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Management of stroke patients submitted to botulinum toxin type A therapy: a Delphi survey of an Italian expert panel of specialist injectors

M. FRANCESCHINI [1], M. IOCCO [2], F. MOLTENI [3], A. SANTAMATO [4], N. SMANIA [5], Italian Spasticity Study Group*

[1]*Department of Rehabilitation IRCCS San Raffaele-Pisana, Rome, Italy*
[2]*P&RM Unit, Medical & Surgical Sciences Department "Magna Graecia" University, Catanzaro, Italy*
[3]*H.Valduce, Villa Beretta, Costa Masnaga (LC), Italy*
[4]*Department of Physical Medicine and Rehabilitation "OORR Hospital", University of Foggia, Italy*
[5]*Neuromotor and Cognitive Rehabilitation Research Centre Department of Neurological, Neuropsychological Morphological and Movement Sciences University of Verona, Italy*

Background. **Spasticity is a common disabling symptom of several neurological conditions including stroke. Botulinum toxin type A (BTX-A) injection represents the gold standard therapy for focal spasticity. Post-stroke management of patients receiving BTX-A therapy has been variously investigated, but general agreement on how and when to implement rehabilitation is lacking.**

Aim. **To perform a national survey of experts on the most appropriate rehabilitation procedures after BTX-A therapy for the focal treatment of spasticity.**

Design. **The study employed the Delphi technique through the COSMO project (Consensus on Post-Injection Management in Post-stroke Spasticity).**

Methods. **Italian neurologists and physiatrists with experience in BTX-A therapy were selected to participate in the survey. Their anonymous opinions on key issues in treatment strategies in post-stroke spasticity were collected in three sequential rounds facilitated by a web platform. Consensus on a given issue was defined as agreed opinion by at least 66% of the survey participants.**

Results. **In all, 44 Italian experts were involved. Positive consensus was reached on the need to start rehabilitation during the first week after BTX-A injection therapy, with a rehabilitation program comprising both stretching combined with electrical stimulation and exercise therapy. Functional surgery may be considered only after 12-24 months in cases of BTX-A therapy failure. The use of commercial or custom-made orthoses in selected cases was recommended. The appropriate time interval between two BTX-A injections is 3-6 months, and clinical assessment should be performed 1 month after injection.**

Conclusion. **The results of this national survey confirm that clinical experts on the use of BTX-A therapy for spasticity after stroke agree on the need to initiate rehabilitation treatment immediately after BTX-A injection: muscle stretching exercises, eventually combined with neuromuscular electrical stimulation, may enhance the effect of BTX-A therapy. Outcome after BTX-A therapy should be assessed at repeated follow-up visits.**

Clinical Rehabilitation Impact. **This expert panel survey can provide guidance for clinicians in the assessment of patients treated with BTX-A therapy.**

KEY WORDS: Botulinum toxins - Muscle spasticity - Delphi technique - Rehabilitation.

In poststroke patients, spasticity reduction is a major goal to increase the recovery of upper and lower limb movement, reduce pain and deformity, and facilitate personal hygiene and tolerance of orthoses. Spastic and reversible muscle hypertonia management includes several effective procedures, among which botulinum toxin type A (BTX-A) therapy represents the first choice for focal spastic-

*List of authors of the Italian Spasticity Study Group included in the Appendix.

Corresponding author: Dr. A. Santamato, MD, Department of Physical Medicine and Rehabilitation, University of Foggia, "OORR", Viale Pinto, 71100 Foggia, Italy. E-mail: andrea.santamato@unifg.it

ity.[1] BTX-A acts by blocking neuromuscular transmission via the inhibition of acetylcholine release. Since 1989 when the use of BTX-A to treat spasticity was firstly reported,[2] many papers have demonstrated its safety and effectiveness,[3-5] and several international consensus statements on dosage, injection technique, patient selection, and outcome measures have been proposed.[6-8]

In 2009, the Royal College of Physicians, with the British Society of Rehabilitation Medicine, the Chartered Society of Physiotherapy and the Association of Chartered Physiotherapists Interested in Neurology, published national guidelines entitled Spasticity in Adults: Management Using Botulinum Toxin.[9] Several international consensus statements on the assessment, treatment and aftercare associated with the use of BTX-A have been also published.[7, 10] These documents illustrate the management of patients submitted to BTX-A therapy. There is general agreement on the need of physiotherapy, but a general consensus on timing (*e.g.*, whether to start immediately or days or weeks after BTX-A injections), duration (*e.g.*, how long a rehabilitation program should last), type of rehabilitation procedures (*e.g.*, multimodal or single procedure or both), as well as the cost-effectiveness of such treatments has not yet been reached.

Numerous studies have demonstrated an enhanced therapeutic effect on hypertonia reduction when BTX-A therapy is combined with other post-injection treatment techniques;[11-13] however, there is no general agreement on how rehabilitation procedures should be implemented and which are more recommended. The evidence basis for the effectiveness of multidisciplinary approaches is unclear.[6] Previous consensus statements have underlined that the effects of BTX-A should be monitored over time and that standardized assessment and evaluation should be performed at realistic intervals. The team members involved in pre-injection assessment should be included in the post-injection treatment, measurement of outcome, reassessment and review of goal achievement. Clinical re-evaluation post-injection guides management decisions to identify the need for orthotics/splinting, to define whether the treatment goals have been achieved, to verify any adverse effects, to control patient compliance, and to evaluate the need for any further injections. Defining which procedures should be applied to increase the BTX-A effect remains controversial. Indeed, while casting, taping and muscle stretching are considered efficacious, there is no agreement about electrical stimulation. Further studies are recommended to demonstrate the optimal timing, duration, intensity, and combination of multiple physical therapies.

Starting from previously published international guidelines and consensus statements, the aim of this study was to perform a survey among Italian experts on the use of BTX-A to treat spasticity after stroke and on the rehabilitative procedures in common clinical practice after BTX-A injection. The Delphi method was employed to obtain expert opinion in this project entitled COSMO (Consensus on Post-Injection Management in Post Stroke Spasticity).

Materials and methods

Study design

A Delphi technique to obtain national consensus on the management of patients receiving BTX-A therapy was used for this study.

The Delphi technique is an anonymous structured approach, in which information is gathered from a group of participants (*e.g.*, BTX-A therapy experts) through a number of rounds.[14] In the first round, participants evaluate and comment on a number of items listed in a questionnaire: based on the group response, participants then re-evaluate these items in subsequent Delphi rounds. The process is repeated until a consensus has been reached. Usually, this technique is chosen for situations where individual opinions and knowledge are selected, compared, and combined in order to address a lack of agreement or an incomplete state of knowledge. The web-based, anonymous nature of the Delphi technique ensures that a single individual cannot dominate consensus formation and that all participants are equally able to change their opinion in the course of the process.

The referee opinion leaders (ROL) prepare the content of the Delphi statements and supervise the process, but don't participate in the survey. Furthermore, the ROL group is also responsible for selecting the experts participating in the study.[14] These experts should be researchers, lecturers, and experienced physicians who work extensively in the field of interest. In order to guarantee heterogeneity

as an important quality criterion,[15] experts can be identified through an intensive literature search and in the referee members' network. As there are no clear guidelines about the number of experts,[16, 17] in line with a previous study,[18, 19] we considered a panel size of at least 30 experts to be appropriate. Therefore, for this study, a national ROL group composed of neurologists and physiatrists was selected according to their experience in the management of post-stroke spasticity, particularly after BTX-A injections. The clinicians were chosen from among those with experience in evaluating and administering BTX-A therapy in more than thirty subjects/year and with more than three years of experience with this type of therapy. In all, 44 experts were invited by email to give their opinion on clinical control after BTX-A injection, quality of life (QoL) in post-stroke patients treated with BTX-A injection, rehabilitation approach in the post-injection phase, and rehabilitation therapy timing and setting after BTX-A injection. The expert panel was representative of northern (31.9%), central (36.7%) and southern (31.4%) areas of Italy. The expert panel was composed of neurologists (54.5.%) and physiatrists (45.5%).

In the first round of the survey, the questionnaire consisted of 11 statements phrased so as to allow five levels of consensus (1=strong disagreement, 2=moderate disagreement, 3=agreement with high reservation, 4=agreement with minor reservation, 5=strong agreement). Negative consensus was defined as ³66% of responses expressing disagreement with a statement (levels 1+2); positive consensus was defined as ³66% of responses expressing agreement with a statement (levels 3+4+5). Responses were collected until 8 November 2012. The second and third rounds were mainly based on the findings from the earlier ones and consisted of two parts: in the first part, the responses from the former rounds were further verified, and the second part focussed on new aspects. A second list of 8 statements was posted on the web platform from 6 December 2012 to 17 January 2013. After complete review of the opinions of all participants, the ROL group developed 10 final statements for comment which were posted between 12 April 2013 and 17 May 2013. Finally, the consensus survey results were presented at the Italian Physical Medicine and Rehabilitation Congress on 16 October 2013. The Delphi process is illustrated in Figure 1.

Results

The return rate was 100% for the first and second rounds, and 81.8% for the third round.

To the question what type of setting is required for patients treated with BTX therapy, the experts agreed that BTX-A therapy should be administered either on an outpatient (N.=39/44; 88%) or a day hospital basis (N.=34/44; 77%). They also agreed that patients receiving BTX-A therapy should be immediately referred for rehabilitation after BTX-A treatment (N.=34/44; 77%), whereas negative consensus (N.=29/44; 66%) was expressed about starting rehabilitation 2 weeks after injection.

If requested where rehabilitative program after BTX-A therapy should be develop, the answer was that treatment should be performed in a clinic specialized in neurological rehabilitation (within the same unit [N.=40/44; 90%] where BTX-A is administered or another specialized rehabilitation unit [N.=42/44; 95%]). In addition, 86% (N.=38/44) of the experts agreed that post-injection procedures should be performed in a multidisciplinary rehabilitation setting.

To the question who is involved in the rehabilitation after BTX-A treatment? It was strongly recommended that post-injection treatment should be managed by a physiatrist (N.=39/44; 88%) or by a physiotherapist (N.=36/44; 81%) but not by the patient's caregiver.

When asked whether it was possible to involve a trained caregiver in the autonomous treatment of a patient, no consensus (N.=27/44; 62%) was reached. However, the experts agreed that a physiotherapist should carry out post-injection rehabilitation treatment (N.=33/36; 91.7%) and that a trained caregiver can help in completing the treatment performed in the hospital setting (N.=32/36; 88.8%).

Positive consensus was reached on the benefit of rehabilitation activities to enhance the effect of BTX-A, either with muscle stretching alone or combined with electrical stimulation (N.=33/44; 75% and N.=32/44; 72%, respectively).

Another questions were related to the time useful to start rehabilitation after BTX-A injection, and the rehabilitative procedures used. The experts agreed that active (N.=36/44; 81%) and passive (N.=39/44; 88%) mobilization, muscle stretching (N.=42/44; 95%), and open kinetic chain exercises for injected muscles (N.=33/44; 75%) were useful within 2 weeks

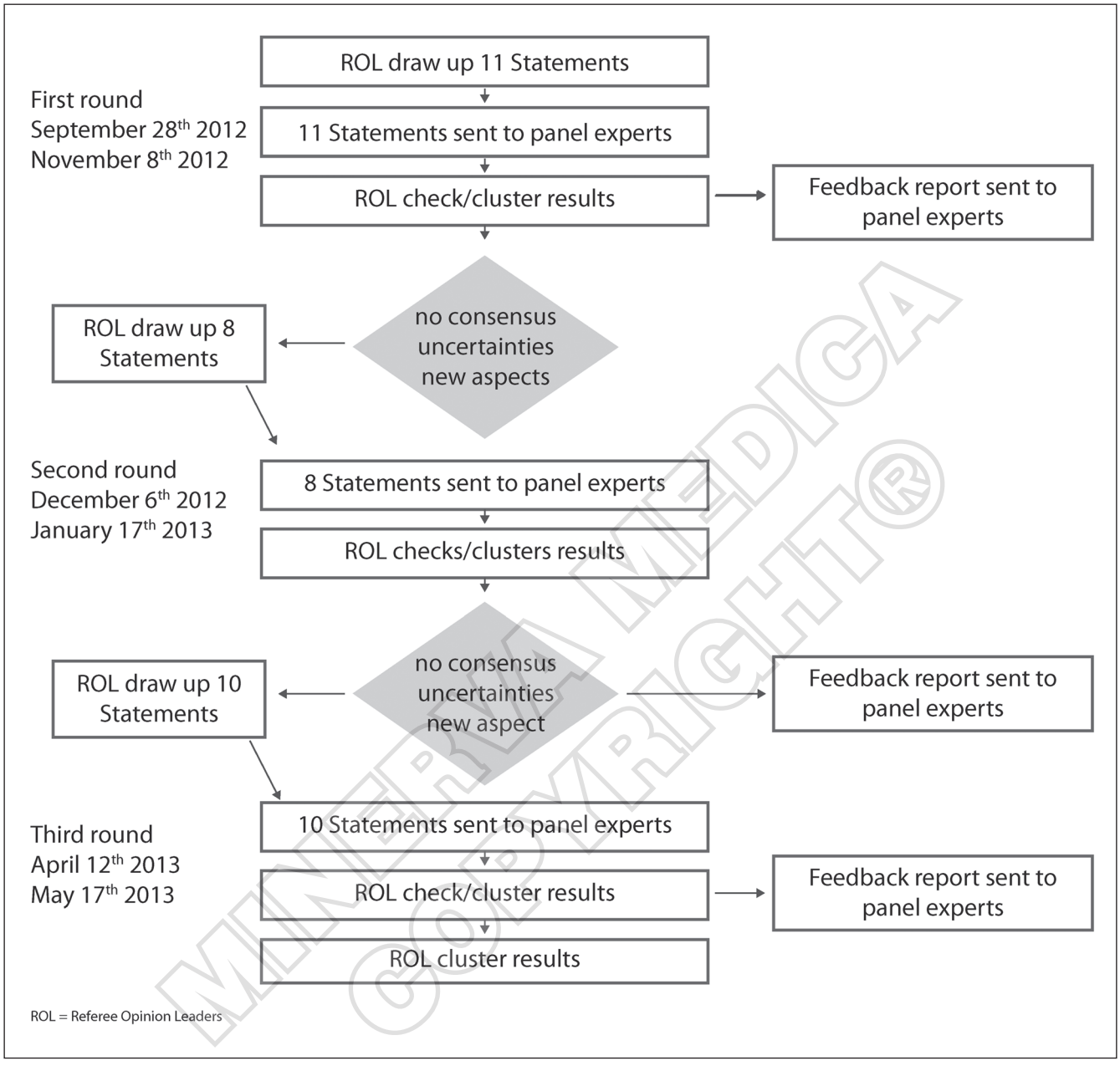

Figure 1.—Flow chart of the Deplhi method (squares=process steps; rhomboids=decision steps).

after injection, whereas activities to increase several tasks can be performed in the third and fourth weeks after BTX-A therapy (N.=41/44; 93%). Moreover, a positive consensus was reached on closed kinetic chain exercises (N.=31/44; 70%), open kinetic chain exercises (N.=37/44; 84%), stretching (N.=35/44; 79%), gait rehabilitation and upper limb mobilization for treated muscles (N.=41/44; 93%) during weeks 3 and 4 after BTX-A therapy.

Consensus was reached on the utility of task-oriented exercises (N.=41/44; 93%) and antagonist muscle reinforcement exercises (N.=32/44; 72%).

Broad consensus was recorded for post-injection electrical stimulation (N.=43/44; 98%) but not for cryotherapy, hyperthermia or ultrasound therapies.

To the question if muscle stretching was used alone or combined with other techniques after BTX-A therapy, a positive consensus was obtained on muscle stretching combined with casting, taping and splinting to enhance BTX-A action (N.=32/36; 89%) and to improve post-stroke lower limb spasticity (N.=34/36; 94.5%) and pharmacological effects (N.=35/36; 97.3%).

The application of pre-formed and custom-made splints for continuous muscle lengthening was considered useful (N.=28/36; 77.8%); such devices can be static or dynamic (N.=29/36; 80.5%).

The employment of a muscle electrical stimulation protocol after injection has been investigated: one session of muscle electrical stimulation applied during the first hour after injection was considered to be an optimal means to enhance the effect of BTX-A therapy (N.=27/36; 75%), whereas no consensus was reached for stimulation delayed 3 or 5 days after BTX-A therapy.

Consensus was unanimous on performing several different types of exercises to improve activities of daily living (N.=36/36; 100%). Rehabilitation techniques should be developed so as to increase patient motivation (N.=35/36; 97.2%) and caregivers should be appropriately trained to assist patients following injection therapy (N.=34/36; 94.4%).

Consensus was unanimous on planning and setting specific goals before initiating BTX-A therapy (N.=36/36; 100%), involving both the patients (N.=36/36; 100%) and their caregivers (N.=35/36; 97.1%).

To the question how much time should be between two BTX-A treatments, the experts agreed that the optimal time for re-injection was 3 months (N.=35/44; 79%) or 6 months (N.=34/44; 77%), whereas if requested when the patient treated must be evaluated, early unanimous consensus was obtained on the need to evaluate the patient at 1 month after BTX-A therapy (N.=43/44; 97%). Evaluation at 6 months was considered necessary, especially in naïve, sub-acute and chronic stroke patients without considering the need for further injection (N.=33/36; 91,7%). However, follow-up assessment at 3 months was recommended in naïve (N.=35/36; 97.2%) and in sub-acute patients (N.=33/36; 91.7%).

When functional surgery of upper and lower limbs treated with BTX-A therapy must be considered? The experts answered that it must be considered useful for rehabilitation only after 12-24 months (N.=30/34; 83.4%), especially if injection therapy fails (N.=33/35; 94.2%). Response to BTX-A therapy was considered a useful criterion in the choice of appropriate surgical treatment (N.=41/44; 93%).

Another question was related to the quality of life: the quality of life improvement after BTX-A therapy in stroke patients can be evaluated by physicians (N.=37/44; 84%) caregivers (N.=35/44; 79%) or both (N.=42/44; 95%). Support from family members was considered important (N.=32/44; 72%). Quality of life can be measured using a subjective evaluation tool (N.=28/35; 80%), an objective method (N.=32/35; 91.5%), the Goal Attainment Scale (N.=25/36; 69.5%) or caregivers' observations (N.=31/36; 86.1%).

Discussion

Previously published documents recommend the global management of patients submitted to BTX-A therapy only in general terms, without indicating timing, duration and type of rehabilitation procedures, or the role of caregivers. On the other hand, a short paragraph on the recommendations on pre- and post-injection treatment has been included in the European Consensus Table by clinical experts on the use of BTX-A; the authors agreed that there is little information on the measures that can modify and/or increase the efficacy of botulinum toxin injections and that more studies are required to ascertain the optimal type, duration and intensity of physical therapy after botulinum toxin treatment.[6]

The purpose of COSMO project was to compare the current experience of Italian specialists on the management of stroke patients after BTX-A injection with respect to the European Consensus and international guidelines. The survey results confirmed that the focal treatment of spasticity with BTX-A therapy in stroke patients must be included in a multidisciplinary process to increase the effect on spasticity reduction. Based on our knowledge, the literature and international consensus statements provide no clear evidence on the best practices to improve BTX-A therapy or manage patients treated with BTX-A therapy.

Despite the absence of a standardized method to increase the effect of BTX-A injection using different

procedures, common results have been documented in the international published literature. The 44 experts participating in the COSMO project reached agreement on several key topics, including objectives of intervention, setting, follow-up, qualified rehabilitation services and programs, adjunctive therapies, and caregiver participation.

The panel experts agreed on the need to treat patients in the same clinic where BTX-A therapy is administered. An ideal multidisciplinary team will include medical specialists, physiotherapists, occupational therapists, and orthotists with appropriate training in the management of neurological disease and working in a specialized clinic.

In contrast, the experts confirmed that an adequately trained caregiver could complete the rehabilitation program only after the intervention of a physiotherapist. This result reflects the principles of the international guidelines for spasticity in adults treated with BTX-A, as endorsed and issued by the Royal College of Physicians (UK) [9]and by the European Consensus Table.[6]

A positive consensus was obtained regarding that patients injected with BTX-A should be referred for rehabilitative therapy immediately after or during the first week after BTX-A treatment, whereas consensus was negative on starting rehabilitation 2 weeks post-injection. This result differs from other guidelines [7, 9] that recommend planning adjunctive therapy at approximately 7–14 days after injection to permit the use of adjunctive techniques that are not possible prior to BTX-A injection, such as muscle stretching or fitting orthotics to improve passive function, or motor training for active functional goals.

Early physiotherapy after BTX-A injection can enhance its beneficial effects on spasticity reduction, especially with the use of therapies to maintain muscle length through passive or active exercise and stretching of the injected area: manual stretch procedures can normalize muscle tone, maintain or increase soft-tissue extensibility, reduce pain and improve function.[20, 21] Stretching may change the muscle's viscoelastic, structural, and excitability properties.[22]

Continuous muscle lengthening as a treatment can vary in many ways, also with the use of splinting, taping, casting and orthotics. In such cases, as outlined in the UK international guidelines for spasticity,[9] it's important to assess the degree of patient compliance and the need for orthotics/splinting or review existing orthoses as appropriate when the clinical effect of muscle weakening is observed (usually 7-14 days postinjection). Regarding the use of these devices, the Cosmo project participants agreed that it is useful to enhance the effect of injection therapy because there is no evidence that any other treatment is better for upper or lower limb spasticity in post-stroke patients.

Carda and Molteni showed that adhesive taping for 24 h/day for 6 days at the wrist and finger flexor spastic muscles after BTX-A injection significantly reduced spasticity in conjunction with daily stretching exercises and electrical stimulation of injected muscles for 5 days; the treatment required less time than thermoplastic palmar splint application.[23]

In a single-blind, randomized pilot study of BTX-A combined with non-pharmacological treatment for spastic foot, Baricich et al. showed that 30 min of stretching for 7 days and electrical stimulation for 30 min. twice daily for 5 days were sufficient to reduce modified Ashworth scale (MAS) scores, as compared with stretching alone (30 min twice daily), thus improving the ankle passive articular range of motion, gait parameters and compound muscle action potential (C-MAP).[11]

The panel experts agreed that one session of electrical stimulation of injected muscles during the first hour after injection could be beneficial, whereas no consensus was reached on multiple treatments over the next 3 and 5 days. Indeed, the use of electrical stimulation after BTX-A therapy is still controversial and several protocols have been described. In addition, there is no clear agreement concerning the optimum frequency of electrical stimulation, time of onset and duration of application (*e.g.*, 20 min of electrical stimulation before BTX-A therapy doesn't produce the same neurophysiological effect as electrical stimulation applied after injection),[24]whereas another study showed no differences between high and low frequency stimulation.[25] The panel experts agreed that immediate electrical stimulation treatment is better than delayed stimulation to enhance the antispastic effects of BTX-A therapy. This was confirmed by a recent study in which electrical stimulation at 4 Hz administered to the biceps brachii and adductor digiti minimi muscles immediately after BTX-A injection was found to reduce MAS scores and C-MAP amplitude more than delayed electrical stimulation treatment.[26]

The panel experts agreed on the need to increase

the muscle strength of opposing muscle groups, when indicated, by means of electrical stimulation or functional electrical stimulation of the antagonist muscle in order to build up muscle strength and enhance functional benefits, as previously reported.[27]

In line with the literature, previous consensus statements [7]and international guidelines,[9] there was positive consensus regarding the role of motor training to increase active participation in tasks, thus helping to improve active function.

Constraint-induced movement therapy [28] motor imagery and motor observation [29, 30] or task-oriented [31]exercises combined with BTX-A therapy are effective in promoting motor recovery after chronic stroke, as recommended in an active program of occupational therapy.

If motor recovery cannot be achieved, with or without BTX-A therapy, functional surgery may be considered in patients with upper and lower limb spasticity. Surgery may be useful for rehabilitation only after 12-24 months. Moreover, BTX-A therapy can be used to discriminate if and what type of surgical treatment should be done. To date, the effect of this type of intervention, particularly for equinovarus foot deformity, has been reported to improve kinetic and kinematic gait parameters.[32, 33] However, further validation of surgical correction of spastic foot following stroke is desirable, with higher-level study designs and validated assessment tools.

According with international guidelines,[9] the panel experts agreed that clinical review can range from 3 to 6 months after treatment; follow-up assessment at 4 weeks is recommended to determine whether or not the treatment goals have been achieved and to identify adverse effects and patient compliance with the post-injection regime. The recommendation of clinical review depends on the patient's clinical condition (sub-acute or chronic stroke) and on the need for additional instrumental assessment or further injections.

Follow-up decisions concerning outcome measures should involve the whole team attending to the patient's care, the patient and carer.[34]Verbal or visual analogue rating scales, patient and carer satisfaction questionnaires, and goal attainment rating can be used for global assessment of the patient's experience.

In line with international consensus recommendations,[6, 7, 9, 35] the expert panel agreed that re-injection of the naïve patients may be performed after a minimum of 3 months, if it is clear that the spastic motor over-activity is returning.

Careful physical management between injections can help to reduce the frequency of BTX-A treatments and reduce the likelihood of secondary non-response. The general advice is to avoid repeating injections within 3 months.

Conclusions

The results of this survey confirm that international published guidelines, consensus statements, and studies on the use of BTX-A in the treatment of spasticity after stroke represent a useful starting point for Italian clinicians in the rehabilitative management of stroke patients receiving BTX-A therapy. This study doesn't represent a national consensus but, rather, the real state of the art in this field. Furthermore, the geographical distribution of the study participants offers a representative picture of rehabilitation management and assessment of patients after BTX-A injection in the clinical practice of rehabilitation services in Italy. The results of this national survey of experts can provide guidance for clinicians on the valid assessment and management of patients treated with BTX-A for upper and lower limb spasticity.

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APPENDIX

"Italian Spasticity Study Group":

Antonacci R., Osp. Civile-Pescara; Balestrieri F., Osp. "Sant'Annunziata"-Firenze; Baricich A., AO "Maggiore" - Novara; Bertoni M., Osp. "Macchi" - Varese; Castagna A., Fond. "Don Gnocchi" - Milano; Cavazza S., Osp. "Nuovo S.Agostino Estense" - Baggiovara (Modena); Chisari C. Osp. "Cisanello" - Pisa; Coleschi P., Osp. "San Donato" - Arezzo; Cosma M., Osp. "S. Giorgio" - Ferrara; Crisci C., "Clinic Center" - Napoli; Currà A., Osp. Terracina - Latina; D'Aurizio C., Osp. "SS Rosario" - Venafro (Isernia); D'Avenia L., AO "San Carlo" - Potenza; Dell'Accio D., Osp. "Marconi" - Cesenatico (Forlì-Cesena); Di Lorenzo L., AO. "G. Rummo" - Benevento; Dimanico U., Osp. Civile - Fossano (Cuneo); Forcellini Marco Elio, Osp. "Galmarini" - Somma Lombardo (Varese); Fresu M., Osp. CTO - Iglesias (Carbonia-Iglesias); Galardi G., Osp. "G. Giglio" - Cefalù (Messina); Gennaro L., Osp. Riabilitativo "Gervasutta" - Udine; Giovanelli M., Osp. "S. Andrea" - Roma; Lazzarini C., Spedali Civili-Brescia; Leo L., AO. "SS. Annunziata" - Cosenza; Lucangeli A., Osp. Riabilitativo di Alta Specializzazione-Motta di Livenza (Treviso); Maggioni G., Fond. "Maugeri" - Pavia; Manca M., Osp. "San Giorgio" - Ferrara; Milletti D., SOP. Bellaria-Bologna; Misceo S., Osp. "San Paolo" - Bari; Morgante F., Policlinico-Messina; Mori L., Clinica Neurologica - Genova; Picelli A., Dip. di "Scienze Neurologiche, Neuropsicologiche, Morfologiche e Motorie" - Università degli Studi di Verona; Pinto F., Osp. "Careggi" - Firenze; Pisano F., Fond. "Maugeri" - Veruno (Novara); Posteraro F., Osp. Civile Lido di Camaiore (Lucca); Quatrale R., Osp. "Dell'Angelo" - Mestre (Venezia); Romano M., Osp. "Villa Sofia" - Palermo; Salghetti A., Osp. "Maggiore" - Parma; Sandrini G., Osp. "Mondino" - Pavia; Sanguinetti G., "Montecatone Institute for Rehabilitation" - Imola (Bologna); Santoro A., "Casa Sollievo Sofferenza" - San Giovanni Rotondo (Foggia); Schierano S., Osp. Riabilitativo "Gervasutta" - Udine; Sciarrini F., Centro Riabilitativo-Passignano sul Trasimeno (Perugia); Servodio Iammarrone C., Università "Federico II"-Napoli; Servodio Iammarrone F., Università "Federico II"-Napoli; Terranova C., Policlinico - Messina; Trompetto C. Clinica Neurologica - Genova; Vecchio M., Osp. "Vittorio Emanuele" - Catania.