited: 4/100 points for the MI and 1/5 points for the FAT. Usual interpretations of these limited improvements refer to the lack of precision and responsiveness and the non-linearity of these scales [20,21]. Another explanation that holds for Botuloscope refers to the chronic phase several years after the stroke, which would limit

Table 4
Evaluation of the main therapeutic objectives (whatever their priority order) at 1, 3 and 12 months after BoNT-A injection.

	VAS score (0–10)		
	1 month	3 month	12 month
Getting the member position less uncomfortable ($n = 180$)	5.4 [3.0–7.0]	5.0 [2.3–6.9]	5.0 [2.7–7.0]
Improve comfort ($n = 170$)	5.0 [3.0–7.0]	5.0 [2.2–7.0]	5.2 [3.2–7.0]
Permit easier dressing ($n = 162$)	4.5 [2.4–6.5]	4.1 [1.5–6.1]	4.9 [2.0–6.4]
Improve upper limb function ($n = 156$)	3.0 [0.8–5.0]	3.0 [1.0–5.5]	3.7 [0.0–6.0]
Improve hand hygiene ($n = 136$)	6.0 [3.4–7.3]	4.5 [2.0–6.0]	5.0 [2.5–7.0]
Decrease pain ($n = 89$)	5.5 [2.0–7.6]	5.3 [3.0–7.6]	6.0 [3.5–8.0]
Improve aesthetic style ($n = 76$)	5.0 [2.5–7.4]	4.0 [2.0–6.5]	5.0 [2.0–7.5]
Improve gait and balance ($n = 72$)	4.3 [0.0–6.9]	4.9 [0.6–6.5]	5.4 [3.5–7.0]

Data are median [Q1–Q3]; VAS: visual analog scale.

the potential for improvement. An alternate explanation might be the wide variety of therapeutic objectives, possibly very different among individuals. This variability within the cohort may explain the contrast between low average functional gains and good individual satisfaction.

4.2. Individual satisfaction

Therapeutic expectations were more frequently expressed in terms of well-being and quality of life than functional improvement of the spastic upper limb. These findings agree with two main publications on the topic, the randomized placebo double-blind trial by Brashear et al. [8] and the largest open-label study by Elovic et al. [14]. Both studies used the Disabling Assessment Scale as a principal criterion and found beneficial effects of upper limb BoNT-A injections for items dealing with comfort and nursing cares. The VAS is an appropriate tool to assess individual satisfaction after spasticity treatment [17,35]. It is independent of the nature of therapeutic objectives. In Botuloscope, half of the participants estimated that their main therapeutic goal was achieved by more than 50%. Regardless of the priority order of objectives, results were better for those dealing with well-being and autonomy than function. These general results were likely related to the severity of the motor impairment, the poor functional capacities, and the time since stroke, thereby limiting the possibility to improve function. One cannot expect to improve upper limb function with BoNT-A injections if there is no residual motricity before injection. In contrast, Botuloscope revealed that when improving function was the first therapeutic priority (patient–physician agreement), BoNT-A injections met expectations. Of note, this improvement was obtained even with low doses of BoNT-A and after every injection during 1 year. These findings underline the importance of the physician experience for helping patients determine realistic objectives, an issue rarely pointed out until now [17].

4.3. Pain

Botuloscope is one of the first studies showing several convergent findings concerning pain [15,36]. Pain prevalence was high because 1 in 3 patients selected "pain release" as one of the therapeutic objectives, and 1 in 10 selected this as the primary objective. These novel findings might have been underestimated because physicians were mostly unaware of this issue of pain (study conducted in 2004–2006). Moreover "pain release" was the best-achieved objective at 12 months, regardless of its priority ranking, and 30% of individuals reporting pain at inclusion reported no pain at 1 year. This concerned as much participants feeling pain at rest (contracture or neuropathic pain) as those feeling pain during mobilization (stretch of spastic muscles). Finally, 30% of participants who took analgesic drugs at inclusion stopped this treatment 1 year later. These findings positively affect both clinical practice and the cost-effectiveness balance of BoNT-A.

4.4. Quality of life

Botuloscope is one of the first studies showing an improvement in quality of life of individuals receiving BoNT-A injections for upper limb spasticity after stroke. Among previous studies analyzing the quality of life after BoNT-A injections, 2 did not find any difference using the Stroke Impact Scale [15,34], and 1 found improvement with the VAS of the European Quality of Life (EQ-5D) instrument [14]. Because we hypothesized that a better quality of life would be due to cumulative effects of repeated injections, quality of life was measured only twice in Botuloscope, at M0 and M12. The possibility of a placebo effect or any other bias seems unlikely for several reasons. The gain was substantial. The interval between the first and the second assessment was quite long, and the risk that patients remembered their first answer 1 year later is weak. This positive result was obtained despite a scale (RNLI) supposed to be poorly sensitive to change [23]. This observation argues in favor of a real cumulative effect of repeated injections. All patients had several personalized objectives and were allowed to change them during the 1-year treatment. We assume that patients could feel beneficial therapeutic effects on numerous symptoms, some neglected. Some objectives could be viewed as minor for physicians, but because they were reached at the end of follow-up indicated a sufficient cumulative effect on improving quality of life.

4.5. Adverse effects

At the time of the study, Botuloscope was the first study to comprehensively report adverse effects, by a list prepared a priori. After each injection session, data were systematically collected by face-to-face interviews planned at 1, 3 and 12 months. Although no major adverse effect was reported, we found a prevalence of adverse effects greater than that usually reported in the literature, probably because we systematically searched for events shortly after injections, according to a determined list. Half of the events were related to the procedure: pain during injection, electric stimulation, haematoma. Half were related to drugs but, although in agreement with other studies, were not influenced by the dose of BoNT-A injected [12,37]. This study, the first to analyze adverse effects by brand name, found no difference between the 2 formulations equally used, abobotulinumtoxin A and anabotulinumtoxin A.

4.6. Study limitations

Botuloscope was an open-label study designed and started 15 years ago. However, some findings are novel and others add to the literature. Satisfaction was assessed by a VAS and not by modern tools [16,26,38]. Despite the lack of placebo treatment, the improvement seemed reliable given that 30% of patients were not satisfied at all in terms of at least one of the pre-determined objectives. The non-blinded procedure was compensated in part by assessments performed by independent physiotherapists or occupational therapists, and not by injectors.

5. Conclusions

This is the first open-label study independent of the industry that followed a large sample over 1 year. It showed that treating post-stroke upper limb spasticity with BoNT-A is a complex procedure with various objectives. It strengthens the idea that personalized objectives of treatment magnify the treatment's efficacy. This is the first study to show that treating spasticity with BoNT-A improves quality of life even several years post-stroke. It reveals that BoNT-A is a powerful analgesic drug when pain is related to spasticity. It also clearly points out the need to systematically collect adverse effects, found in almost 1 in 5 patients when appropriately sought.

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Disclosure of interest

The authors declare that they have no competing interest.

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