Combination Therapies with FES

14

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14.1 Introduction

Functional electrical stimulation (FES) is used for a wide variety of applications in neurorehabilitation, as described in detail in the previous chapters. The variety of neurological symptom manifestations, which show up in clinical routine, often require the modification of the different therapeutic approaches. From this requirement, the combination of FES with other successful therapies emerged.

The combination of FES with other therapeutic approaches, such as mirror therapy or botulinum neurotoxin therapy (BoNT-A), has proven to be effective in rehabilitation. Both mirror therapy and BoNT-A are recognized and established treatment methods in neurorehabilitation. The combination of these therapies with FES has proven to enhance the therapeutic effects and, in some cases, to produce lasting improvements (Sect. 14.2).

Several studies showed that the combination of FES and mirror therapy in neurorehabilitation of stroke patients [1–3] brought benefits in motor recovery. A systematic review and meta-analysis [4] in 2020 highlight the synergistic effects of mirror therapy combined with EMG-triggered FES. Section 14.2 provides a detailed overview of this combination modality.

▶ The combination of functional electrical stimulation (FES) and mirror therapy is well suited for the treatment of motor deficits in stroke patients in neurorehabilitation.

FES, applied in addition to BoNT-A therapy, can have a beneficial effect on spastic movement disorders.

The use of mirror therapy in stroke rehabilitation is excellently suited for the treatment of stroke patients with severe motor deficits [5]. This also explains why the combination of FES and mirror therapy is preferred here. Furthermore, it was shown that the usually available treatment time of 30 min does not inhibit the successful implementation of these combined therapy procedures [1].

The combination of BoNT-A therapy with immediately following (F)ES is clinically useful in spastic movement disorders. It is described in a systematic review [6] and discussed in Sect. 14.3.

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T. Schick (ed.), *Functional Electrical Stimulation in Neurorehabilitation*,
https://doi.org/10.1007/978-3-030-90123-3_14

This chapter is intended to provide a basis from which consistent stimulation protocols, supported by further studies, can be developed in the future. Furthermore, it should be understood as a basis for discussion in order to use both therapy methods combined in a standardized way for the treatment of spastic movement disorders.

14.2 Combination of Functional Electrical Stimulation and Mirror Therapy

Christian Dohle

14.2.1 Introduction

The effect of electrical stimulation on recovery after stroke is based on different mechanisms. On the one hand, electrical stimulation elicits movements that should resemble those that were performed prior to the stroke, promoting motor learning. On the other hand, electrical stimulation causes direct afferent stimulation that might contribute to recovery as well. However, both effects (proprioception, sensory electrical stimulation) are mediated by peripheral sensory afferent pathways that might be affected by the stroke as well.

Thus, especially for severe arm paresis, therapies with direct (central) stimulation of motor representation are recommended, such as movement observation, mental imagery, or mirror therapy. During mirror therapy, a mirror is placed in a patient's mid-sagittal plane in such a way that the mirror image of the non-affected limb appears as if it were the affected one. Imaging studies demonstrated that the effect of the mirror illusion on brain activity can also be recorded neurophysiologically: When presenting a moving limb via a mirror, there is additional brain activity in the hemisphere contralateral to the visual image, i.e., the affected hemisphere in patients. The number of studies providing evidence for the effect of mirror therapy after stroke has virtually exploded over the last years. In their search in August 2018 for a Cochrane review, Thieme and co-workers (2019) identified 62 randomized controlled studies with a total number of 1982 participants, employing mirror therapy either isolated or in combination with other therapies [7]. As mirror therapy does not require any motor capabilities at all, it is a very suitable candidate for combination with electrical stimulation.

14.2.2 Evidence

The Cochrane review (2019) already found seven studies on the combination of mirror therapy with electrical stimulation. A hand search in February 2020 identified two additional studies in which these therapy regimes were combined. These studies should help to answer two different questions:

1. Can the effect of mirror therapy be enhanced by electrical stimulation?
2. Can the effect of electrical stimulation be enhanced by application of a mirror?

For both questions, three randomized controlled studies could be identified. Additionally, three studies with a three-arm design were found, comparing electrical stimulation and mirror therapy isolated with its combination. However, for electrical stimulation, different protocols were applied. In the following, the results of the studies are summarized.

14.2.3 Improvement of the Effect of Electrical Stimulation by Mirror Therapy

In the study of Kim and co-workers 2014 [8], 23 subacute stroke patients received functional electrical stimulation in addition to their regular therapy program. Patients could switch on stimulation of the musculi extensor digitorum, musculi carpi radialis longus and brevis by performing a similar

movement with their non-affected side. During the procedure, patients were instructed to move both hands simultaneously. In the experimental group, the image of the non-affected side was presented via a mirror. When comparing the relative improvement of the three Fugl Meyer subscores, patients receiving the combination therapy showed stronger improvement in the distal scores (finger and hand), but not in the proximal ones. In the Box and Block test, there was no significant difference between the two groups.

Schick and co-workers [9] applied bilateral EMG-triggered multichannel electrical stimulation of the Musculi extensor carpi radialis longus and Musculi flexor digitorum superficialis on both sides in 33 subacute stroke patients (Fig. 14.1). In this design, stimulation was elicited by the EMG signal of the non-affected side. In this study as well, therapy procedure of both groups only differed in the additional placement of a mirror between both sides. After the intervention, there was no difference between both groups as a whole. However, in a subgroup analysis, a significant difference in the proximal Fugl Meyer score in patients with very severe paresis (total Fugl Meyer score < 17 points) was found.

In the study of Lee and Lee 2019 [10], a total number of 30 chronic, ambulatory stroke patients received afferent stimulation with a "mesh sock." In the intervention group (15 patients), this therapy was combined with mirror therapy during dorsiflexion of the foot. Here, significant differences between both groups in muscular strength and balance (Berg Balance Scale) as well as in specific gait parameters (gait velocity, step length, stride length) were recorded.

14.2.4 Improvement of the Effect of Mirror Therapy by Electrical Stimulation

Unfortunately, studies for the reverse question are sparse. Only one study by Lin and co-workers 2014 [11] compared the effect of the application of a "mesh glove" in addition to mirror therapy of the upper extremity. In this small study with 2 × 8 patients, the additional stimulation appeared to result in significant improvements in the Action Research Arm Test (ARAT) and the Box and Block test, but not spasticity.

Two other studies focused on the lower extremity: Ji and co-workers 2014 [12] treated three groups with 10 chronic stroke patients each. Two groups trained with a mirror. In one of these groups, this was combined with electrical stimulation, eliciting a foot dorsiflexion of the affected side by a dorsiflexion switch on the non-affected side. A third patient group received a sham therapy with neither mirror therapy nor electrical stimulation. Outcome variables were different parameters of a gait measurement system. In this study, both mirror groups showed improvement in gait velocity when compared to the sham group. Step length and stride length only improved in the combination therapy.

A further study with a similar design, but higher number of participants, was presented by Xu and co-workers 2017 [13]. In this study with

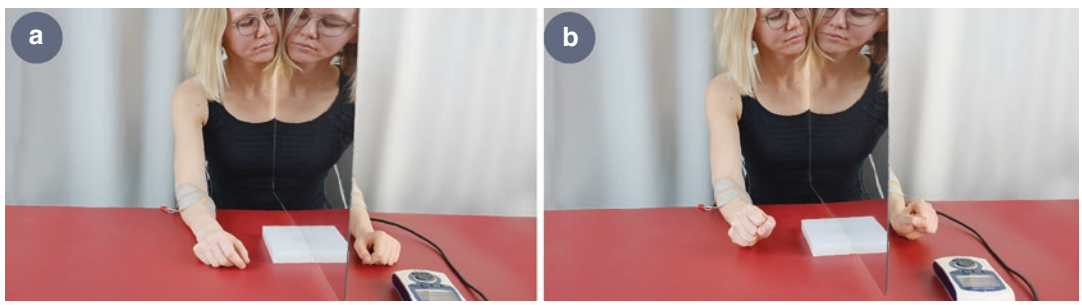

Fig. 14.1 Combination of bilateral functional EMG-triggered multichannel electrical stimulation with mirror therapy. (**a**) mirror therapy before pulse triggering by EMG-triggered multichannel electrical stimulation, (**b**) mirror therapy with EMG-triggerered multichannel electrical stimulation. (from Schick and Co-workers, 2017 [9])

3 × 23 subacute stroke patients, there was greater improvement in the primary outcome variable (10 m gait test) in the combination therapy when compared to mirror therapy group and control therapy group (without additional therapy). The Brunnström stages of motor recovery of the lower limb showed greater improvement in both therapy groups receiving mirror therapy when compared to the control group. However, in this variable, there was no additional effect of the electrical stimulation. The same picture appeared in the passive range of motion. For spasticity (Ashworth scale), the combination therapy was found to be superior to isolated mirror therapy and the control group.

14.2.5 Combination Studies

In the three-arm study of Yun and co-workers 2001 [3] 20 subacute stroke patients in each group received either cyclical electrical stimulation of the Musculi extensor digitorum communis and extensor pollicis brevis, mirror therapy, or a combination of both. This study showed no difference between both isolated therapy regimes. However, the combination of both regimes showed to be superior in all subtests of the upper extremity Fugl Meyer score and hand extension force.

In another three-arm study, Nagapattinam and co-workers 2015 [14] compared the effect of electrical stimulation, mirror therapy, and its combination in three groups of 20 subacute stroke patients each. In all conditions, patients had to grasp for a bottle cyclically (task-specific training). In the primary outcome variable, the Action Research Arm Test (ARAT) with its four subtests, no significant difference between the therapy groups could be established, even as visual inspection of the data suggested a slight advantage for the combination therapy.

The third study of Mathieson and co-workers 2018 [15] applied a similar design and compared the two isolated therapies with its combination. A total of 50 subacute stroke patients participated. Here as well, functional electrical stimulation was cyclical with stimulation of the Musculi extensors digitorum and extensor pollicis brevis. In this study, the per-protocol analysis showed no difference between the three therapy regimes in any of the outcome variables (Fugl Meyer scores, ARAT, ADL scales), but with slightly different baseline values. An additional ANCOVA of the ARAT, considering these differences, provided a superior effect of functional electrical stimulation compared to mirror therapy and the combination.

14.2.6 Summary

Taking all evidence together, most of the studies detailed above suggest that the effect of functional electrical stimulation in subacute stroke patients can be enhanced by means of a mirror. The data of Nagapattinam and co-workers hint, however, that this effect is more prominent on the ICF functional level (e.g., Fugl Meyer score) when compared to ICF activity level (e.g., Action Research Arm Test).

For the reverse question (can mirror therapy be enhanced by electrical stimulation?) there are fewer studies. Two out of three studies described treatment of the lower extremity, where the rationale of employing mirror therapy is less clear. These few data suggest that mirror therapy might be enhanced by electrical stimulation.

Thus, taking all evidence together, there are clear hints that mirror therapy and electrical stimulation are complementary therapy approaches. The studies available so far do not allow a direct comparison of the effect of both therapies. Apparently, however, the combination provides additive effects. Data are more robust for enhancing electrical stimulation by means of a mirror than vice versa.

14.3 Botulinum Toxin A and (Functional) Electrical Stimulation

Klemens Fheodoroff

Abstract

This section presents the impact of spastic movement disorder (SMD) on movement control and the ability to act as well as treatment approaches. Injections with botulinum toxin A have become the gold standard of medical treatment for SMD, opening a "therapeutic window" in which the affected individuals can exercise under therapeutic guidance how to deal with SMD (stretching, positioning) and how to practice residual control of voluntary movements (strengthening, repetitive exercise) which may be disguised by muscle tone increase or synkinesis.

Electrical stimulation has been increasingly established as an ideal supplement. Through neuromuscular electrical stimulation (NMES), muscle tone in spastic agonists can be reduced and the effect of botulinum neurotoxin type A (BoNT-A) injections can be enhanced. By means of functional electrical stimulation (*FES*), action-related movement patterns can be reinforced and trained with frequent repetitions.

The foundations, the practical implementation, and goals for a combined treatment are discussed in detail.

Keywords

Spastic movement disorder; Botulinum toxin A; Neuromuscular and functional electrical stimulation; Treatment goals

14.3.1 Spastic Movement Disorder

Spastic movement disorder (SMD) [16] is one of the most frequent consequences of a central nervous system impairment (brain/spinal cord). Nowadays, only the plus phenomena of the pyramidal tract syndrome (upper motor neuron syndrome, UMNS) are subsumed under the term SMD. Prominent features of SMD are: enhanced proprioceptive muscle reflexes, a velocity-dependent increase in muscle tone during passive stretching, and the appearance of involuntary movement reactions (synkinesis, spastic dystonia). The minus phenomena—impaired muscle strength, impaired control of voluntary movements, and reduced muscle endurance—must be distinguished from SMD. Furthermore, muscle tissue changes developing over time with muscle shortening and restricted segmental joint mobility up to the development of contractures is considered as a consequence of SMD/UMNS [17–19].

b760 Control of Voluntary Movement Functions [20]
Functions associated with control and coordination of voluntary movements. *Including*: Functions of control of simple and complex voluntary movements, coordination of voluntary movements, supportive functions of arm or leg, right left motor coordination, eye-hand coordination, eye-foot coordination; impairments such as control and coordination problems, e.g., dysdiadochokinesia. *Excluding*: muscle power functions (b730); involuntary movement functions (b765); gait pattern functions (b770).

The Fugl-Meyer test has become standard for assessing control of voluntary movement with or without synkinesis. 30 instructions with increasing level of difficulty are used for assessing arm function (max. 60 points); 11 instructions with increasing difficulty are used for assessing leg function (max. 22 points). Reflexes, coordination, sensitivity, and balance tasks are evaluated separately [21–23].

▶ The systematic evaluation of control of voluntary movements functions should be an integral component of initial and final disability assessment for each intervention.

According to the International Classification of Functioning, Disability and Health (ICF), all of the above-mentioned parameters belong to the body functions components. As described in Chap. 5, body function impairments constitute internal barriers for the performance of various actions and tasks and constitute a need for external facilitators (aids/assistance) to partially compensate these internal barriers.

To categorize individual capacity in walking (d450), the *Functional Ambulation Categories*—a 6-point scale (from "*cannot walk/assistance of 2 persons*" to "*can walk everywhere independently, including stairs*") has been well-established.

Table 14.1 Arm-hand activity scale [27]

no activity	No usable activities in everyday life.
fixing objects	**Arm** or **Hand** can be passively or actively moved to a horizontal plane to secure objects (e.g. a piece of paper) in place.
holding objects	**Arm** can be stabilised on a horizontal plane. Muscle tone can be roughly controlled. **Hand** can perform minimal grasping/releasing activities and can be used to secure larger objects in place.
auxiliary arm/ hand activities	**Arm** can be moved against gravity. **Hand** can be used as an aid when performing fine motor tasks with both hands (e.g. eating using cutlery with built-up handles).
near-normal arm/hand activities	**Affected arm** can be used in bimanual tasks, possibly with slight restrictions (slight coordination disorder and muscle tone fluctuation, moderate deceleration), such as grasping objects and handling them bimanually (driving in nails with a hammer, eating with cutlery, etc.).

[24–26]. Regarding arm-hand activities, a similar 5-point scale has been developed recently, facilitating the choice of appropriate treatment strategies according to the current level of arm-hand activities [27] (Table 14.1).

In recent years, reliable clinical parameters have been published allowing to predict recovery of mobility within first 6 months after stroke already 48/72 h after onset of symptoms.

If the affected person can sit stable and without assistance 72 h after onset of stroke symptoms and can move hip/knee/ankle joint of the affected leg voluntarily to a small extent, there is a high (98%) probability that he/she will be able to walk independently and without aids 6 months after the stroke. Conversely, individuals who cannot sit unassisted for at least 30 s only have a 27% probability of being able to walk independently [28]. Here it is worth noticing that changes in gait pattern persist for a long time and are characterized by an abnormal muscle tone, gait asymmetry, and flexion synkinesis of the affected arm. Affected persons use up 50–70% more energy when walking compared to healthy individuals walking at the same gait speed [29, 30].

Similar parameters were determined for recovery of arm and hand activities. If the affected person is able to voluntarily abduct shoulder and stretch fingers of the paretic arm within 48 h after stroke, there is a high probability (98%) for near-normal arm/hand activities 6 months after the stroke. On the contrary, individuals without control of voluntary movements only have a 25% chance to regain arm/hand activities usable in daily routine. If shoulder abduction/finger extension still cannot be actively performed on day five and nine, this probability is reduced to less than 15%; on the contrary, there is a 13-fold increased risk for developing a SMD in the next months [31, 32].

Motor recovery after stroke has been described in six stages by Brunnström [33]. Yet it must be emphasized that, depending on the extent of the CNS damage, motor recovery can stop at any of these stages (Table 14.2).

In the early stages after brain lesions, a (flaccid) paresis usually is present. Depending on size and localization of brain lesion, the grade of the paresis, and the presence of pain and sensory and proprioceptive functions, an increase in muscle tone develops within the first 4 weeks after stroke in 4–27% of affected persons; in another 19–27% of affected persons, SMD develops within the first 3 months. 17–42% of stroke patients suffer from a chronic SMD [34]. With persisting SMD, muscle tissue changes in the paretic muscles

Table 14.2 Stages of motor recovery (Brunnström 1966)

level	denomination	characteristics
1	muscle hypotonus	no voluntary movements
2	developing spasticity	basal flexor/extensor synergies
3	marked spasticity	components of flexor/extensor synergies can be initiated voluntarily
4	decrease in spasticity	voluntary movements deviating from basal flexor/extensor synergies can be initiated
5	disappearance of spasticity	voluntary movements can be initiated independent from basal flexor/extensor synergies
6	minimal spasticity	near-normal movements/coordination

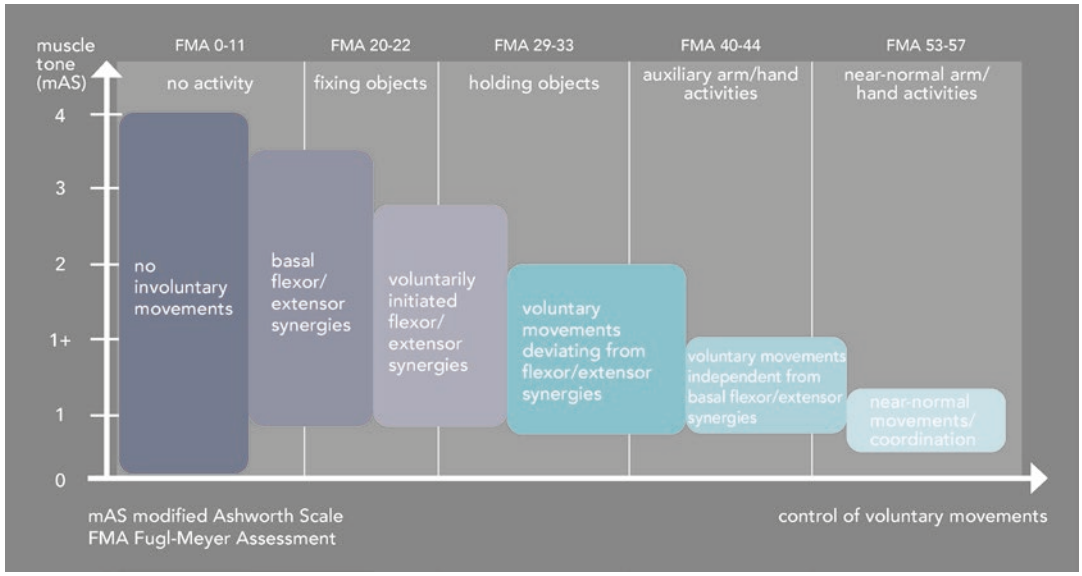

Fig. 14.2 Impact of muscle tone on control of voluntary movements

(loss of elastic fibers, increase of connective and fatty tissue, ion channel proteins alterations) appear frequently [35]. These changes lead to further reduction of passive range of motion (pROM) in the spastic segment. Therefore, an early treatment of SMD appears reasonable [36]. However, further research is required if secondary changes can be prevented by early BoNT-A treatment (Fig. 14.2).

Given the development of SMD over time, different treatment goals should be considered. In the first 6–12 months, the focus is on reducing

spasticity-associated muscle pain, maintaining the (passive) range of motion in the spastic segment, and reducing muscle tone to promote control of voluntary movements for arm/hand activities such as securing objects in place, grasping and releasing objects as well as standing up/sitting down and walking (barefoot). In the chronic phase of SMD, however, the focus should be on goals such as reducing involuntary movements/synkinesis and enabling (self) stretching exercises in the spastic movement segments to facilitate self-care activities (such as washing oneself/caring for body parts/dressing) [37–39] (Table 14.3).

Here it is important to emphasize that neither the paresis nor the muscle tone itself can be directly influenced by the affected individuals themselves, but by medication (BoNT-A injections), by (electrical-) stimulation, and by soft tissue surgery. However, during neurorehabilitation, affected persons should learn to deal with these impairments as efficiently as possible by being taught interventions related to a (guided) self-management. This also helps patients to optimize their self-determination by learning to counteract SMD through regular stretching and positioning as well as moving segments repetitively within their residual control of voluntary movements, including synkinetic movement patterns, to carry out tasks and actions (e.g., to secure objects in place; to carry objects in a bag with a flexed elbow)—if necessary, supported by dynamic splints and electrical stimulation.

For treatment of moderate/severe SMD, BoNT-A injections have proven effective.

14.3.2 Botulinum Toxin: Pharmacology, Mode of Action, and Use

14.3.2.1 Botulinum Toxin—Pharmacology

Botulinum neurotoxins (BoNT) are produced by anaerobic, spore-forming bacteria of the species *Clostridium botulinum*. These naturally occurring complex protein molecules are characterized by high neurotoxicity. All BoNTs bind to peripheral cholinergic nerve endings in both, smooth and striated muscle and to glands with cholinergic transmission inhibiting the release of the neurotransmitter acetylcholine (ACh) at the presynaptic membrane. Thus, they cause a reversible slack paralysis of the skeletal muscles or a secretion inhibition of the treated glands.

14.3.2.2 Mode of Action (Onset of Action—Maximum Effect—Duration of Action)

Of the seven known serotypes (A-G), almost exclusively serotype A (BoNT-A) is used for clinical purpose at the moment. BoNT-A consists of a heavy (100 kDa) and a light (50 kDa) chain connected by a disulfide bond. The heavy chain is responsible for binding BoNT-A to the presynaptic nerve terminals as part of ACh vesicle recycling process and for translocating from the ACh vesicles into the cytosol of the neuron. BoNT-A uptake into the terminal nerve ending is thus dependent on ACh release. Only when ACh vesicles fuse with the presynaptic nerve cell membrane, the specific binding receptor for the heavy BoNT-A chain is displayed (Fig. 14.3). The more ACh released after the injection, the more BoNT-A is incorporated into the presynaptic nerve endings. Thus, inactivity after BoNT-A treatment (e.g., bed rest) should be avoided.

The light chain causes the biological response by destroying proteins responsible for fusing ACh vesicles with the presynaptic membrane. Depending on the BoNT type and the destroyed fusion proteins, ACh release into the synaptic cleft is suppressed for a type-specific time period (between 2 and 24 weeks) [40, 41].

Due to this biological transformation, BoNT-A does not take effect right after the injection but three to five days later. The maximum effect of BoNT-A-induced chemodenervation can be expected after seven to ten days and lasts for 8–12 weeks. As ACh release is reduced at both, the extrafusal and the intrafusal (muscle spindle) endplates, the neuromuscular afferents (as part of the spastic reflex arc) are also blocked.

The neurotoxin is subsequently degraded by proteases in the preterminal axon; no further fusion proteins are destroyed. The fusion

Table 14.3 Common patterns in spastic movement disorders, muscles involved, and goals for treatment

pattern	involved muscles	treatment goals
shoulder adduction, - internal rotation, - retraction	- pectoralis major - latissimus dorsi - teres major/minor - subscapularis - rhomboideus major/minor	- sitting/standing/walking with mild arm flexion synkineses - cleaning armpit - dressing upper body - resting arm on table - reaching for objects
elbow flexion	- biceps brachii, brachialis - brachioradialis - pronator teres	
pronated forearm	- pronator teres - pronator quadratus	- resting arm on table - reaching for objects
wrist and finger flexion (clenched fist)	- flexor carpi ulnaris/radialis - flexor digitorum superficialis/ profundus - flexor pollicis longus	- washing/caring for hand - stretching fingers against low resistance - securing objects in place/ grasping/releasing
thumb flexion, "lumbrical hand" (MCP joint flexion)	- flexor pollicis brevis - oppones/adductpr pollicis - interossei volares	
hip adduction	- adductor longus, brevis, (magnus) - pectineus	- performing intimate hygiene/urinary catheterisation against mild resistance - putting on trousers - walking without crossed legs (scissor gait)
hip and knee flexion	- psoas major/iliacus - gracilis/semimembranosus/ semitendinosus	- putting on trousers - standing up/standing with leg extended
knee extension	- rectus femoris - quadriceps group	- sitting in (wheel) chair without thigh spasms/cramps - walking with knee flexion in leg swing phase
spastic plantarflexion (pes equinovarus)	- soleus, gastrocnemius - tibialis posterior/(anterior) - flexor digitorum longus	- standing up/standing/walking with heel/sole/forefoot contact - walking without splint/barefoot
toe claws	- flexor digitorum/hallucis longus - flexor digitorum/hallucis brevis	- putting on shoes - walking without splint/barefoot - walking without foot cramps
tonic hallux extension (striatal toe)	- extensor hallucis longus	- putting on shoes - walking with shoes without foot cramps

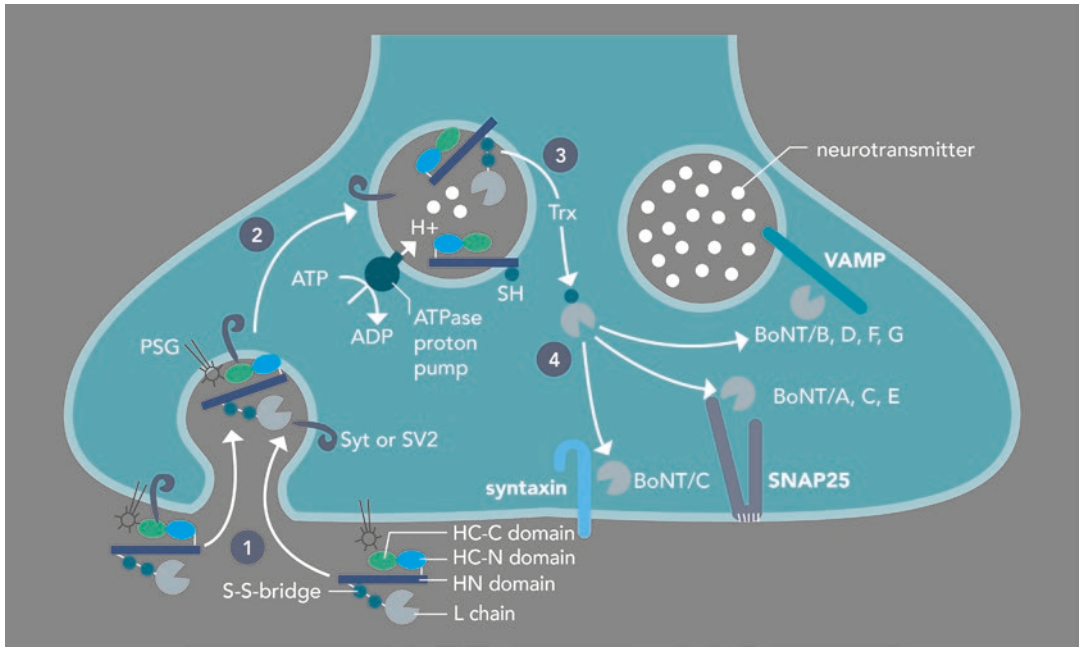

Fig. 14.3 Mode of action of botulinum neurotoxins. The heavy BoNT chain with its carboxy-terminal end ("HC-C domain") specifically binds to a polysialoganglioside receptor ("PSG") of the presynaptic membrane and to one of two protein receptors (syntagmin—"Syt" or "SV2") located in the ACh vesicle membrane. It is then taken up into the terminal nerve end as part of ACh vesicle recycling process (1). The vesicle content is enriched with protons ("H^+") via ATPase proton pump to reabsorb excess ACh into the vesicle. In this acidic environment, a structural change of the BoNT molecule occurs. The N-terminal end of the heavy chain ("HN domain") forms a kind of pore in the vesicle membrane through which the light BoNT chain ("L chain") is discharged from the vesicle (2). The enzyme thioredoxin reductase ("Trx") cleaves the light chain at the disulfide bond ("S-S bridge"/"SH"). Now the light chain can develop its proteolytic activity in the cytosol (3). The protein complex for fusing the ACh vesicles with the presynaptic membrane and for ACh release into the synaptic cleft consists of three proteins that twist helically around each other: Syntaxin, SNAP-25 (Synaptosomal-Associated Protein), and VAMP (Vesicle-Associated Membrane Protein). BoNT types B, D, F, and G cleave VAMP, BoNT types A, C, and E cleave SNAP-25 (at different sites), and BoNT type C cleaves syntaxin (4), all of which result in neurotransmitter release inhibition and neuroparalysis (4). *ATP* adenosintriphosphate, *ADP* adenosindiphosphate

complexes necessary for exocytosis are newly formed so that the synapse can resume its function 8–12 weeks after treatment with BoNT-A. Particularly in the treatment of spastic movement disorder, this period of blocked neuromuscular transmission is also labeled as the "therapeutic window", which can be used to work out new movement patterns. Thus, the clinical duration of action can be extended.

The various commercially available BoNT-A products differ in protein content and excipients and thus also in potency. Therefore, the products are only comparable to a limited extent. So far, direct comparative studies of the different products regarding duration and strength of action as well as safety and effectiveness in different indications are lacking. Therefore, the choice for one of the registered BoNT-A products heavily depends on the regional availability of the product and the clinical experience of the treating physician [41].

14.3.2.3 Licensed Indications—Off-Label Use

BoNT-A injections are medically indicated for diseases associated with increased striated or smooth muscle tone and spasms and for diseases with increased glandular secretion (saliva, sweat).

Table 14.4 Licensed BoNT-A treatments and off-label use

licensed indications[1]	related indications[2]
blepharospasm, hemifacial spasm	meige syndrome (blepharospasms plus oromandibular dystonia)
cervical dystonia (torticollis spasmodicus)	oromandibular dystonia; lingual and laryngeal dystonia, spasmodic dysphonia; focal dystonia of the arms/legs (writer's cramp); head and hand tremor
arm and hand spasticity after stroke	trunk and shoulder muscle spasms after stroke or severe traumatic brain injury
spasticity of the lower leg/ankle after stroke or severe traumatic brain injury	hip and thigh muscles after stroke/severe stroke/ severe traumatic brain injury
dynamic toe walking in children with cerebral palsy from age 2 onwards	hip and thigh musculature in children with cerebral palsy from age 2 onwards
axillary hyperhidrosis	palmoplantar hyperhidrosis
excessive saliva production with involuntary loss of saliva from the oral cavity (sialorrhoea)	
symptomatic treatment for chronic migraine	
overactive bladder with urinary incontinence	

[1] for details: see country-specific licensing and summary of product characteristics
[2] Standardised information leaflets for obtaining written informed consent are available.

Up to now, a number of diseases have been officially registered for treatment using BoNT-A. However, BoNT-A is also used for off-label treatment in similar conditions (Table 14.4).

14.3.2.4 Treatment Techniques

Due to the size of the molecules, BoNTs can neither cross the skin barrier nor the blood-brain barrier. The protein must therefore be injected into the target structures. Consequently, knowledge of functional anatomy and spastic movement patterns to appropriately select overactive muscles as well as a precise injection technique are essential for treatment success. In addition to anatomical landmarks, ultrasound (US), electromyography (EMG), and electrical stimulation (ES) are used for localization control. A review by Grigoriu et al. demonstrated that the use of US or ES for injection control leads to better treatment results in both, arm and leg spasticity, than using anatomical landmarks or EMG-guided injections. [42]. Depending on severity of SMD, the spastic movement pattern, and the treatment goals, an average of five muscles in arm spasticity and four muscles in leg spasticity are treated with BoNT-A (see Table 14.3. Common patterns in spastic movement disorders).

14.3.2.5 Adverse Effects

Apart from pain and haematomas at injection sites, excessive local weakness and generalized weakness may occur in individual cases. Especially at higher dosages, dry mouth and eyes, double vision, dysphagia, flu-like symptoms, gallbladder motility disorders, and bladder emptying disorders have been observed. The

adverse effects are reversible similar to the desired effects. Thorough information of patients and relatives on the expected effects and goals for treatment, possible local and systemic adverse effects should therefore be discussed and documented in a standardized way and written informed and signed consent should be obtained before injections.

14.3.2.6 Follow-up Examinations

As treatment effects vary individually and are dose-dependent, follow-up examinations on a regular basis are of importance. If not determined otherwise, the need for concomitant treatment should be assessed and determined after seven to fourteen days. After 4–6 weeks, it should be assessed whether or to what extent the treatment goals have been achieved, if the concomitant therapies have been carried out as planned, and if any adverse effects have occurred. At the same time, treatment plan modifications for the next injection (need for treatment of additional muscles, dosage adjustment) can be determined. After 12–20 weeks, the pharmacological effect of the treatment has subsided. By now at the latest, the need for further treatment cycles should be evaluated and further treatments should be planned/carried out [43].

14.3.3 Combined Treatment BoNT-A and Electrical Stimulation

Treatment of SMD with BoNT-A opens a "therapeutic window" which allows for applying non-pharmacological treatments aiming to develop new movement patterns and to expand the ability to act. By now, sound data for a number of combined treatments are available [6, 44].

As BoNT-A uptake depends on motor endplate activity, it is reasonable to force muscle contraction of the treated muscles by means of cyclic neuromuscular electrical stimulation (NMES). In fact, best clinical evidence for enhancing the effect of BoNT-A injections currently exists for NMES of the injected muscles immediately and in the first few days after treatment [45–47]. Duration of stimulation per NMES session should be 30 min. The level of intensity should be chosen so that visible muscle contractions are elicited without provoking unwanted movements of non-involved muscle groups. Depending on the size of the affected muscle groups, the current intensities are usually between 15 and 90 mA. Direct current rectangular pulses with a duration of 200 μs are most frequently used in existing studies. Biphasic rectangular pulses with pulse widths of 200 μs to 400 μs, as delivered by some mobile electrical stimulation devices, are also suitable for therapy. The frequencies range from 3 to 8 Hz (to reduce muscle tone in the agonists) and 20 to 35 Hz (to increase muscle tone in the antagonists or activate the antagonists).

Only two high-quality studies have been conducted and published so far on functional electrical stimulation (*FES*) after BoNT-A treatment. The study by Weber and colleagues [48] examined combined treatment of BoNT-A injections in the forearm flexors and *FES,* compared to task-oriented training in chronic patients. The agonists as well as the antagonists of the group that received *FES* treatment were stimulated with a prefabricated myoelectric orthosis for 60 min per day for a total of 12 weeks from day seven onward after BoNT-A injections to induce grasping movements. Each stimulation cycle consisted of stimulating the forearm extensors (opening/closing fingers) for five seconds, followed by stimulating the finger flexors (5 s) and a break of 2 s. The reaching movement (moving the arm towards an object) was used as *FES* trigger. The control group completed a task-oriented training (stacking objects, wiping surfaces, sorting coins) with a similar level of intensity. The results, however, did not confirm any significant improvements in the group which received FES compared to the control group (activities were measures using the Motor Activity Log and the Action Research Arm Test).

In their study, Johnson and colleagues [49] combined BoNT-A treatment of the calf muscles with *FES* (biphasic electrical pulses with a frequency of 40 Hz, a pulse width of 30–350 ms, and currents up to 100 mA of the peroneal and the anterior tibial muscle for ankle joint extension

and eversion in the leg swing phase, caused by a heel switch) and compared this course of treatment to conventional physiotherapy (two to three times per week for 45 min) without BoNT-A therapy. All patients were in their first year after stroke and were experiencing problems with heel contact at initial stance phase due to premature calf muscle activation during walking (measured through surface EMG). Although the study was only conducted in a small number of patients, a significant reduction in calf muscle tone, an increase in gait speed, and a decrease in effort (measured with the Physiological Cost Index) were evidenced.

At present, there are still insufficient data to make definitive recommendations on indications, stimulation parameters, programs, and outcome parameters for *FES*. Future studies on combined treatment of BoNT-A and *FES* should also consider and include standardized comparisons of different stimulation parameters (reduction of muscle tone in spastic agonists/increase of muscle tone in atrophic paretic antagonists, frequency and duration of ES) while trying to achieve the most homogeneous grouping possible (in terms of chronicity, control of voluntary movements and ability to act).

14.3.4 Case Example and Recommendations

The case described in Chap. 5 is presented here in detail.

61-year-old farmer suffering from the consequences of a hypertensive right basal ganglia hemorrhage. Three months after onset, he exhibited spastic plegia of the left arm and hand. Passive elbow and wrist extension as well as finger extension were painful against a moderate resistance (mAS 2°); stretching fingers was painful at the end of passive range of motion. Moderate spastic flexor synkinesis of left elbow and hand. Minimal control of voluntary elbow flexion was present; distally no selective movement control retrievable. Due to finger and wrist flexor spasticity, performing daily hygiene of the left hand was painful and possible only to a very limited extent.

A combined treatment consisting of BoNT-A injections and *(F)ES* was used to treat left arm flexor spasticity.

14.3.4.1 Treatment Goals

Stretch fingers against low resistance without pain—within 4 weeks (d210). Wash and towel off left hand independently—within 6 weeks (d520). Secure objects in place on a table using the paretic hand—within 6 weeks (d440).

The following muscles in the left arm were treated:

m. brachialis	0.5 vials	(2 sites)
m. pronator teres	0.3 vials	(1 site)
m. flexor carpi radialis	0.3 vials	(1 site)
m. flexor carpi ulnaris	0.3 vials	(1 site)
m. flexor pollicis longus	0.3 vials	(1 site)
m. flexor digitorum profundus	0.3 vials	(2 sites)
m. flexor digitorum superficialis	1.0 vial	(2 sites)
In total:	3.0 vials	(6.0 ml)

Chemodenervation was performed in a sonography-targeted manner and was well-tolerated.

Immediately afterward and during the following three days, the injected upper and forearm flexors were stimulated for 30 min using neuromuscular electrical stimulation (NMES) with biphasic rectangular pulses at a frequency of 3 Hz and a pulse width of 200 µs. Subsequently, also the antagonistic elbow and forearm extensors were stimulated using NMES with biphasic rectangular pulses for over 30 min once per day. Additionally, a positioning and stretching program for the left arm was compiled.

After ten days, the muscle tone in the elbow and wrist had reduced considerably (however still against moderate resistance—mAS 2°); stretching fingers against low resistance (mAS 1+) was possible free of pain. For the first time, minimal voluntary elbow extension and voluntary finger flexion within flexion synkinesis could be noticed; no selective finger extension retrievable. Only low-degree spastic flexion synkinesis in the left elbow and hand.

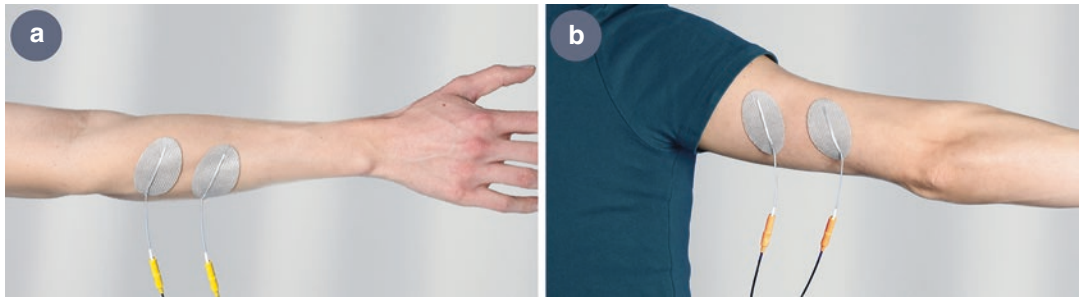

Fig. 14.4 Electrode placement for *FES*

In the following weeks, an EMG-triggered *FES* of the antagonistically acting wrist, finger, and elbow extensors was performed daily (see Fig. 14.4. Electrode placement for *FES*). Again, biphasic rectangular pulses with a frequency of 30 Hz and a pulse width of 200 µs were used for FES. Predefined plateau and pause times were included in the timed sequence of stimulation channels. M. triceps brachii served as trigger muscle for EMG function. This allowed for initial extensor activity that was enhanced by means of additional electrical stimulation. The stimulation of the second channel for the hand and finger extensors was performed with a time lag of 2 s. To avoid a stimulation-induced increase in flexor muscle tone via stretch reflex, an adequately long current rise time of 3 s and a corresponding fall time of 2 s were chosen. The current intensity was selected individually and on a daily basis in order to allow the target muscles to contract as clearly visibly as possible, but to avoid a simultaneous spill over on the arm flexors. In parallel, an occupational training (washing, dressing, fixing objects) was established.

Four weeks after start of treatment, the muscle tone in the elbow, wrist, and fingers was significantly lower (mAS 1+); stretching the fingers continued to be pain-free and against low resistance (mAS1+). Repetitive voluntary elbow extension and finger flexion was possible deviating from basal flexion synkinesis. Selective finger extension was retrievable to some extent but rapidly exhausted. Mild spastic flexion synkinesis in the left elbow and the hand were occurring only in phases of simultaneous tension of several muscle groups, e.g., when standing up or walking. After a little stretching preparation, the hand could be placed on the table with the fingers extended.

14.3.4.2 Goal Evaluation

Stretch fingers against low resistance free of pain—within 4 weeks (d210)—achieved. Wash and dry the left hand independently—within 6 weeks (d520)—partially achieved. Secure objects in place on a table using the paretic hand—within 6 weeks (d440)—partially achieved.

The family members were trained to continue the *FES* therapy program at home. A check-up appointment for further BoNT-A treatment (if needed) and for modification of *FES* (if necessary) was set and agreed on 12–16 weeks after the first treatment.

14.3.5 Summary

Treatment of SMD using BoNT-A injections has become a standard intervention in neurorehabilitation. Various goals, depending on the duration and severity of SMD, can be pursued. There are now sufficient data on combined treatment using NMES after BoNT-A injections available supporting the use of ES for the therapy of SMD in routine clinical practice.

Both, muscle tone reduction in spastic muscles and voluntarily triggered electrical stimulation of paretic-atrophic antagonists by a proximal muscle in the context of rudimentary actions (e.g., reaching for something) should be offered for treatment. When using *FES*, control of

voluntary movements, endurance, and ability to act should be carefully recorded in addition to changes in SMD.

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