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Patient Registry of Spasticity Care World

Data Analysis Based on Physician Experience

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Objective: The aim of the study was to report physician experience–based "real-world" treatment patterns with botulinum toxin type A in patients with stroke and traumatic brain injury.

Design: A prospective, multicenter, international observational registry design was used.

Results: Six hundred twenty-seven participants with stroke and 132 participants with traumatic brain injury were assessed and treated by 17 more experienced physicians and 12 less experienced physicians. Due to the limited usage of abobotulinumtoxinA Dysport and incobotulinumtoxinA Xeomin, data were reported on onabotulinumtoxinA BOTOX only. Based on physician experience, onabotulinumtoxinA doses were statistically different with larger mean doses injected by more experienced physicians in the upper limb (59.9[39.0], $P = 0.001$) and in the lower limb (101.8[69.2], $P < 0.001$). Treated deformities significantly differed for both upper limb and lower limb ($P < 0.001$). More experienced physicians showed a larger mean change in Ashworth Scale scores from baseline for the equinovarus/equinus foot and stiff knee ($P = 0.001$ and 0.03). Less experienced physicians showed a larger mean change in Ashworth Scale scores from baseline for the adducted thigh ($P = 0.05$). Less experienced physicians had statistically significant larger change in hand pain scores for clenched fist deformity treatment at follow-up compared with more experienced physicians ($P = 0.01$). Physician experience demonstrated a significant difference on patients reported satisfaction toward their secondary goal with higher scores for more experienced physician ($P = 0.04$).

Conclusions: This international registry provides clinical nuances of treatment based on physician clinical experience in a robust sample size.

Key Words: Botulinum Toxin, Muscle Overactivity, Stroke, Traumatic Brain Injury

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Every year, 15 million people worldwide are adversely affected by a stroke, and according to the World Health Organization, traumatic brain injury (TBI) will surpass by 2020 many other diseases as the major cause of death and disability.[1] Functional problems caused by stroke or a TBI may include paralysis, cognitive and speech changes, and impaired motor control and dexterity as well as abnormal muscle activity that include spasticity, clonus, dystonia, co-contraction, associated reactions, and flexor and extensor spasms as seen in the upper motor neuron syndrome.[2] Spasticity as a motor behavior is a specific physiologic sign that has classically been described by Lance et al.[3] as one component of the upper motor neuron syndrome, distinguishable from other positive features of muscle overactivity (e.g., dystonia, co-contraction). For simplification, all of these abnormal muscle activation patterns are frequently referred to as "spasticity."[4] We have elected the term spastic muscle overactivity as a more encompassing and better suited term.[5–7] Muscle overactivity can result in multiple patterns of clinical motor dysfunction affecting the lower (e.g., equinovarus, stiff knee, striatal toe, adducted thighs, flexed hip) and/or upper limbs (flexed elbow, internally rotated shoulder, flexed wrist, clenched fist, thumb-in-palm, intrinsics).[4]

Botulinum toxin has become a widely used biological toxin for a growing number of clinical applications. Clinical trials provide evidence that botulinum toxin can improve symptoms of muscle overactivity when appropriate muscles, doses, and the number of injection sites are selected.[4,7] The proper use of these treatments in a "real-world" setting is not restricted to a regimented dosing structure provided by a clinical trial requires appropriate training and education. As in other

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areas of medicine, physician experience may play a role in care delivery. Physician level of experience may serve as a surrogate in understanding physician practice patterns variation that can inform healthcare services use[8] and reduce physician care variations.[9] Given these information void, we proposed and conducted a global, multicenter, observational study of participants treated with botulinum toxins in patients with stroke- or TBI-related spastic muscle overactivity to generate real-world data. The use of botulinum toxin A varies internationally; onabotulinumtoxinA (onaBoNTA) BOTOX has been approved for use in the United States for many years, whereas abobotulinumtoxinA (aboBoNTA) Dysport and incobotulinumtoxinA (incoBoNTA) Xeomin were only recently approved (2016). The onaBoNTA and aboBoNTA have been in use in Europe for more than 20 yrs, and incoBoNTA was approved only 10 yrs ago. Published registries have presented real-life data on the treatment of spasticity with onaBonTA[10–12]; however, to our knowledge, this is the first international registry that includes real-world longitudinal data that include baseline, injection, and outcomes when using the various botulinum toxins available while considering physician experience for its stratification and analysis. Despite the available evidence of botulinum toxin use, it is unclear whether physician level of experience may play a role in the appropriate delivery of toxin-related care. We hypothesized that the physician experience level may impart differences in care patterns in the use of botulinum toxin for spasticity management. Specifically, we focus on analyses based on the physician experience related to the identification of the problem presentation, muscle selection for treatment, formulation selected, dosing, injection technique, dilution, and number of injection sites. We also recorded the primary and secondary goals for treatment as selected by the patient and agreed upon by the treating physician. The primary purpose for this registry was to describe treatment patterns and clinical presentation used in these populations from a global perspective on the basis of clinical experience. Ashworth Scale (AS), presence of pain, and patient-reported satisfaction after treatment were stratified on the basis of reported physicians' clinical experiences to determine treatment effect.

METHODS

PROS World is a prospective, multicenter, observational registry that enrolled participants with stroke and TBI from 29 sites (17 sites from the United States and 12 international sites) from the following countries: Italy, Germany, Spain, Australia, Israel, Canada, Argentina, Mexico, and the United States. This international registry is an extension of PROS Care a previously published study focused only on data from the United States.[10] Because the aim of this study was to describe the use of approved botulinum toxin A products in participants with stroke or TBI, the sample size was determined as the number of participants who could be recruited within a set time frame. A comprehensive description of the methods of PROS Care and the electronic registry used for data collection has been previously published.[10]

The study was approved by the respective institutional review boards at each participating center. If no institutional review board was available for the site, a central institutional review board was used. Written informed consent was provided by all participants or caregivers. This study conforms to all STROBE guidelines and reports the required information accordingly (see Checklist, Supplemental Digital Content, http://links.lww.com/PHM/A446).

Physician Experience

Physician recruitment of PROS World was completed through outreach to physicians in the physical medicine and rehabilitation and neurology fields using botulinum toxin for spasticity and muscle overactivity treatment and interested in participating. When identified, each physician completed an online questionnaire about their clinical experience responding to the following seven questions: (1) years of residency training completion, board certification, year board certified, number of years managing patients with spastic muscle overactivity with injectable chemodenervating and neurolytic agents, training field, type and years in specialty practice, and number of patients with spastic muscle overactivity treated in the previous year.

After completion of the questionnaire, the principal investigator determined the experience level using a predetermined set of parameters to differentiate and assign them to one of two groups (more experienced physicians [MEP] and less experienced physicians [LEP]). Less experienced physicians were registered as currently evaluating and treating at least 25 to 49 patients/yr and with less than 4 yrs of experience managing spastic muscle overactivity with injectable chemodenervating agents. More experienced physicians were registered as currently treating more than 50 patients/yr and have more than 5 yrs' experience treating spastic muscle overactivity with injectable chemodenervating agents.

Participants

Participants had spastic muscle overactivity due to stroke or TBI of at least 2 months duration treated with onaBoNTA, and both naive and repeat treatments participants were enrolled if they met the inclusion criteria. The exclusion criteria were spinal cord injury or other neurodegenerative disease, anoxia, cerebral palsy; neurological injury before the age of 6 yrs; documented allergies or immunoresistance to any BoNTA; diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis or, any other disease that may interfere with neuromuscular function; profound atrophy of the muscles in the target area(s) of injection; pregnancy; and any other condition or situation that, in the investigator's opinion, could place the participant at risk, confound the registry data, or interfere significantly with participant inclusion in the registry.

Study Design

All investigators and research assistants were trained in the use of a custom-developed web-based registry previously described[10] before the site's registration. Participants received onaBoNTA, aboBoNTA, and incoBoNTA for the treatment of muscle overactivity in the affected limb segment. Participants were enrolled in the study for up to 6 mos and received at least one injection and one follow-up. Because the study design is observational, the amount of repeated treatment injections was based on clinical need and at the discretion of the treating

physician. The study allowed independence to physicians in the selection of the treatment agent, dose, and muscle selection.

Baseline Visit

Upon informed consent from each participant, the baseline visit was undertaken on the basis of the routine standard of care at each clinic. Review of the inclusion/exclusion criteria was required to determine eligibility to participate. Before each participant's treatment, demographic data and clinical assessment were obtained. The AS scores,[13] the 0 to 10 Numeric Rating Scale for pain, and a modified version of the Goal Attainment Scaling[14] specifying patient desires and treatment goals were administered. Treatment goals were organized using the classification of (upper motor neuron) syndrome-related problems proposed by Esquenazi and Mayer.[6] Participants were asked at their baseline visit to identify and prioritize their treatment goals. Treatment goals were agreed upon by both the site principal investigator and the patient or a surrogate. Participants prioritized their selection of a single goal as wanting relief from a specific symptom or type 1 (e.g., pain, stiffness, clonus, spasm flexor, spasm extensor, disfigurement, spasm frequency and fatigue), wanting to improve a specific passive function or type 2 (e.g., increase range of motion, hygiene, dressing, improve skin condition, and feeding), or wanting to improve a specific active function or type 3 (e.g., walk, climb steps, stand/transfer for the leg and release and transport, grasp and reach for the arm). For each treatment session with onaBoNTA, injection details regarding muscles injected, dosage, dilution, number of injections, needle length, and method of injection guidance were recorded.

Follow-Up Visit

Collection of follow-up data continued for a period not to exceed 6 mos after the most recent treatment. At each follow-up visit, participants were interviewed about their overall satisfaction with their treatment as well as questioned about their treatment goals. If pain was selected as a treatment goal at their baseline visit, the participant rated their level of pain at the follow-up for each of the treated areas. Data entry was made about reported adverse effects. No additional visits were required beyond what was normally expected for the participant's medical care.

Study Endpoints

Ashworth Scale

Muscle tone was evaluated by the principal investigators at baseline and all follow-up visits using the 5-point AS (0, none, no increase in muscle tone to 4, very severe, limb rigid in flexion or extension).[13] The assessment is applied manually to the desired joint to determine the resistance of muscle to passive stretch at a constant velocity. For the purpose of this observational study, the AS was used to signify the presence of a biologic effect of the injected agent.

Pain

The Numeric Rating Scale was selected to assess pain intensity, because of its ease of use and evidence of consistent results across a wide range of languages and cultures.[15–17] If pain was identified as an agreed-upon goal, the location and level of pain at baseline and at all follow-up visits were rated using the 0 to 10 Numeric Rating Scale (0, no pain; 10, worst possible pain).

Goal Attainment Scale–Satisfaction

At the baseline visit, the participant and physician determined the primary and/or secondary goals as type 1, type 2, and type 3. At the participant's follow-up visit, the overall response to treatment using modified Goal Attainment Scaling −2 lost a lot of ground toward goal to 2, and complete achievement of goal was obtained. Participants also rated their satisfaction using this scale: (−2, very dissatisfied; 2, very satisfied). There were no baseline measurements in these domains.

The questionnaire was administered at all centers at each follow-up visit using an electronic standardized format. If the participant was seen in the clinic, the participant answered a series of verbal questions. If the participant was not seen in clinic for follow-up, the questionnaire was administered over the telephone. The same questions were asked to assure consistency with what the participants understood was being asked. The database was stored centrally and contained alarms to assure that all data acquisition was completed.

Protocol Approvals and Informed Consent

Each participating center obtained institutional review board or ethics committee approval locally, and written informed consent was obtained from each participant or their caregiver before recruitment in the study.

Statistical Analysis

For categorical and ordinal variables, numerator, denominator, percentages, and 95% confidence intervals are presented. For continuous variables, descriptive statistics (n, mean, median, SD, minimum and maximum) are presented. Missing data were not included in the analyses.

R software Version 3.2.1 was used for all analyses (R Core Team (2015), R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org).

RESULTS

A total of 29 sites enrolled 757 participants between December 2006 and November 2014. The United States reported the largest participant enrollment (Fig. 1).

Public insurance was the most common insurance in both groups (Table 1).

Participants included 627 persons with stroke and 132 persons with TBI. A total of 17 MEP and 12 LEP contributed to the registry. The analysis included any participant with stroke- or TBI-related spasticity treated with onaBoNTA, aboBoNTA, or incoBoNTA. A total of 645 participants received a follow-up with an average of 78 days from the first contact with 112 missing follow-up data. One hundred ninety participants were injected at the follow-up visit. Eighty-seven percent of the participants received their follow-up in the clinic. Participants with missing data were excluded from the analysis. Table 2 represents participants' etiology history and time interval from onset to registration. Demographic characteristics stratified by

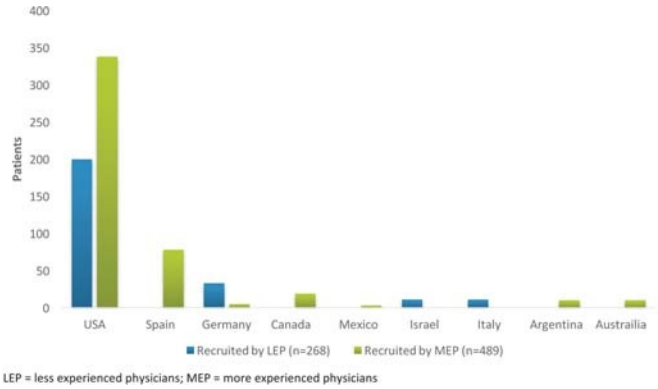

FIGURE 1. Patient enrollment by country.

physician experience are shown in Table 3. A description of the patient population use of oral medications for muscle overactivity and mobility status and other modalities/treatments/devices are shown in Tables 4 and 5. Most participants were able to ambulate and ranged from home ambulation to expanded ambulation. Type 1 symptomatic problems were most commonly presented in both physician groups (Table 6).

Treatment Injections

In the lower limb, 24 injections were performed with incoBoNTA (2.4%) and 10 injections with aboBoNTA (1.0%). Due to the small number of injections for aboBoNTA and incoBoNTA, only onaBoNTA data were analyzed and reported in detail to derive conclusive results. More than three fourth (75.9%) of the patient did not receive chemodenervation treatment in the 6 mos before the current lower limb treatment. A summary of treatment administration for the lower limb is presented in Table 7. Mean doses were statistically different with larger doses injected by MEP (101.8 [69.2]). The number of sites injected was similar in both groups. Dilution, injection method and needle length were significantly different ($P < 0.001$).

In the lower limb, electromyography (EMG) was the most common localization technique for MEP and LEP, whereas MEP used electrical stimulation more frequently than LEP who use anatomical localization. Ultrasound (US) was used more frequently by LEP. There was a statistically significant difference between the physician groups and the lower limb deformities treated ($P < 0.001$). The most commonly treated deformity for both physician groups was the equinovarus/equinus foot for 174 participants (Fig. 2).

In the upper limb, 16% of injections used incoBoNTA and 4 injections used aboBoNTA (<1.0%). Similar to the lower limb due to the relatively small number of injections for aboBoNTA and incoBoNTA, only onaBoNTA data were analyzed and reported in detail to derive conclusive results. More than half (61.2%) of the patients enrolled in the registry did not receive chemodenervation treatment in the 6 mos before their current upper limb treatment. A summary of upper limb treatment administration is presented in Table 8. Mean doses were statistically different with larger mean doses injected by MEP. Less experienced physicians injected more sites compared with the MEPs group.

Electromyography was the most common localization technique used by both MEP and LEP in the upper limb. Less experienced physicians used anatomical localization more frequently and electrical stimulation less when compared with MEP. Ultrasound was used more frequently by LEP. There was a statistically significant difference when considering the physician experience and the upper limb posture treated. The most commonly treated deformity for both physician groups were the flexed elbow and flexed wrist.

Four adverse events were reported, all of which were unrelated. These adverse events included arm fracture, elective surgery followed by inpatient rehabilitation, elective surgery, and CAT scan due to change in mental status. Three serious adverse events were reported, which were unrelated to the study and included forearm hematoma, death, and a stroke.

Outcomes

The purposes of this registry are to report clinical patterns in the treatment of muscle overactivity based on physician experienced, and we also included AS scores that were well

TABLE 1. Patient insurance information

	LEP ($n = 235$)	MEP ($n = 430$)
Public ($n = 438$)	155	283
Private ($n = 194$)	69	125
Self-pay ($n = 29$)	10	19
Insurance nonspecified ($n = 4$)	1	3

LEP, less experienced physicians; MEP, more experienced physicians.

TABLE 2. Etiology history

	Stroke ($n = 627$)	TBI ($n = 132$)
Interval from most recent neurological deficit onset to registration, n	594	132
Mean (SD), mo	66.9 (69.7)	106.8 (117.4)
Second previous stroke—interval from onset to registration, n	58	—
Mean (SD), mo	75.0 ± 81.4	
Third previous stroke—interval from onset to registration, n	15	—
Mean (SD), mo	95.3 (84.6)	

TBI, traumatic brain injury.

TABLE 3. Participants demographic characteristics stratified by physician experience

	Recruited by LEP (n = 268)	Recruited by MEP (n = 489)
Age, mean (SD)	60.7 (15.5)	55.1 (17.4)
Sex, %		
Female	51.2	42.7
Male	48.8	57.3
Body mass index, kg/m^2	27.6 (6.4)	26.1 (4.7)

LEP, less experienced physicians; MEP, more experienced physicians.

understood and in clinical use by all the participating physicians, and pain and patient-reported satisfaction scores as outcomes to determine treatment effects. The AS scores improved within physician groups; however, they were not significantly different between groups. More experienced physicians showed a larger mean change in AS scores from baseline with the equinovarus/equinus foot and stiff knee (P = 0.001 and 0.03). Less experience physicians showed a larger mean change in AS scores from baseline with the adducted thigh (P = 0.05). The AS changes from baseline to follow-up are shown in Figure 2.

Pain scores were selected as type 1 symptomatic treatment goal in 72 participants. One hundred sixty-six participants received pain medications. At baseline, the mean pain score for LEP was 5.9 (n = 40) and 5.7 for MEP (n = 163). At follow-up, the mean pain score for LEP was 1.9 (n = 15) and 4.1 for MEP (n = 16). The change in pain score for the hand was statistically significant (P = 0.01). Less experienced physicians achieved larger pain reduction compared with MEP. In general, most participants reported they were "somewhat satisfied" with their overall treatment or "made some progress toward their treatment goal" for their primary goals. Physician experience did not produce a significant difference in overall patient satisfaction or in patients' primary goal improvement. However, physician experience resulted in a significant difference on patients reported satisfaction toward their secondary goal with higher scores for MEP (P = 0.04).

DISCUSSION

In this observational, international, multicenter study, the main objective was to document real-world patterns of treatment by physicians with different levels of experience (LEP and MEP) in the use of BoNTA. PROS Care/World 28 investigators in 26 worldwide sites enrolled 757 participants with stroke and TBI. Data included 2975 treatment injections for the upper limb and 1004 for the lower limb.

There are many similarities in the patient demographics; however, there are some differences in Ashworth rating because of the complexity of patients in each group. The use of the AS in this study was intended to determine pharmacological effect and should not be seen as an outcome measure. The AS along with the Modified Ashworth Scale is the most used rehabilitation scales to measure tone. Both have limitations,

TABLE 4. Oral medications for muscle overactivity used during the study

	No. Patients on Medication	
Oral Medications	**LEP (n = 87)**	**MEP (n = 156)**
Baclofen (n = 13)	47	85
Tizanidine (n = 73)	26	47
Benzodiazepines (n = 25)	9	16
Dantrolene (n = 13)	5	8

LEP, less experienced physicians; MEP, more experienced physicians.

TABLE 5. Mobility status and other modalities/treatments/devices used for the 6 mos before study enrollment

Mobility/Modalities/Treatments/Devices	LEP	MEP
Ambulation level		
Home nonambulatory (n = 114)	40	74
Home ambulation (n = 287)	102	185
Limited community ambulation (n = 247)	88	159
Community ambulation (n = 194)	69	125
Expanded community ambulation (n = 197)	70	127
Lower limb orthotics		
Ankle and foot (n = 315)	112	203
Knee, ankle, and foot (n = 41)	15	26
Knee (n = 6)	2	4
Upper limb orthotics		
Wrist and hand (n = 184)	65	119
Wrist (n = 20)	7	13
Elbow and shoulder (n = 25)	9	16
Assistive device		
Cane (n = 326)	116	210
Walker (n = 81)	29	52
Crutch (n = 15)	5	10
Other interventions		
Splinting (n = 76)	27	49
Casting (n = 32)	11	21
Oral prescription medications		
Pain (n = 166)	59	107
Seizure (n = 149)	53	96
Antihypertensive (n = 383)	136	247
Diabetes (n = 107)	38	69
Other (n = 454)	161	293
Intrathecal pump		
Baclofen (n = 32)	11	21
Formal therapies		
Physical therapy (n = 400)	142	258
Occupational therapy (n = 268)	95	173

LEP, less experienced physicians; MEP, more experienced physicians.

TABLE 6. Type of goal selected in agreement agreed upon by both physician and participant

	LEP	MEP
Type 1, symptomatic (n = 527)	184	343
Type 2, passive function (n = 324)	115	209
Type 3, active function (n = 406)	144	262

Participants were able to selected more than one type of goal.
LEP, less experienced physicians; MEP, more experienced physicians.

TABLE 7. Summary of lower limb injections with onaBoNTA

	LEP (n = 374 Injections)	MEP (n = 630 Injections)
onaBoNTA, mean (SD), units	76.4 (49.2)	101.8 (69.2)
No. sites injected per muscle	2.2 (1.2)	2.2 (1.4)
onaBoNTA dilution, % (CI)		
1:1	35.6 (30.7–40.8)	14.0 (11.5–17.0)
2:1	42.4 (37.2–47.7)	72.6 (68.9–76.1)
3:1	7.1 (4.8–10.3)	11.3 (9.0–14.1)
Other	15.0 (11.6–19.2)	2.0 (1.2–3.5)
Needle length, mm		
Min–max	10.0–75.0	10.0–75.0
Median	38.0	50.0
Injection method, % (CI)		
Anatomical	20.3 (16.4–24.9)	3.9 (2.7–5.8)
Electrical stimulation	6.8 (4.5–9.9)	62.8 (58.9–66.6)
EMG	58.5 (53.2–63.6)	28.1 (24.7–31.8)
Other	0.3 (0.0–1.6)	3.8 (2.5–5.6)
US	13.8 (10.6–17.9)	1.3 (0.7–2.6)
Motor point	0.3 (0.0–1.6)	0.0 (0.0–0.6)

LEP, less experienced physicians; MEP, more experienced physicians.

TABLE 8. Summary of upper limb injections with onaBoNTA

	LEP (n = 1175 Injections)	MEP (n = 1800 Injections)
onaBoNTA, mean (SD), units/site	55.3 (34.4)	59.9 (39.0)
No. sites injected per muscle	1.9 (1.2)	1.8 (1.0)
onaBoNTA dilution, % (CI)		
1:1	34.2 (31.5–37.0)	41.3 (39.0–43.7)
2:1	43.9 (41.1–46.8)	44.9 (42.5–47.3)
3:1	6.2 (4.9–7.7)	12.2 (10.7–13.9)
Other	15.8 (13.8–18.0)	1.6 (1.1–2.3)
Needle length, mm		
Min–max	10.0–75.0	10.0–50.0
Median	38.0	38.0
Injection method, % (CI)		
Anatomical	20.4 (18.2–22.9)	6.1 (5.0–7.3)
Electrical stimulation	13.0 (11.2–15.1)	29.6 (27.5–31.9)
EMG	54.8 (51.9–57.7)	59.3 (56.9–61.6)
Other	2.3 (1.6–3.3)	2.6 (2.0–3.5)
US	9.4 (7.9–11.3)	2.1 (1.5–2.9)
Motor point	0.0 (0.0–0.3)	0.3 (0.1–0.7)

LEP, less experienced physicians; MEP, more experienced physicians.

but the AS has been reported to be more reliable than the Modified Ashworth Scale.[18] Based on the data, the population groups are very similar, but the treatment implemented was different. The difference seems to be related to the dosing and number of injections as well as the selection of the limb segment likely indicating increase comfort by MEP with using larger per muscle doses and injecting deeper muscles. Generally, treatment injection patterns were significantly different between the two physician groups. For all injections, MEP used larger doses of onaBontA in fewer sites and for the lower limb with a larger dilution compared with LEP, which may be attributed to their attempt to leverage diffusion of the toxin into larger muscles and being more comfortable using larger doses. Published reports indicate that adult patients with upper limb spasticity benefit from injections of onaBoNTA at total doses ranging from 30 to 400 units.[19–24] Based on literature reviewed in treating adult lower limb spasticity with onaBoNTA, doses ranged from 25[25] to 610 units[26] depending on the muscles injected.[27] When evaluating three doses of onBoNTA (means = 167, 322, and 540 units), it was concluded that the medium dose of 320 units distributed in two to five muscles was optimal.[28] A published international consensus statement[29] recommended a maximum onaBoNTA dose of 400 units in adult lower limb spasticity in a single injection session and a 2010 German consensus paper provided a higher maximum recommended dose of 500 units for onaBoNTA and 1500 units for aboBoNTA to obtain adequate effect without undesirable adverse effects.[30] Dose-dependent effect on spasticity is well

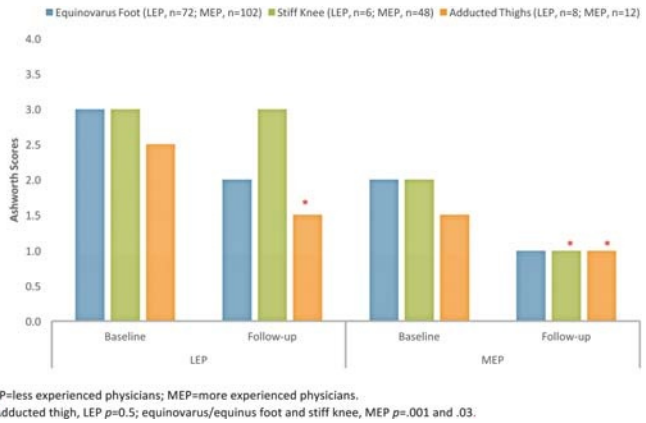

FIGURE 2. Baseline and follow-up Ashworth score by physician group. Illustrated above are the equinovarus foot, stiff knee, and adducted thigh deformities. These deformities present statistically significant change at follow-up. LEP showed a larger mean change in AS scores from baseline to follow-up for the adducted thigh deformity (P = 0.05). MEP showed a larger mean change in AS scores from baseline to follow-up for the equinovarus/equinus foot and stiff knee deformities (P = 0.001 and 0.03, respectively).

known in botulinum toxin spasticity management. Using larger doses per muscle may have been one possible factor in improved outcomes for patients treated by MEP.

Overall, LEP injected more sites compared with MEP in the upper limb. The flexed wrist was the most commonly treated deformity in the upper limb. In the equinovarus deformity, which is the most commonly treated problem in the lower limb, MEP injected more sites compared with LEP (mean number of sites = 3.5 vs. 2.6, respectively). This may be attributed to their level of experience and being more comfortable with their knowledge of functional anatomy.

A variety of techniques have been used to target botulinum toxin injections. Anatomical guidance has been the most common and in this registry, EMG was the preferred technique for both groups when injecting the upper and lower limbs. The advantage of EMG guidance over anatomical localization is the confirmation of the needle's placement within a muscle. Electromyography cannot confirm the muscle identity. Less experienced physicians used US more frequently than MEP. One possibility is that not all centers may have had access to US equipment or training. Because this was an observational study, each physician had the liberty of using their preferred method of localization. Furthermore, to our knowledge, there is no literature to substantiate outcome differences based on localization technique when dose is not controlled. Generally, MEP used longer needles for lower limb injections, likely because MEP frequently included injection of deeper calf muscles (long toe flexors and tibialis posterior) in their treatment plan.

Outcomes

Although not conclusive, onaBoNTA treatment showed some significant and sustained improvements in muscle tone as measured by the AS (equinovarus foot, adducted thighs, and stiff knee). As documented in a preceding publication,[10] the usefulness of monitoring change in the AS score was intended to document the toxin biologic effect. Because all participants had experience in the use of the AS, we selected it over the Modified Ashworth Scale because the AS has been reported to be more reliable than the Modified Ashworth Scale.[18] Although participants reported a significant difference in hand pain reduction between MEP and LEP, there was an overall reduction in pain scores in both groups.

Most participants in this registry reported that they were satisfied or very satisfied with their overall treatment regardless of physician experience. When asked whether the treatment met the participant's secondary goal, there was a significant difference between the physician groups. The difference in sample sizes reported in both primary and secondary goals may affect the results power for the GAS.

Study Limitations

PROS Care/World aimed to collect real-world data and reflects a broad range of treatment practices without the constraints of research trials. However, this is to be expected in an observational, real-world registry. Registry studies often enroll a broader participant population, do not have a protocol-defined treatment or follow-up schedule, and may have variable study duration.[31] Consequently, it is difficult to determine whether a particular dose, distribution, or injection technique had effect optimization because, we did not dictate or control them. For example, dosing strategy may be influenced by previous experiences and the physician comfort level with botulinum toxins treatments. More experienced physicians may be more familiar and comfortable using larger doses of onaBoNTA and able to select muscles based on their experience or education based on published guidelines. Moreover, practice setting was not used to stratify the data. For example, the difference in the use of injection techniques (e.g., EMG, US, etc.) may be due to accessibility of each center to the equipment. Within Europe, the reimbursement for botulinum toxin coverage is highly varied and largely impacted by indications, doses approved on label by local authorities, and insurance coverage.[32] The availability of botulinum toxins varied internationally, and therefore, the data represent those patients treated with onaBoNTA. This was a consequence of the predominate US sites and the timing of the study.

Six-month duration of the study may have impacted our outcomes measure because a single injection of onaBoNTA is less likely to achieve changes in functional outcomes in a chronic population that needs time and longer-term adjuvant interventions to achieve and adjust to new joint biomechanics and new found motor control.[29]

CONCLUSIONS

PROS/World is a clinical data repository that can be helpful as a reference guide for physicians in the treatment of spastic motor overactivity. The data provided can assist physicians with different levels of clinical experience in identifying the most frequent patterns of deformity and in selecting muscles for treatment as well as supporting selected dosing and injection techniques on the basis of real-world experience. A major strength of the study is the robust participants sample size, its international nature, and the stratification based on physician experience that provides clinical nuances of treatment that are not generally obtainable from other study designs and not previously researched.

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