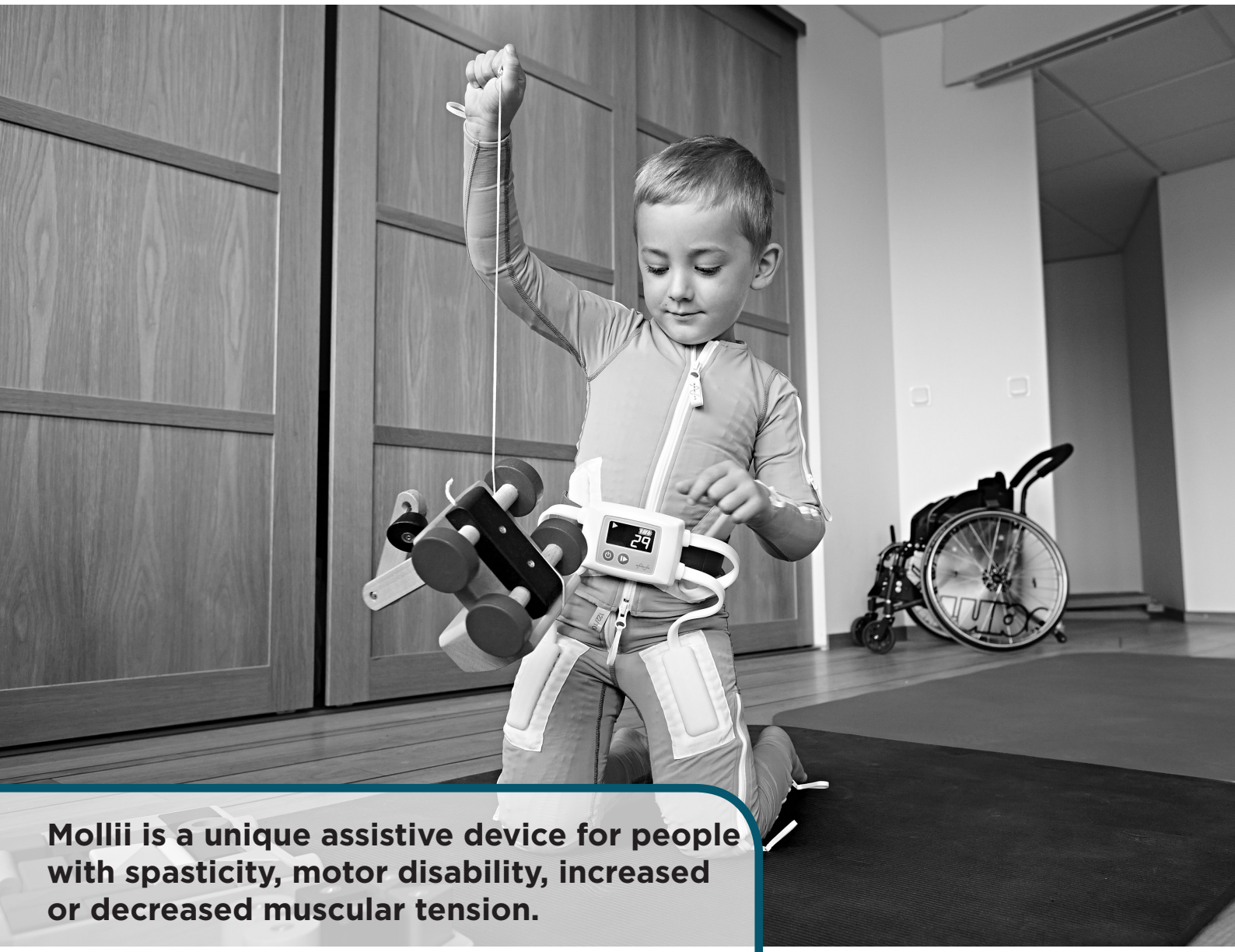
Mollii



Mollii is a unique assistive device for people with spasticity, motor disability, increased or decreased muscular tension.

Mollii provides electrical stimulation via a specially designed garment, thus helping the body to relax and increase movement, function and activity.

INERVENTIONS

Mollii is used for spasticity and increased or decreased muscular tension

Mollii prevents and counteracts different forms of muscle shortening and rigidity. The assistive device helps the user to regain control over muscular tension.

Who is Mollii for?

Mollii is an assistive device for people with spasticity and other forms of motor impairment due to cerebral palsy, stroke, brain damage, spinal cord injury or other neurological injuries. Molli can also be used to alleviate chronic pain.

How does it work?

Molli is a functional garment that consists of a pair of trousers, a jacket and a detachable control unit which sends electrical signals to the user via electrodes on the inside of the garment. The suit has 58 electrodes which can be combined in various ways. Mollii has a control unit which is individually programmed for each user. The person prescribing Mollii uses a computer program to adapt the active electrodes and the intensity (which muscles are to be activated by means of current). The settings are then saved in the Mollii control unit, making it simple for the device to be used at home.

What happens in the body when Mollii is used?

Mollii uses low level electric current to produce basic tension in the musculature. The current stimulates the antagonist to the spastic muscle. If, for example, the biceps is spastic, the triceps is stimulated which in turn makes the biceps relax. Relaxing the muscle enables active movement and a gradual improvement in function. The physiological mechanism is called reciprocal inhibition.

User-friendly:

Mollii is a functional assistive device that is designed to be used in the home environment. It is simple to use. If a person can put on an ordinary garment him/herself, then he/she can put Mollii on him/herself. There is a button for on/off and a button for play/ pause. A single push of the button starts muscle stimulation, which proceeds automatically for 60 minutes.

Use:

The device is used for approximately one hour on 3-4 occasions per week. For optimum effect, Mollii should be used together with physiotherapy, training, activity and movement. The effect is individual and remains for up to 48 hours.

Safety:

Mollii is not to be used with electrical implanted devices or medical devices that are affected by magnets, such as shunts. Consult a doctor at: epilepsy, cardiovascular disease, malignancy (cancer), infectious disease, fever, pregnancy, rashes or skin problems and if Mollii is intended for use with other medical devices or other medical treatment. The product is to be used according to the user manual.

Sizes:

Available in 25 sizes for children from size CL 104 to ladies and mens sizes.

Children (CL): 104, 110, 116, 122, 128, 134, 140, 146, 152

Ladies: XXS, XS, S, M, L, XL, XXL, XXXL

Mens: XXS, XS, S, M, L, XL, XXL, XXXL

Supplied with:

Jacket, trousers, control unit (with bag), belt, laundry bag and user manual.

Washing instructions:

40 degrees delicate wash once per month. In between the garment can be hand washed in lukewarm water.

Warranty period:

2 years

Classification:

Mollii is a medical device, class IIa.

Technical information

Power supply:	4 batteries (AAA)
Voltage:	20 V
Pulse width:	25-175 us
Frequency:	20 Hz
Pulse apperance:	Square wave
Channels:	40
Electrodes:	58
Electrode material:	Silicone rubber
Fabric material:	Nylon 82 %, Spandex 18 %

INERVENTIONS

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The Inerventions Method

- follow up and long term use of a new possible therapy for patients with spasticity

Mimi Olofsson Westerlund PhD, Emma Sjöberg, Jörgen Sandell, Christian Sandström, Hanne Kine Lauritsen and Fredrik Lundqvist

Please address any questions to info@inerventions.se

Facts about the Inerventions method

- The principle of the method is based on reciprocal inhibition.
- It reduces muscle tonus and improves locomotion in patients with spasticity.
- It is effective in relieving spasticity caused by cerebral paresis, stroke, multiple sclerosis as well as other forms of brain injury.
- 100% of the patients in the present study experienced improvements of function or quality of life and 90% were overall positive to the therapy.
- Only few and mild side effects have been reported.

Introduction

Spasticity is a sign of upper motor neuron dysfunction caused by brain injury and it results in paresis, immobilization and adaptive shortening of joints and muscles (Gracies, 2005). The chronic disuse of paretic muscles is accompanied by long-term adjusting rearrangements of the central and peripheral nervous systems. For patients with spasticity, the physical limitations caused by the condition often have severe impact on daily living and it will result in high societal costs due to sickleave and expensive treatments. However, a paretic limb may in some cases also be beneficial for the patient since it facilitates activities such as standing or walking which in turn protects against formation of deep venous thrombosis.

Electrical stimulation has previously been shown to be effective in reducing spasticity and increasing mobility (Robertson et al., 2006). Based on this finding, the Inerventions method was developed as a new and refined strategy for treating patients with spasticity. The principle of the method is based on reciprocal inhibition, i.e. upon contraction of a muscle, the antagonistic muscle will relax to not counteract the movement. Through stimulation of antagonistic muscles, the Inerventions method will hence reduce tonus of the spastic muscles. The majority of patients using the Inerventions method today have been diagnosed with spastic or dyskinetic cerebral palsy, however, it has also been used to successfully reduce spasticity in patients with multiple sclerosis, spinocerebellar ataxia, dystonia, stroke and other forms of acquired brain injury. The device is easy to apply and can readily be used at home, at care centers or at work as well as during physical exercise or rehabilitation. To obtain optimal effect, the recommended use of the Inerventions method is approximately 60-90 min every other day which in most patients will result in reduced spasticity and improved locomotion for up to 48 hours.

Materials and Methods

The Inerventions method

The Inerventions method is used to stimulate skeletal muscles (antagonistic to the spastic muscles) at a frequency of 20 Hz, and a pulse width of 30 µs. The electrodes cover both the upper and lower part of the body. The selection of stimulation sites is dependent on clinical diagnosis and the voltage applied to the electrodes is adjusted to suit every patient individually. A map of representative electrode positions is shown in Fig 1. The recommended use of the Inerventions method is 60- 90 minutes/day, 3-4 times a week, and 80% of the patients has used it weekly during the study period (Fig 2A). For optimal effect, the method can be used in combination with conventional physiotherapy and it may continue as long as a positive effect of the method is obtained.

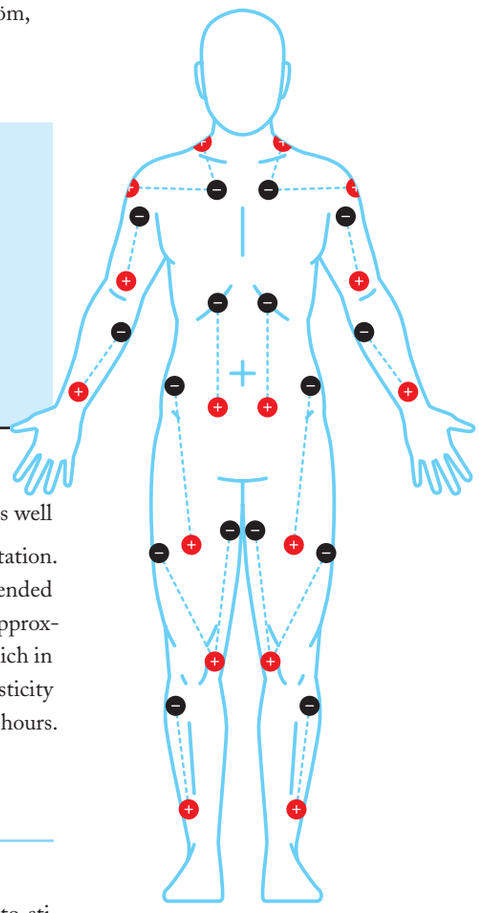
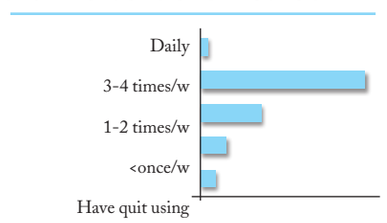


Fig 1. Representative map of the electrode positions used by the Inerventions method.

Reported use of the Inerventions method



Diagnoses

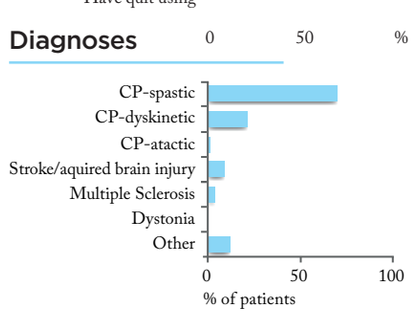


Fig 2 A,B. A) Reported use of the Inerventions method by the subjects participating in the study. B) Diagnoses included in the study. The data is presented as percentage of the total number of patients (n=117). w=weeks.

Study group

We evaluated the use of the Inerventions method in 117 male and female subjects with different neurological diagnoses covering cerebral palsy (79%), acquired brain injury or stroke (8%), and other diagnoses (13%) such as dystonia and multiple sclerosis (Fig 2B). The majority of the subjects participating in the study were children or young adults, however, some subjects above the age of 50 were included (Fig 3). All included subjects have used the method 6-24 months at the time of the survey (average 12-15 months) also included. The patient's physical condition at the start of the therapy was defined as baseline level and all positive and negative changes observed thereafter were registered. The survey was completed by the Inerventions method users themselves or when necessary, by an assisting caregiver.

Results

Based on the finding that low frequency electrcial stimulation can reduce spasticity, we evaluated the use of the Inerventions method in patients with spasticity. The results from the study showed an overall improvement of the general condition in 90% of the patients. Studying individual parameters (Fig. 5), the most pronounced effect was seen on locomotion which improved in 61% of the patients, while general spasticity was reduced in 60%. The ability to straighten the hand/fingers was improved in 46% and 34% of the patients respectively. In addition, the patients also reported improved balance, trunk stability, range of motion, mobility, speech, digestion, better mood, reduced pain, improved sleep quality, and an overall improved quality of life.

Age of patients

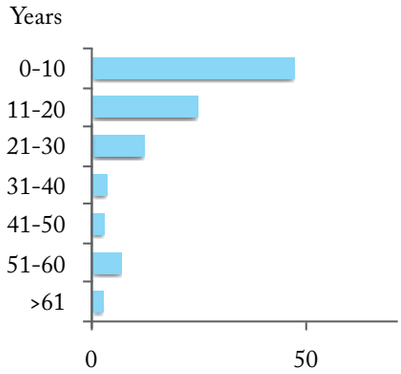


Fig 3. Age distribution of the subjects participating in the study evaluating the Inerventions method. The data is presented as percentage of the total number of patients (n=117).

32% of the patients had planned spasticity treatments at baseline, and 90% of these patients could cancel these treatments due to improvement (fig 4A-B & 4D). 24% of the patients could stop using one or more assistive devices, such as wheelchair and walker (fig 4C and 4E). Interestingly, 100% of the patients participating in the study reported some form of improvements on either physical function or quality of life after being treated with the method. Only as little as 4% reported negative effects on digestion, mobility, spasticity and/or pain. In summary, the results from the present study showed that 90% of the patients were positive to therapy with the Inerventions method, whereas only 3% were negative and 7% were neutral (Fig 4).

Discussion

The Inerventions method offers a new strategy for treating patients with spasticity caused by brain injury. By applying low frequency electrical stimulation to antagonistic muscles, the tonus of a spastic muscle can be reduced. The method can be used as single therapy or in combination with other forms of treatments such as conventional physiotherapy. Several beneficial effects of the method have been reported such as improved mobility, reduced muscle tonus and pain as well as higher quality of life. The primary effects of the therapy may also be accompanied by secondary effects such as less need of personal assistance, medication and surgery as well as lower societal costs.

The strategies commonly used for treating spasticity today involve different forms of medication, surgery, botulinum toxin injections and physiotherapy. These treatments may be effective in reducing spasticity, but they all have limitations and are associated with negative side effects. Baclofen for example, modulates pain by binding to gamma-aminobutyric acid (GABA) receptors however, an undesirable side effect of the treatment is muscular weakness, sedation and respiratory problems and not all patient benefit from the treatment (Ørsnes et al., 2000). Moreover, the drug has limited capacity to cross the blood-brain barrier and has to be administered through intratechtal injection into the cerebrospinal fluid to reach high concentrations. Tizanidine on the other hand acts as an alpha-2 adrenergic receptor agonist and has been shown to exert positive effects on spasticity in patients with stroke (Milanov et al., 1994). It is easy to use since it can be administered orally however, like baclofen, tizanidine is associated with undesirable side effects such as sedation, dry mouth and prolonged QT interval and in some cases also hallucinations (Brashear et al., 2008; Montane et al., 2004). Botulinum toxin injection is another form of treatment commonly used in patients with spasticity. It causes inhibition of acetylcholine release at the neuromuscular

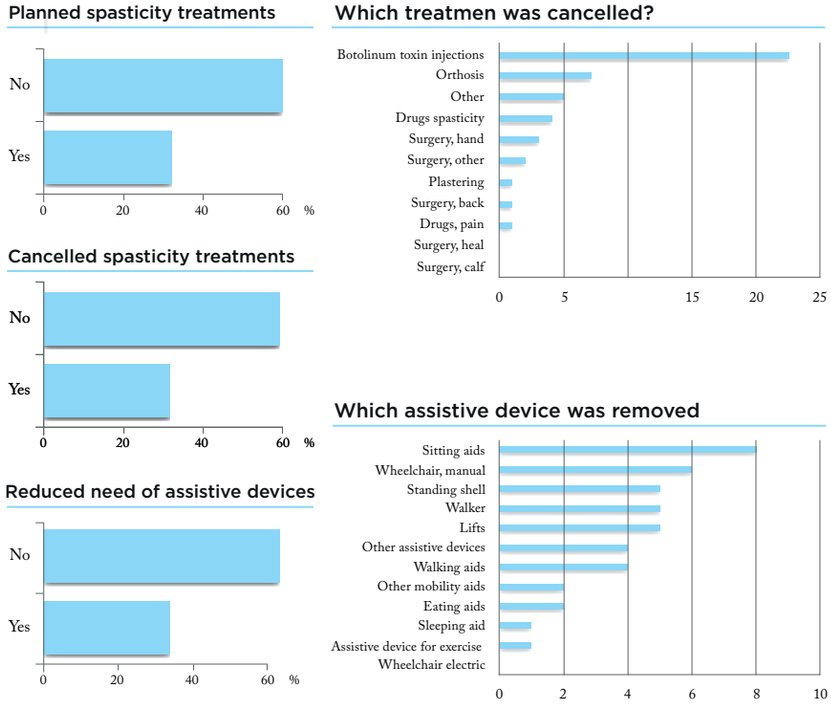


Fig 4A-E. A Percentage of patients with planned spasticity treatments, B Percentage of patients with one or more cancelled spasticity treatments, C Percentage of patients with one or more removed assistive devices, D Type of treatment cancelled, E Type of assitive device removed.

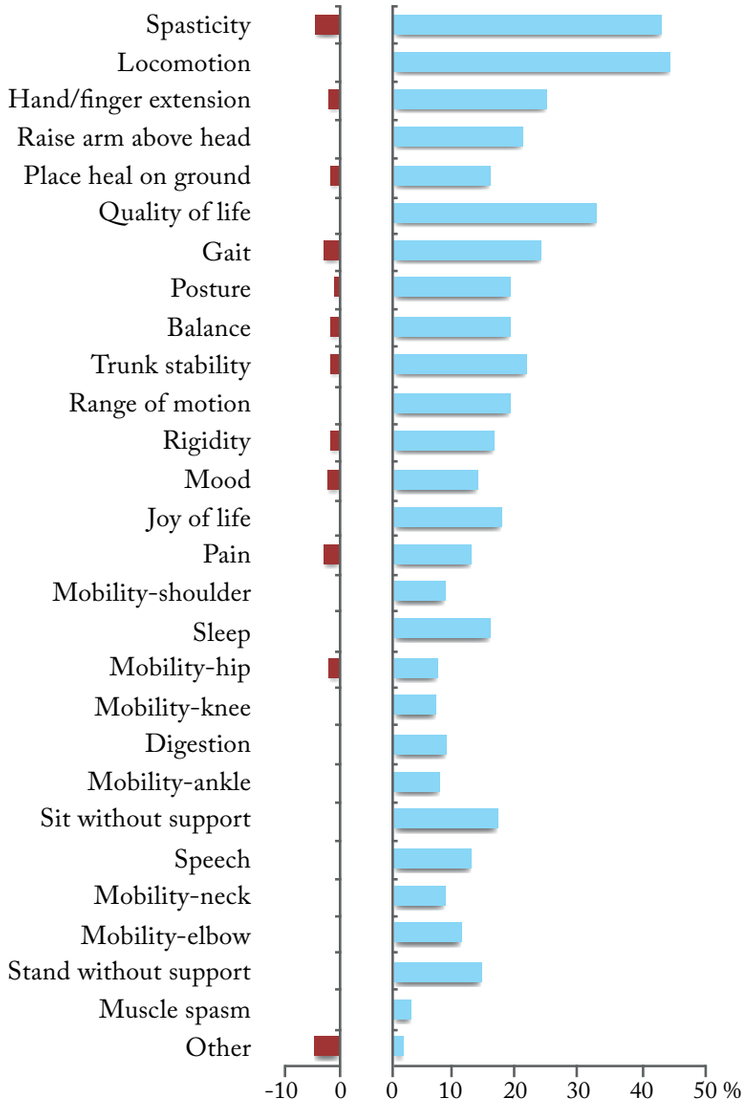


Fig 5. Reported effects of the Inerventions method. Blue bars represent the percentage of patients reporting positive effects of the therapy whereas red bars represent patients reporting negative effects.

junction and a reversible block of synaptic transmission. The therapeutic effect is most pronounced two months after injection and the procedure has to be repeated as the effect wears off. Moreover, long-term treatment with the toxin may also result in formation of antibodies (Müller et al., 2009).

The Inerventions method has been shown to have several beneficial effects in patients with spasticity and at the same time, it is associated with relatively few side effects. The effects of the therapy are evident already after 5-20 minutes which gives a direct quality control of the method. It is also highly motivating for the patient to observe such an instant effect of the therapy. Since the degree of spasticity may vary between patients depending on the clinical diagnosis as well as in a patient over time, it is important to treat every subject individually and adjust the device accordingly. The effect of the Inerventions method usually lasts for 24-48 h (range 4-72 h) after which it gradually wears off. To obtain optimal effect, the therapy should be repeated 3-4 times/ week. The Inerventions method is not exclusive. It can be used in parallel with other treatments such as medication or botulinum toxin injections. It can also be used in combination with physiotherapy and physical exercise to reduce the activity of the α-motor neurons in the spinal cord (Gracies, 2001). Since the Inerventions method was introduced in 2009 only few and relatively mild side effects such as urticaria around the site of the electrodes have been reported. Attention should be given to patients with different forms of heart conditions and it is not recommended to use the therapy in patients with heart failure or a pacemaker.

The mechanisms responsible for the direct effects of the Inerventions method may partly be explained by reciprocal inhibition and possibly also by other reflex mechanisms. Preliminary unpublished data from our studies have also indicated long-term effects of the therapy. By following the patients for several months, a gradual improvement of mobility has been observed. The underlying mechanism of this effect is still unknown, however it has been suggested that synchronized firing of neurons can result in increased synaptic strength according to the Hebbian theory ('cells that fire together, wire together').

In conclusion, the Inerventions method has been shown to be successful in reducing spasticity, particularly when used in combination with physical activity. This can result in increased mobility, reduced pain and an overall improved quality of life for the patients. Based on the many positive effects and the relatively few side effects, we suggest the Inerventions method as a new possible therapy for patients with spasticity.

References

Brashear A, Lambeth K. Spasticity. Curr Treat Options Neurol 2009;11:153–61. Gracies JM. Pathophysiology of impairment in patients with spasticity and use of stretch as a treatment of spastic hypertonia. Phys Med Rehabil Clin N Am 2001;12:747– 68. vi. Gracies J-M. Pathophysiology of spastic paresis I: paresis and soft tissue changes. Muscle Nerve 2005;31:535–51. Milanov I, Georgiev D. Mechanisms of tizanidine action on spasticity. Acta Neurol Scand 1994;89:274-9. Montane E, Vallano A, Laporte JR. Oral antispastic drugs in nonprogressive neurologic diseases. Neurology 2004;63:1357–63. Müller K, Mix E, Saberi FA, Dressler D, Benecke R. Prevalence of neutralizing antibodies in patients treated with botulinum toxin type A for spasticity. J Neural Transm 2009;116:579–85. Robertson V, Ward A, Low J, Reed A. Electrotherapy Explained: Principles and Practice, Elsevier 2006. Ørsnes GB, Sørensen PS, Larsen TK, Ravnborg M. Effect of baclofen on gait in spastic MS patients. Acta Neurol Scand 2000;101:244–8.

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Inerventions is a company in the field of medical technology that has developed a new and unique assistive device for people with spasticity, inmobility and increased muscle tension.

Mollii provides electrical stimulation trough a specially designed garment and helps the body to relaxation, increased movement through activity.

Mollii is an assistive device for people with spasticity and increased muscle tension due to cerebral palsy, stroke, Multiple Sclerosis, Parkinson´s disease, spinal impairment or other neurological impairment. Mollii can also be used for rehabilitation in pain management.

Mollii previously called Elektrodress.

Throughout out the development of Mollii, Inerventions has worked together with researchers at CTMH, Centre of Medical Technology and Health, Smart Textiles, MedTech West.

CTMH Centre is a collaboration between the Karolinska Institutet, Kungliga Tekniska Högskolan and Stockholms läns landsting.

Smart Textiles is a center of expertise on textile inovation and textile solutions.

MedTechWest is a collaboration between Chalmers Tekniska Högskola, Sahlgrenska Universitets sjukhuset and Västra Götalandsregionen.

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Health economy

Cost-effectiveness analysis of the Inerventions method

– A pilot study comparing Inerventions method to other interventions for spasticity treatment for children with Cerebral Palsy in Sweden.

Jingwen Shi, jingwen.shi@ki.se, Emma Sjöberg, Fredrik Lundqvist

Abstract:

Background: Cerebral palsy (CP) is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes, often resulting in impaired voluntary muscle control, difficulty relaxing muscles, difficulty initiating rapid movements, and the inability to regulate controlled movements. Objective: To assess the cost-effectiveness of Inerventions method and compare it with conventional medical treatments, e.g. baclofen, botolium toxin, surgery, for children with cerebral palsy in Sweden. Methods: An analytic model, based on both qualitative and quantitative research, was used to study the cost-effectiveness of Inerventions method compared to alternative treatments. Standardized measurements (CPUP, uppföljningsprogram för cerebral pares) and patient interviews/surveys, was used to assess the treatment effectiveness in randomly selected patients' medical conditions. Costs (in sek at April 2012 values) were obtained by estimations from suppliers, hospitals and healthcare agencies. Sensitivity analysis was performed to compensate for data uncertainty. Results and conclusion: Preliminary results showed that Inerventions method was more effective than all alternative treatments in this study, and less costly than baclofen and surgery (with similar costs as botulinum toxin). This points to a new treatment method for children with cerebral palsy worth paying by decision makers.

Introduction

Cerebral palsy (CP) is the most common cause of physical disability in children, with a prevalence of about 2 per 1000 newborns in western countries (about 200 newborns every year in Sweden) (1). Cerebral palsy in childhood is often associated with spasticity, a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (2). This often results in impaired muscle control, difficulty relaxing muscles, difficulty initiating rapid movements, and the inability to regulate controlled movements. Spasticity of cerebral origin can severely impair a child's ability to perform basic tasks such as speaking, eating, and walking (3). Moreover, these patients are at risk of secondary conditions that cause a loss of musculoskeletal function, spine and lower extremity joint deformities, and deterioration in quality of life (4). These often cause an enormous emotional and financial burden for the patients and caregivers (5).

Current treatments for children with cerebral palsy include oral and intrathecal administered baclofen (3), injections of botulinum toxins (4), as well as selective dorsal rhizotomy and orthopedic surgery (6). Baclofen is a small molecule drug with inhibitory effects on spinal cord reflexes and the brain (7). Botulinum toxins bind to neuromuscular junction and result in partial flaccid paralysis (4). Selective dorsal rhizotomy isolates the spasticity-causing nerves to be destroyed, whereas orthopedic surgery lengthens the tendons or cuts part of the affected muscles to release the tightness and spasticity related to cerebral palsy (6). Inerventions method is a new treatment method based on electrodes stimulation of muscles, which simultaneously stimulate the body's reflex system to reduce spasticity. The positioning of electrodes is tailored to the patient's specific medical needs (Inerventions AB).

The aim of this study is to assess the cost-effectiveness of Inerventions method compared to conventional treatments in the context of the Swedish healthcare system.

Methods

We studied the costs and health benefits for patients before and after implementing Inerventions method, and compared it with conventional treatments for the phase of treatment. The selection of patients was randomized. The perspective of cost-effectiveness analysis was that of the healthcare, meaning that all relevant resources consumed within the care sector were taken into account.

Specific cost sections to be included in this study was investigated by means of patient interviews, expert opinions and literature, as listed in Table 1. Unit costs were obtained from suppliers, hospitals, and healthcare agencies (Table 1). The quantities of various resource usages are collected from patient interviews and surveys. Total annual costs were calculated from unit costs multiplied by quantities of usage. The costs were valued using the Swedish guidelines for pharmacoeconomic research and real unit prices including taxes (8). Costs were estimated for the year 2012 in Swedish kronors (SEK). Due to the roughness of the estimates, we did not take into account the interest over the depreciation periods. We discounted costs that were not available for the year 2012 with 3% per year according to the Swedish pharmacoeconomics guidelines.

Resource category	Resource content	Unit cost (SEK)	Source of information
Intervention	Baclofen (oral)	928-2,1960per year	FASS
	Botulinum toxin	2,000-8,000 per injection	FASS, Literature
	Surgery	41,400	Akademiska sjukhus
	Elektrodress	9,000-16,200 per year	Inerventions AB
Combined medication	Alvedon, Ipren	1-5 per dosage	FASS
Physiotheraphy	Salary, adminitrative costs	256 per hour	Försäkringskassan
Assistive device	Wheelchair	45,000-200,000	Hjälpmedel Stockholm
	Seat/chair	15,000-30,000	Anatomic SITT AB
	Stand and walk support	6,820-37,500	Etac Sverige AB
	Back and leg support	500-1,000	
Personal assistence	Salary, education, administrative costs	267 per hour	Försäkringskassan
Measurment tests	X-ray	250 per visit	Literature[9]
Special medical care	Primary care	1,617 per visit	Literature[10]
	Specialist care	4,808 per visit	Literature
	Hospitalization	30,269 per stay	Literature[10]
Oppurtunity costs	Study absence for patient	477 per day for primary school 516 per day for high school	SCB
	Study/work absence for caregiver	2,218 per day	Försäkringskassan
Adjustive living	Bath and toilet device	10,460-11,850	Etac Sverige AB
	Lifting device	18,750-31,250	
Extra resources in school	Personal assistance	267 per hour	Försäkringskassan
Complications	Side effects, repeated surgery	variable	Akademiska sjukhus

Table 1 Unit costs of healthcare related to the treatment of children with cerebral palsy.

Outcome measures: For assessment of the health benefits, we used the CPUP (uppföljningsprogram för cerebral pares) standard measurement criteria on hip, knee, and foot, as well as patient interviews/ surveys. Surveys included the application of VAS (Visual analogue scale), a straight horizontal line with anchor points 'completely unhelpful' (score 0) and 'completely helpful' (score 100) as a measure for rating pain, anxiety, fatigue, etc (11). The VAS has previously shown preliminary reliability and validity for both child self-report and parent-proxy report (11). We used VAS for individually formulated problems (Table 2). We plotted these estimates on a cost-effectiveness plane. Cost-effectiveness plane has a horizontal axis representing the effect and a vertical axis representing the costs.

Ethics

The study was anonymous, and we obtained informed consent from the parents, and in some cases from the patients if they were aged 12 years or older and capable of understanding the nature and impact of the study.

Results and Discussion

Cost: The unit costs of different interventions as well as related resources are listed in Table 1.

Effectiveness: The medical conditions of children with cerebral palsy were measured before and after implementing Inerventions method, according to the CPUP criteria.

Among the 34 patients measured, all patients showed mild to significant degree of improvements on hip, knee and foot (Figure 1). Among the 15 patients interviewed and 17 patients surveyed, 30 patients reported mild to significant improvements whereas 2 reported none to worse effects of implementing Inerventions method (Figure 2C). Common improvements were muscle relaxation, body strength (e.g. hand grasp) and daily activities (e.g. speaking, toilet use). Interestingly, patients who have experienced positive effects reported that the improvements last longer with time, whereas the incremental improvements became smaller with time. Potential negative sides include irritation on the skin and the difficulty to use Inerventions method treatment on the foot (due to bone structures). Nevertheless, Inerventions method remains the least invasive method of treatment. Patients also rated the effectiveness of Inerventions method as well as alternative treatments (baclofen, botulinum toxin, and surgery) on a VAS scale, with the resulting scores Inerventions method > baclofen, botulinum toxin > surgery (Figure 2). The effectiveness of alternative interventions is discussed in the following section 'Cost-effectiveness analysis'.

Gross motor function
Body structure and function (arm, ankle, figure, back, leg, knee, foot)
Sitting and standing
Functional mobility (walking distance, use of stairs, use of wheelchair)
Daily activity (eating, sleeping, physical activity)
Pain
Complications
Need for caregiver

Table 2 Measurement criteria of treatment effectiveness for children with cerebral palsy, using VAS.

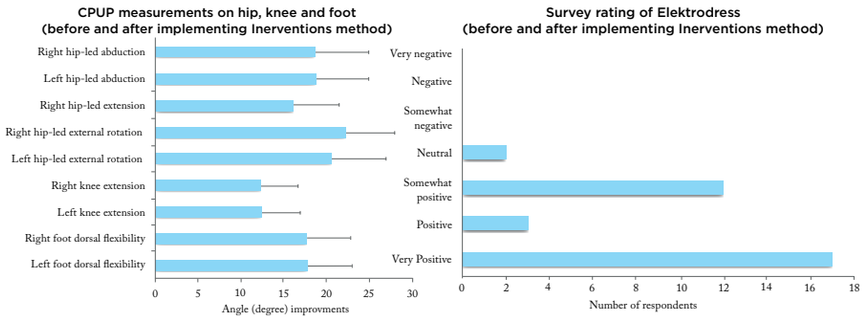

Figure 1A. Improvements of 34 patients' medical conditions on hip, knee and foot angles before and after implementing Inerventions method, as measured following the CPUP criteria.
Figure 1B. Patient satsifaction after using the Inerventions method

Cost-effectiveness analysis: As shown in figure 3, the cost-effectiveness analysis showed that Inerventions method was more cost-effective than: (1) baclofen and surgery, as it was more effective and less costly; (2) botulinum toxin, as it was more effective and similarly costly. Interestingly, baclofen was the most expensive, presumably due to the high frequency and cumulative consumption. On the other hand, surgery was the least effective and the situation varied greatly among individuals.

Baclofen was reported to have efficacy in reducing spasticity among cerebral palsy patients. However, it has side effects such as fatigue, dizziness, headache and nausea (12). Between the two common routes of baclofen administration, intrathecal baclofen has been shown to reduce spasticity with greater efficacy and fewer side effects, compared to oral delivery of baclofen (13- 15). Oral baclofen seems more commonly as all surveyed patients in this study have applied oral baclofen. Oral baclofen is also commonly used as combined medication with surgery. Despite the clinical benefits, cost is a barrier to more widespread use of baclofen therapy (3). Botulinum toxin was reported by patients to reduce spasticity immediately after the first few times of injections, lasting for about three months each time. The conditions are then reversed, and further injections are not as effective --- a phenomenon termed secondary unresponsiveness which has been attributed to the development of neutralizing antibodies against botulinum toxin (4). Moreover, com-

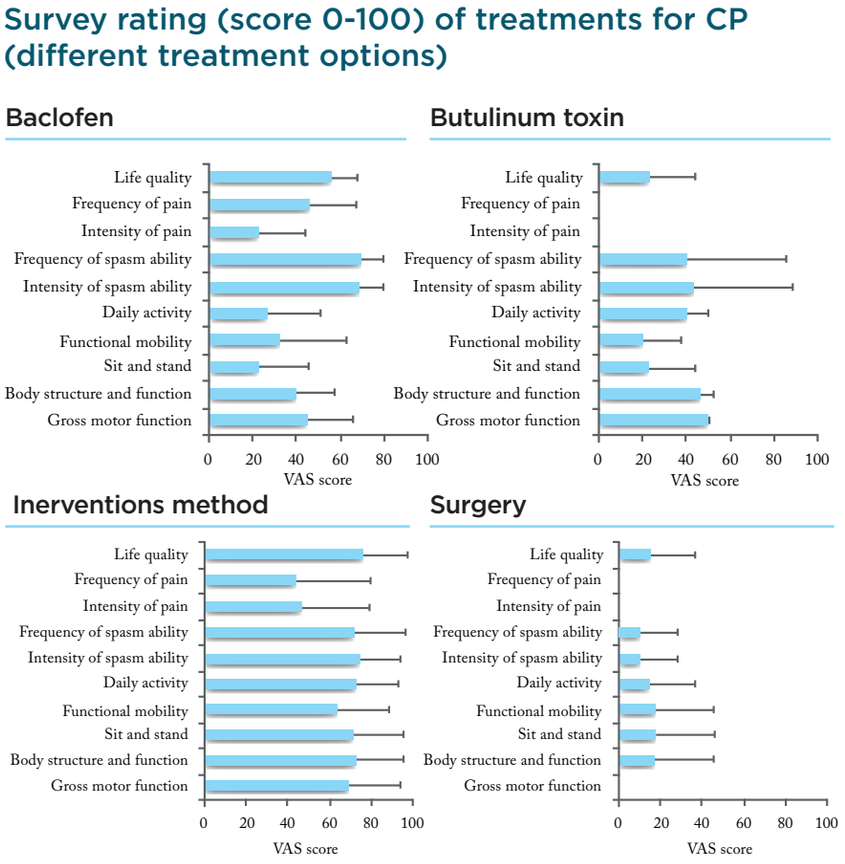

Figure 2 A-D. VAS rating of baclofen (A), botulinum toxin (B), Inerventions method (C) and surgery (D) as treatment methods for children with cerebral palsy.

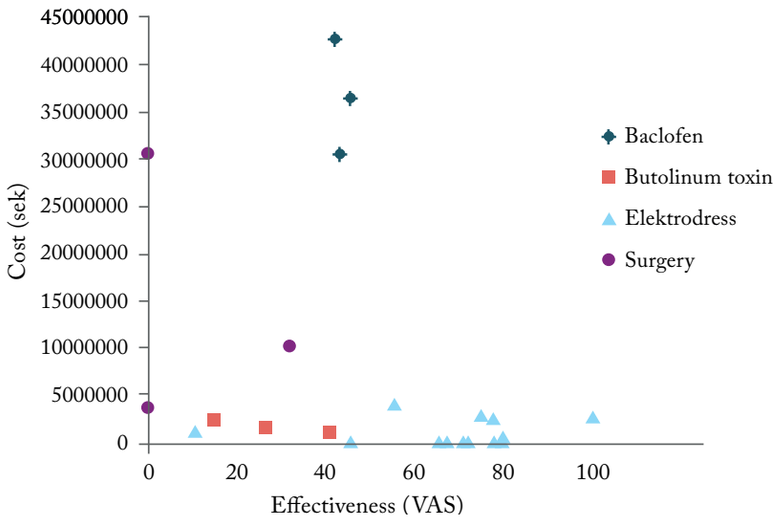

Figure 3. Cost-effectiveness analysis of different treatments for children with cerebral palsy.

monly reported are pain around the injection site, frequent falls from balance problems, and generalized fatigue (4). Botulinum toxin is a relatively cost-effective treatment, as botulinum toxin administration to cerebral palsy children resulted in a 51% reduction in the healthcare cost compared to orthopedic surgery (9). Finally, surgery was the least appreciated measure, and individual variations were significant. Orthopedic surgery is usually used to reduce the effects of spasticity that are resistant to other forms of treatments (16). Some patients also reported surgery failures, where their medical conditions became worse after the surgical procedures (e.g. the patient could not stand up after surgery whereas this was possible before surgery). The primary cost driver of surgery was hospital stay, accounting for 63% of the managing costs (9). In addition to the high financial cost, surgery is also closely associated with the intangible cost of pain, probability of adverse consequences, and lost productivity. Therefore, surgery was considered a less favorable option and best delayed until the child's tendons and joints have grown to a reasonable size, since outcome is more difficult to predict in younger child (9).

Sensitivity analysis: Sensitivity analysis showed similar results of cost-effectiveness for different interventions for children with cerebral palsy, with some differences in the magnitude of costs (figure 4).

Moreover, during the interviews of 15 patients, several potential cost changes before and after implementing Inerventions method were identified:

-cost increase: increase of assistive device such as leg support (increase 500-1000 sek).

-cost decrease: intake of Baclofen decreased from 3 to 2 pills/day (saving 928 sek/year); physical therapy decreased from 4-5 times/week to 2-3 times/week (saving 24,576 sek/year); operations were cancelled (saving 41,400 sek); study absence for patients decreased from 20% to none (saving 30,000 sek/year); work absence for caregivers decreased from 1-2 days/week to none (saving 106,464-212,928 sek/year).

This could potentially range from a yearly cost increase of 1000 sek to a yearly cost saving of 309,832 sek/year per patient.

Limitations: There are a few limitations in this study: first, the study only encompass a limited number of subjects (34 for CPUP measurements, 15 interviews and 17 surveys); second, there might be potential biases where patients that have experienced significant positive (or negative) effects are more inclined than others to answer the survey; third, more follow-up studies will be needed to study the incremental costeffectiveness and lifetime cost-effectiveness of Inerventions method as compared to alternative treatments.

Conclusions

This pilot study suggest the superior cost-effectiveness of Inerventions method (as compared to baclofen, botulinum toxin and surgery) for children with cerebral palsy and, from an economic point of view, justify the reimbursement of Inerventions method for this group of patients in Sweden.

Least-costly scenario

Most-costly scenario

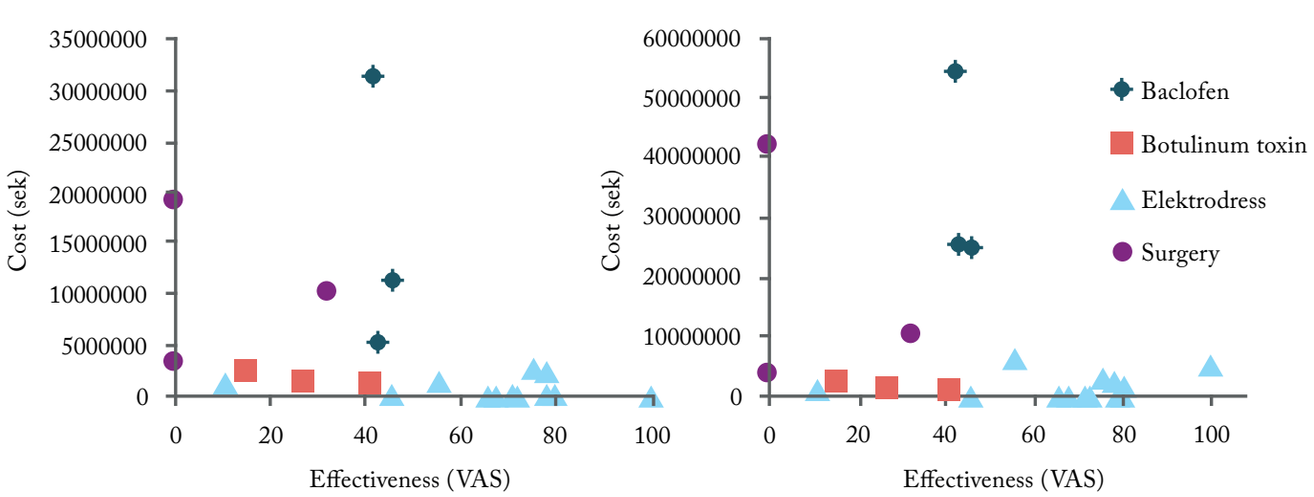

Figure 4. Sensitivity analysis of cost-effectiveness for different treatments for children with cerebral palsy: (A) least costly scenario, (B) most costly scenario.

References:

1. Koman, L. A.; Smith, B. P.; Shilt, J. S., Cerebral palsy. Lancet 2004, 363, (9421), 1619-31.

2. Lance, J., Spasticity: Disorder of Motol Control. Chicago, IL: Year Book Medical 1980, 485-494.

3. de Lissovoy, G.; Matza, L. S.; Green, H.; Werner, M.; Edgar, T., Cost-effectiveness of intrathecal baclofen therapy for the treatment of severe spasticity associated with cerebral palsy. J Child Neurol 2007, 22, (1), 49-59.

4. Jefferson, R. J., Botulinum toxin in the management of cerebral palsy. Dev Med Child Neurol 2004, 46, (7), 491-9.

5. Rawlins, P., Patient management of cerebral origin spasticity with intrathecal baclofen. J Neurosci Nurs 1998, 30, (1), 32-5, 40-6.

6. Chicoine, M. R.; Park, T. S.; Kaufman, B. A., Selective dorsal rhizotomy and rates of orthopedic surgery in children with spastic cerebral palsy. J Neurosurg 1997, 86, (1), 34-9.

7. Bensmail, D.; Ward, A. B.; Wissel, J.; Motta, F.; Saltuari, L.; Lissens, J.; Cros, S.; Beresniak, A., Cost-effectiveness modeling of intrathecal baclofen therapy versus other interventions for disabling spasticity. Neurorehabil Neural Repair 2009, 23, (6), 546-52.

8. General guidelines for economic evaluations from the Pharmaceutical Benefits Board. Pharmaceutical Benefits Board (LFN). 2003.

9. Ruiz, F. J.; Guest, J. F.; Lehmann, A.; Davie, A. M.; Guttler, K.; Schluter, O.; Dreiss, G., Costs and consequences of botulinum toxin type A use. Management of children with cerebral palsy in Germany. Eur J Health Econ 2004, 5, (3), 227-35.

10. Bolin, K.; Lundgren, A.; Berggren, F.; Kallen, K., Epilepsy in Sweden: health care costs and loss of productivity- a register-based approach. Eur J Health Econ 2011.

11. Sherman, S. A.; Eisen, S.; Burwinkle, T. M.; Varni, J. W., The PedsQL Present Functioning Visual Analogue Scales: preliminary reliability and validity. Health Qual Life Outcomes 2006, 4, 75.

12. Cryan, J. F.; Kelly, P. H.; Chaperon, F.; Gentsch, C.; Mombereau, C.; Lingenhoehl, K.; Froestl, W.; Bettler, B.; Kaupmann, K.; Spooren, W. P., Behavioral characterization of the novel GABAB receptor-positive modulator GS39783 (N,N'-dicyclopentyl-2-methylsulfanyl-5-nitro- pyrimidine-4,6-diamine): anxiolytic-like activity without side effects associated with baclofen or benzodiazepines. J Pharmacol Exp Ther 2004, 310, (3), 952-63.

13. Butler, C.; Campbell, S., Evidence of the effects of intrathecal baclofen for spastic and dystonic cerebral palsy. AACPDM Treatment Outcomes Committee Review Panel. Dev Med Child Neurol 2000, 42, (9), 634-45.

14. Gilmartin, R.; Bruce, D.; Storrs, B. B.; Abbott, R.; Krach, L.; Ward, J.; Bloom, K.; Brooks, W. H.; Johnson, D. L.; Madsen, J. R.; McLaughlin, J. F.; Nadell, J., Intrathecal baclofen for management of spastic cerebral palsy: multicenter trial. J Child Neurol 2000, 15, (2), 71-7.

15. Albright, A. L., Intrathecal baclofen in cerebral palsy movement disorders. J Child Neurol 1996, 11 Suppl 1, S29-35. 16. Cheng, J. C.; So, W. S., Percutaneous elongation of the Achilles tendon in children with cerebral palsy. Int Orthop 1993, 17, (3), 162-5.

Inerventions is a company in in field of medical that has developed a new and unique assistive device for people with spasticity, inmobility and increased muscle tension.

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Throughout out the development of Mollii, Inerventions has worked together with researchers at CTMH, Centre of Medical Technology and Health, Smart Textiles, MedTech West.

CTMH Centre is a collaboration between the Karolinska Institutet, Kungliga Tekniska Högskolan and Stockholms läns landsting.

Smart Textiles is a center of expertise on textile inovation and textile solutions.

MedTechWest is a collaboration between Chalmers Tekniska Högskola, Sahlgrenska Universitets sjukhuset and Västra Götalandsregionen.

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INERVENTIONS

THE INERVENTION´S METHOD

Summarize of electro-thearapy and background in treatments against spasticity

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2014

mollii elektrodress

Introduction

The Upper Motor Neurone Syndrome (UMNS) is defined as alterations in the physiological motor control in the skeletal muscle after an insult and/or lesion in the Central Nervous System (CNS). One of the main components and outcomes is spasticity, known collectively as a "positive" phenomenon characterize by muscle overactivity. Hyperactive spinal reflexes mediate most of these positive phenomena as lesions or insults in the CNS lead to disturbances of the control of spinal reflexes. When spasticity produces a clinical disability interfering with daily activities, medical treatment is recommended. Currently there are available many different approaches including pharmacological, physical, surgical and electro therapies that will eventually increase the functionality and quality of life of affected individuals by decreasing the level of spasticity as a result of injuries in the CNS (both in brain and spinal cord).

Many currently available therapies against spasticity rely on pharmacological effects at the spinal and/or neuromuscular junction level. Their action is narrowed to the inhibition and/or blockade of the synaptic impulses between sensory neurons, inhibitory/excitatory interneurons and Motor neurons, *in other words their action mechanism shuts down the normal activity of the cells in charge of the spinal reflexes*. The aim of this document is to point out electro-therapy as a valid option in the treatment of spasticity. More importantly, as we will see, the facilitation of neural circuits (and cell activity induced by Electro Stimulation) in the spinal cord from patients with UMNS could help in the neuroplasticity processes that undergo in the nervous system upon an insult or lesion. We do not claim that electric stimulation should replace other therapies or that is the most suitable for any kind of spasticity regardless of the level and impairment that could induce. But as we will show here it can be used as an effective additional therapy that could help to improve the daily management of patients with spasticity. Of course, no treatment is 100% effective and as in many publications, reviews and editorials regarding the study of the medical management of the spasticity, we agree that the combination of electro-therapy with any other form of therapy could improve impairment movements and quality life among patients.

How do we move?

The motor system compromises a large number of different cell types (neurons, astrocytes, Schwan cells, macroglia,….), nuclei, synapses and a tight relationship between the central and the peripheral nervous systems (CNS and PNS). The process of movement has in the past been considered a sequence of steps like: Idea→Plan→Select→Move. Nevertheless this "step" approach underestimates the degree to which these elements are performed in parallel. The reason is that there are many types of cells in many different region executing actions oriented to initiate, coordinate and adjust one single movement which at the same time ensures a robust system as any damage structure can be compensated, to a certain extent, by activity of other structures.

Much of the brain and nervous system is devoted to the processing of sensory input, in order to construct detailed representations of the external environment. This elaborate processing would be of limited value, however, unless we had a way to act upon the environment that we are sensing, whether that action consist of running away from a predator or seeking shelter against the rain. In some cases the relationship between the sensory input and the motor output are simple and direct, however, our conscious actions require not only sensory input but a host of other cognitive processes that allow us to choose the most appropriate motor output for the given circumstances. In each case, the final output is a set of commands to certain muscles in the body to exert force against some other object or forces (e.g., gravity). This entire process falls under the subject of motor control which task relies in two principles: Functional segregation (different areas controlling different aspect of movement) and Hierarchical Organization (higher areas take decisions whereas lower areas tune the movements). To avoid an exhausting reading we will explain the organization of the motor system in two big hierarchical domains:

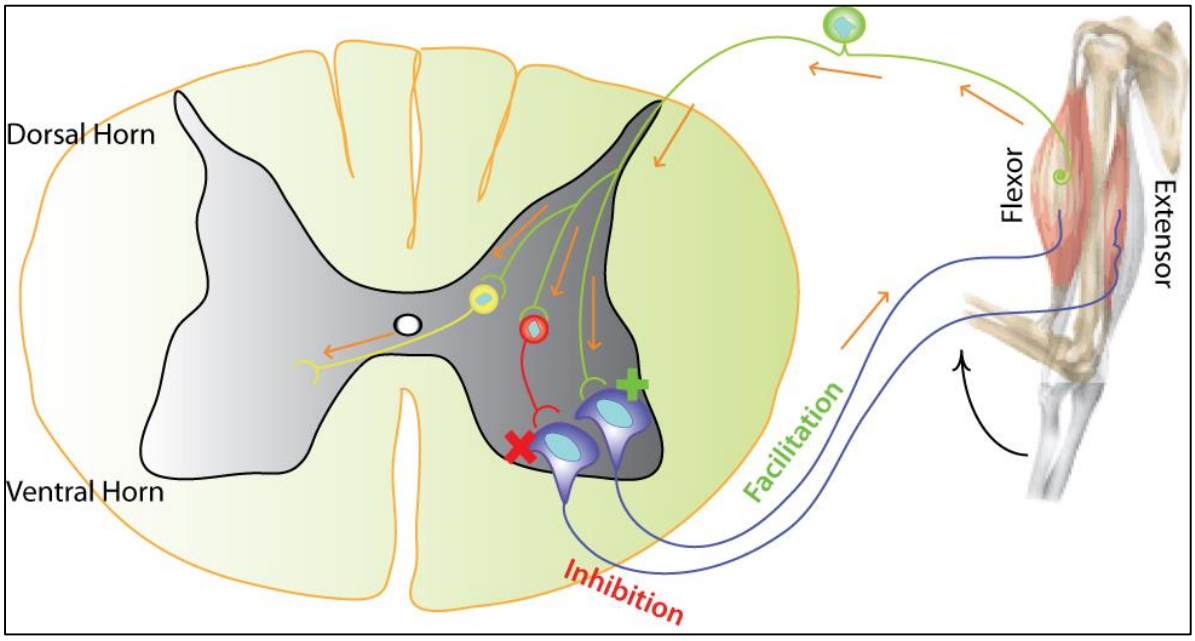
1. The supra-spinal *high hierarchical level*: This is referred to the regions situated dorsally to the spinal cord, which means the brain, cerebellum and brain stem. They have three common functions within the motor system: i) controlling both proximal and distal muscles and are responsible for most voluntary movements, ii) controlling axial muscles and are responsible for posture, balance and coarse of the axial and proximal muscles, and iii) **modulate the reflex circuits in the spinal cord.** There are several tracts named depending on their origin and targets, they run downwards from these high structures to through the spinal cord contacting with muscles at different levels. There is also a high organization in how these fibers run down in the spinal cord.
2. The spinal *low hierarchical level*: The spinal cord is the most important structure between the body and the brain. It runs from the brain to the sacro-lumbar region (just above the waist), and in here we can find the cells (motor-neurons and interneurons) which will trigger the reflexes, movements performed by the body with no implication of our cognitive part, when the body is expose to a dangerous or hazard stimulus. There are several types of reflexes, to exemplified them we will bring up some well know examples when these reflexes are triggered:

    I. <u>The stretch reflex:</u> The most well know examples in this particular reflex is the knee-jerk reflex, upon hitting the knee just over the knee-cap region, the leg performs an involuntary movement of stretch, this is because the sensory organs in the muscle have been stimulated by the hit and they send a signal to the spinal cord that will contact with

neurons allowing the contraction of the stretched muscle (which in turn elicits the elevation of the leg).

II. <u>The flexor reflex:</u> This reflex happens when after an injury or string stimulus in our skin. For example if we are walking and step on a nail, that will trigger the nociceptors (receptor for the pain) that will send a signal to the spinal cord activating the neurons to start the contraction in the muscles of the leg to retreat the foot from the nail. At the same time that information will also go to the other side of the body to start the contraction of the muscles of the other leg to keep the balance when the foot is pull up from the nail. It is a coordinating reflex that helps the body to move out of the harmful signal while keeping the balance.

These are the basics of the movement and reflexes, but any movement involves more than just one muscle, as to achieve a proper movement it is needed to activate an agonist muscle (responsible of the movement) and to inhibit an antagonist one (responsible of the movement in the opposite direction), this is the very basic principle of the *reciprocal inhibition,* put it simply: the activation of one muscle which will elicit the contraction (flexor) and inactivation of the opposite muscle (extensor) in the same joint to allow the first muscle to contract without interfere with the movement (avoiding a co-contraction and spasm in the muscles). See figure for details.



Principles of the reciprocal inhibition. After the muscle (flexor) is stretched the afferent Ia (green) sends a signal to the spinal cord, where it will perform synapse with an alpha-motorneuron and an interneuron. The alpha-motorneuron inervates the same muscle as the Ia afferent (agonist muscle) and achieves contraction of that muscle, while the interneuron inhibits the alpha-motorneuron inervating the antagonist muscle (Extensor), to avoid co-contraction and a successful flex movement of the arm.

The reciprocal inhibition will constitute the main mechanism of action of electro-therapy, as it is based in the stimulation or facilitation of the agonist muscle (flexor) to inhibit the antagonist muscle (extensor) which is often the muscle that is uncontrolled and hyperactive in other words the spastic muscle.

In summary the motor system has different levels of hierarchy, the highest ones control the voluntary and postural movements sending the orders to start the movement, the lowest levels execute these movements and are controlled by the highest levels in order to coordinate, adjust and integrate information. We have explained the most basics reflexes, but we have to keep in mind that those reflexes are all the time being activated while we walk, type in the computer or write, these involves activation of the spinal cord circuits and a parallel regulation of the high level motor centre over theses circuits to perform specifics, finesse tasks.

An insult or injury in one of these hierarchical centres (what usually happens in the upper motor syndrome) can developed unbalance regulation and incoordination of the spinal circuits resulting in spasm, co-contractions, weakness and other outcomes. We will see in the next pages how these injuries and insults affects the proper movement and muscle tone patterns.

The Upper Motor Neuron Syndrom (UMNS)

It is defined as alterations in the motor system at any of its levels having as a consequence the loss of voluntary and fine tuning movements. The UMNS has two classical distinctions in terms of its signs and symptoms, also referred as components:

Positive components	Negative components
Exaggerated tendon reflexes	Spastic co-contractions
Release reflexes	Motor weakness
Babinski sign	Slowed movements
Clonus	Loss of Dexterity
Spastic dystonia	Loss of selective motor control
Spasticity	

Table 1. Following a UMN lesion a person will present with a combination sensory-motor signs and symptoms that are broadly classified as negative phenomena (characterized by a reduction in voluntary motor activity) and positive phenomena (characterized by increased levels of involuntary motor activity).

How do these positive symptoms come about? They can be divided into three main areas. Firstly, spinal reflexes: Abnormal processing of spinal reflexes contributes to most of the positive features of the UMNS. They are all afferent dependent, relying upon some sort of sensory feedback. The third group of positive UMN signs are the various disorders of voluntary muscle movements, although there is much overlap with the negative signs/component, we will focus mainly on the positive side, that is, features characterized by muscle over activity.

Lesions in the CNS leading to a UMNS

1. *Stroke and Cerebral Palsy:* Alteration of descending pathways, affecting mainly to corticospinal and Rubrospinal descending pathways.
   I. Cerebral Palsy (CP) described as a range of non-progressive syndromes of posture and motor impairment as a common cause of disability in childhood, occurring before of within the 2 years of birth. This disorder results from various insults to different areas within the developing nervous system, which partially explains the variability of clinical findings. The motor impairments result from various neurological deficits. CNS pathology associated with cerebral palsy includes: CNS haemorrhage, mechanical spinal cord or brainstem damage, deep CNS hypoxia; cerebral cortex hypoxia and transient or irreversible ischemia resulting in cell necrosis. The unique metabolic demands of the basal ganglia in the foetus at 38-40 weeks create “selective” vulnerability that can result in dystonia or movements disorders. Although causes of CP have been always associated to complications in the delivery, recently more studies point the possibility of a genetic background and hereditable polymorphs as one of the causes of the CP.
   II. Blood vessels that carry blood to the brain from the heart are called arteries. The brain needs a constant supply of blood, which carries the oxygen and nutrients it needs to function. Each artery supplies blood to specific areas of the brain. A stroke occurs when one of these arteries to the brain is either blocked or bursts. As a result, part of the brain does not get the blood it needs, so it starts to die. A transient ischemic attack (TIA) occurs when the blood supply to the brain is blocked for a short time. When this happens, the brain temporarily malfunctions. There are several kinds of strokes (more information available at ww.stroke.org)

2. *Spinal Cord lesions (Injuries) or SCI*. Disruption of the spinal cord circuits and/or descending tracts located in the dorsolateral and medio-ventral regions of the white matter.

It is an insult to the spinal cord resulting in a change, either temporary or permanent, in the cord's normal motor, sensory and/or autonomic function. Patients with spinal cord injury usually have permanent and often devastating neurologic deficits and disability. Common causes of damage are trauma or disease (transverse myelitis, polio, spina bifida, Friedreich's ataxia, etc.). The spinal cord does not have to be severed in order for a loss of function to occur. Depending on where the spinal cord and nerve roots are damaged, the symptoms can vary widely, from pain to paralysis to incontinence. The American Spinal Injury Association (ASIA) has published a list of different categories based in the extend of the injury and the impairment resulted from it.

3. *Neurodegenerative diseases.* This group of disease involved Huntington and Parkinson diseases (Alzheimer is related to cognitive areas such the hippocampus) , characterized for a progressive cell death in some of the main motor areas in the brain, especially at the level of Basal Ganglia. Although some other diseases like hemiballismus or Cerebellum´s disorders are also affecting motor control we are not going to describe them fully in this chapter.
   I. Huntingston´s disease: It is an incurable genetic (autosomal dominant mutation) neurodegenerative disorder that leads to motor (it is characterized by continuous, choreiform movements of the body (especially the limbs and face) and cognitive (dementia) decline. It is caused by an expanded polyglutamine (abnormally large number of repeats of the nucleotide sequence CAG on chromosome 4) tract within the Huntingtin gene, which translates into a toxic mutant of this protein31. This results in a neuronal death in the Striatum (basal ganglia) of inhibitory cells in charge of inhibiting the excitatory outputs coming from the thalamus towards the cortex. As a result the cortex gets too much excitatory input disrupting its normal functioning and sending involuntary movements' commands to the brain stem and the spinal cord.
   II. Parkinson's disease: results from the death of dopaminergic neurons in the substantia nigra pars compacta; characterized by a resting tremor, but the most debilitating symptom is severe bradykinesia or akinesia. In advanced cases, patients have difficulty initiating movements, although involuntary, reflexive movements can be normal. The loss of neurons in the substantia nigra projecting into the basal ganglia means the loss of both excitatory and inhibitory inputs and therefore upsets the fine balance of excitation and inhibition reducing the excitation of the moor cortex.

All these injuries develop in uncontrollable spinal reflexes, which in turn become the major responsible for most of the positive features in the UMNS. All diseases and lesions described above resulted in some kind of unbalance of the supraspinal inhibitory and excitatory inputs, producing a state of disinhibition of the spinal reflexes. The dysregulation of the spinal reflexes can be categorized into: i) disinhibition of the existing normal reflexes, which are involved in walking and all other movements. One form is the propiospinal phasic stretch reflex, also known as the tendon jerks (inflicting enough pressure under the knee-cap can trigger this reflex) in normal conditions, but within the UNMS it is hyper exaggerated and evolving to a hyperactive phasic stretch reflex known as clonus. ii) the nociceptive reflexes including the flexor withdrawal reflex, producing flexor spasm (the normal way this reflex works would be when in contact with something potentially dangerous for the body, t.ex a sharp object or fire) an immediate response from the muscles of the limb takes place

withdrawing it from the potential harmful stimulus. iii) The last form of reflexes would be enclosed in the cutaneous reflexes related to the first two types of reflexes.

As we have already pointed out, one of the main but not an inevitable, neurological impairment consequence of the UMNS is spasticity. It is fairly common in many of these syndromes (especially SCI, stroke and Cerebral palsy), with percentages up to 80% in CP patients. Spasticity is commonly defined using the terms expressed by Lance (1980) as …. *motor disorder characterized by a velocity dependent increase in the tonic stretch reflex (muscle tone) with exaggerated tendon jerks, resulting from the hyper excitability of the stretch reflex, as one component of the upper motor syndrome*…. The pathophysiology (causes) of spasticity varies and it is extensive being involved several regions and affecting many other motor centres. The muscles in the arms, legs, and the trunk are often painful, resistant to movement, difficult to control, and prone to spasms or involuntary movements. Spasticity may be used to help with transfers and walking, or may help keep the muscles from decreasing in size. However, there are problems that result from spasticity. Long-term spasticity can lead to decreased range of motion (ROM), prevent safe positioning, limit mobility, and impede hygiene. Spasticity can also lead to increased discomfort and pain. Spasticity is actually a combination of problems. Specifically, spasticity is not just defined as resistance to movement when an arm or leg is moved quickly. Some persons with spasticity also have spasms and clonus (repeated movement of a body part when positioned with the muscle stretched). It is not yet clear which treatment is best for these different aspects of spasticity. While frustrating for some, the presence of spasticity can be viewed as beneficial for others. For instance, spasticity can aid in maintaining muscle bulk and blood circulation, both of which can prevent pressure sores. Spasticity can also be used to aid in mobility, such as for transfers and walking. However, the less desirable effects of spasticity, such as decreased range of motion (ROM), interference with positioning, mobility, and hygiene, and increased discomfort and pain often outweigh those that are beneficial, making intervention necessary. Clinical interventions include pharmacological approaches, as well as rehabilitation, surgical, and alternative medicine approaches.

Before we head to the next part we should be aware that there are several items to measure the level of spasticity, also call scales. They are subjective to the perception of the clinician and the patient, but throughout many years of clinical research some of them have been well stablish and most commonly used in research. These scales are the main measurements used to address the effect of therapies in patients. We will commonly refer to Ashworth, Tardieu or VAS scales as the main ones to measure spasticity upon injury and treatment, and use them as a comparison to investigate the power or efficacy of a certain treatment.

Management options/Treatments

Spasticity frequently impairs one's mobility, positioning, comfort, care and ability to perform activities of daily living. Successful management of spasticity requires the expertise of a well-integrated team of clinicians. Commonly used management strategies for spasticity include:

- Oral medications, particularly for those with spinal cord injury
- Orthopaedic procedures to correct deformities resulting from spasticity or to augment the effects of other treatments
- Bracing and splinting
- Muscle stretching, positioning and movement exercises

These strategies have been grouped as common or classical treatments against spasticity, however the list is more extensive as several other options are available:

•Injected medications: Mainly oriented to synaptic blockade at the Neuro Muscular Junction, here the main and more extensively used are the Botulinum Toxins

•Intrathecal Baclofen Pump: A major surgery procedure where a pump is inserted in the abdominal cavity and Baclofen is injected directly into the Nervous system through the arachnoid space in the meninges

•Selective Dorsal Rhizotomy: Also a major surgical procedure characterize by the excision of the afferent sensory inputs into the spinal cord.

•Electro-Therapy: A non-invasive method based in the electric stimulation of either muscles or nerves.

In the spasticity treatments it is common that two or more treatments are combined in other to improve the patient's motor functions, and in some cases it has been reported additive effects between different therapies. In this part we will mainly focus on the most common used therapies emphasizing differences, conveniences and disadvantages together with the impact in the quality of life and function of the patients.

Pharmacological methods.

Diazepam was the first one used and Oral Baclofen is also a highly used drug for the spasticity treatment. However due to their multiple and potentially dangerous side effects, these compounds will be omitted in this document in favour of the most specific and powerful treatment of intrathecal baclofen. Nevertheless we do provide a brief list of some references regarding the use of these compounds; these articles constitute a review and meta-analysis of several of the oral medications used in the treatment of spasticity together with other forms of medical management.

Intrathecal Baclofen (ITB): One of the major advantages of ITB compared to the oral administration is the lack of many side effects, as with this system the drug administration is performed locally, besides the concentration needed to obtain same results as the oral medication is just 1% compare to the orally administered Baclofen. The intrathecal baclofen is indicated for patients with severe spasticity and GMFCS scores of IV. Its mechanism of action is exerted at receptor level, acting on the metabotropic receptor GABAb which in turn induces inhibition of the synaptic transmission. This

means and inhibition of the reflex arc as all neurons in the spinal cord stop functioning and therefore stop sending signals towards the muscle.

This method is a proven procedure that ensures a reduction in the level of spasticity rated as a decrease in the Ashworth scales and MAS as well as an increase in Life Satisfaction questionnaires and Quality of Life scores. Among other advantages this system is highly controllable and it also affects Pain-relieving (as it inhibits all signals produced at the spinal level). However as a major surgery process it involves risk of infections during the procedure of pump implantation varying from 1 to 9%. It is also been reported a high rate in incidents per recipient year follow-up up to 0.48, The system itself is highly reliable, but an organized follow-up program is necessary to cope with the procedure-related problems such as catheter dislodgement or other complications. Recently, Awaad and colleagues (2012) reported complications of intrathecal baclofen pump installation where 22 out of 44 patients needed to perform several revision and several failures were detected during the follow up time.

On the other hand even there are not so many side effects compare to the oral medication, however there are still some side effects regarding the action mechanism of the baclofen at the spinal cord level: weakness, hypotension, possible overdose and behavioural changes. We have also to take in account the cost/effectiveness ratio of ITB. As it has been said before Baclofen increase the Quality of life Score, but this increase comes at expense of an increased price. The net result is an incremental cost-effectiveness ratio of $42.000 per quality-adjusted life-year, well within the $50 000 to $100 000 range. The authors consider these results as "…..widely accepted as offering good value for the money." Its efficacy has been also evaluated as cost/success ratio, having ITB as a high success treatment it cost/success ratio is elevated to 75.204£. Some other reports state a total price of 28.473$ the first year but it also reports savings originated from withdrawal of oral medication (1.950-2.800$), job preservation and avoidance or delay of admission to a nursing home (1.047-5.814$).

In summary ITB is an effective method against spasticity as it reduces Ashworth scale scores and increases the Quality of Life, although it entails risk of infections which can discourage a long-term treatment, constant refill of the pump (with additional cost) and some adverse side effects. Nevertheless the main drawback of ITB is related to the price.

Chemodernervation.

In the same fashion as the pharmacological methods, mention will be done to Ethanol and phenol injections in muscles, although no deep analysis of those will be done in favour of the action mechanism exerted by the more well know and more commonly used Botulinum toxins.

Alcohol and phenol are very old approaches to achieve focal chemodernervation on spastic muscles. They are considered neurolytic agents, as their action mechanism is based in denaturalization and non-selective tissue destruction, including nerve coagulation and muscle necrosis. The targets are mainly distal muscles and its action is achieved through two different approaches: motor nerve block (low volume injections) and motor point block (multiple injections at different doses, grading the effect on the muscle). But as said before it is not a safe method and there are significant side-effects.

Botulinum toxins (BoTN) are a widely used pharmacological treatment used against local spasticity. It is achieve by injection of the toxins into the muscle where it will block the release of the neurotransmitter Acetylcholine into the synaptic space and therefore inhibiting the transmission of the axon signal into the muscle abrogating completely the muscle contraction. There are seven different neurotoxins (labelled as type A, B, C (C1, C2), D, E, F and G) which are structurally similar but target different antigens (target proteins). Types A, B and E (rarely F) cause toxicity in humans whereas types C and D affects animals. All different subtypes target the synaptosome, a protein complex in charge of mediate the fusion of vesicles within the cell to their membranes in order to secrete a specific compound within the vesicle. In this document we will not address the different subtypes and targets, as is far from the scope of botulinum toxins as spasticity treatment, whoever Jankovic (2004) describe the pharmacology and action mechanism of the different subtypes in case the reader is interested.

There are available different types of commercially BoNT, each of them is employed under different circumstances and treatments: Botox®, Botox Cosmetic®; AbobotulinumtoxinA (Dysport®); IncobotulinumtoxinA (Xeomin®) and RimabotulinumtoxinB (Myobloc®).

Many reports have stated the positive effects of BoNT in the treatment of spasticity, however Moore (2002) warns about the fact that many of those studies are open, uncontrolled studies, while the BoTN benefits is also present but scarce and less convincing from randomized controlled trials (RCT) and that could be due to a variety of technical reasons. Since then, more RCT have been accumulating positive effects in spasticity, but it is still a concern the lack of more data coming from this high level empirical studies and even if BoTN has positive effects in the treatment of spasticity, the effect in functionality are still somehow controversial, due to the lack of effect of BoNT in the muscle intrinsic properties. This is the main reason that has driven some authors to claim that BoTN treatment works best in combination with other forms of therapy. Garcia Salazar and colleagues (2014)82 performed a systematic review on the effects of BoTN in the treatment of spasticity and functional recovery, showing in the 17 studies analysed the effect of BoTN were evident in the reduction of spasticity, but it did not however increase functionality in the treated muscles. In a two big studies performed over more than 500 and 200 BoNT treated patients respectively, the goal attachment scaled was scored up to 51%, which lead the authors to claim that the efficacy of the BoTN was proven, nevertheless the treatments must be carefully planned and evaluated the risk of long term treatments.

Summarizing we could group the advantages and disadvantages of BoTN in the following table:

Advantages	Disadvantages
Works whatever the cause of spasticity is	Cannot treat widespread spasticity, even for localize spasticity it is best combine with other forms of therapy
Very effective treating focal spasticity	There is a cost implication
Adverse effects can be treated with no high complications	The effects are reversible and slowly wear off, so it has to be repeated[87]
Easy to administrate	Develop of antigenicity in the patients against the toxin. Patients become "immune" to the BoTN treatment
Effective delay of surgical methods	Painful and uncomfortable administration.
Repeated treatments can potentially decrease latency effect and prolonged therapeutic effect	No clear and specific protocols about the specific injections sites (selection of muscles) and concentrations.

Table 2. Summarize of the BoTN treatments in patients with spasticity. Here are included children with CP, and Adults with any form of spinal cord injury and stroke.

Selective Dorsal Rhizotomy (SDR)

SDR constitutes an unselective way of reduction of cutaneous and proprioceptive awareness. The input of the afferent fibers is stopped in order to stop the motor neurons, synapsing with these afferent fibers, from firing. Contrary to the orthopaedic surgery, SDR affects just the nervous fibers coming to the spinal cord in order to inhibit the hyperexcitability of the system. SDR is recommended for patients with scores of II and III in the GMFC scales. We cannot forget that this procedure constitutes a permanent modification of the sensory-motor system at the sub-spinal and spinal levels, this feature of the SDR has its pros and cons; on one hand, it demonstrates an increasing benefit in terms of cost per quality adjusted life year over the time, moreover it leads to a significant reduction in soft tissue orthopaedic surgery but less impact on the need for bony surgery, but on the other side this permanent modification leads to a failure of the patient to be able to perform some basics skeletal muscle functions , leading to higher levels of dependency in the long term, furthermore in patients with high GMFCS scores SDR associated weakness and loss of sensitivity could lead to deterioration of some walking and standing functions. Results in the literature differ in the outcome of the SDR in long term follow up analysis, stating the need of standardized post operatory procedures. Although SDR does decrease the spasticity levels, several reports indicate that the effects in the muscle functionality are either not enough or absent in long term follow ups, or spasticity becomes worse after the surgery or there is still need of other forms of therapy to counter long term side effects.

Electro-Stimulation (ES) and Molli®:

We will not discuss the evidences of this therapy method in this document, as it is a really extensive piece of literature. More information can be found in the **Appendix A** (Summary of Electro-Therapy evidences in research and clinical trials), what we do point out in this section is that ES constitutes the very basic principle of Molli® as it send electrical charges in a certain frequency, amplitude and length in order to stimulate and facilitate the reciprocal inhibition process that occurs naturally in our body when a movement is executed, the difference her is that in the UMNS one of the two muscles responsible of a certain movement it is hyperactivated and therefore contracted all the time

(developing the typical symptoms in spasticity), thus facilitation and/or excitation of the opposite muscle will inhibit the constant activation of the spastic muscle, helping to relax it and therefore helping the clinician to treat and train the muscles in a “more normal and stable” situation.

Modality	Acronym	Characteristics
Functional Stimulation	FES	Surface electrical stimulation to muscles and/or nerves for the porpoise of **overcoming an inability to contract** and execute functionally useful movements
Neuromuscular Stimulation	NMES	Electrical stimulation to muscles **high intensity and short duration** to initiate contraction and movement
Therapeutic Stimulation	TES	**Sub-threshold level stimulation** (low intensity) applied continuously for a short duration.

Table 3. Different ES modalities depending on the intensity, duration and place of application.

Mollii® presents two exclusive features when compared to any other treatment available for patients presenting spasticity as an outcome of the UMNS: the reciprocal inhibition and neuroplasticity in the spinal and cortical circuits elicited by the activation of the peripheral and spinal circuits.

Reciprocal inhibition: It has been described as a plausible mechanism of reduction of spasticity based on the inactivation of the antagonist (spastic) muscle through activation of the agonist muscle. The idea of reciprocal inhibition as the cause behind the ES came from previous reports describing improve of gait and other muscle function after training, leading to the hypothesis that sensory feedback is a critical factor for training spinal locomotor networks, moreover this inhibition has been showed in dynamic modulation during voluntary movements. Taking all this into account there are proven evidences of the fact that activation of the existing neuronal circuits upon an insult or damage can help in the recovery and improvement of locomotion faculties. ES therapy is based in “training” of the spinal cord network. As physical training helps in rehabilitation, electrical stimulation of these same neuronal circuits results in an efficient training of the synapsis and neuronal functions at spinal and sub-spinal levels. This neuronal activity at spinal levels could also affect higher levels of the motor system, as it is not an isolated system, but it sends signals to the motor and sensory cortex, it is plausible to think of the possibility of an effect at the brain level and the ascending and descending tracts communication the brain and the spinal cord.

Neuroplasticity: ES stimulation constitutes a “neural training” therapy, unlike all other forms of therapy, ES does not inhibit the neuronal signal at any level as the baclofen (inhibition of all neurons in the spinal cord) or botulinum toxins (inhibition of the Ach release to the muscle and therefore stopping the contraction signal) or stops the signal sending process as the SDR. Thus, ES works in a completely different fashion as other therapies facilitating the synapses of all neurons involved in the spinal circuits. This neuronal activation helps the neurons to keep their synapses and all elements involved in the synaptic transmission active and working, furthermore this activity sends signals to the cortex where plasticity has been shown as a result of the motor-sensory feedback from the muscles and spinal cord, moreover this “neural training” is been hypothesized as a responsible of a possible plasticity at spinal levels increasing the feedback signals sent to the higher nervous system structures.

INERVENTIONS

THE INERVENTION´S METHOD

Appendix A: Research Evidences on Electro Therapy in the treatment of spasticity

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Inerventions AB
2014

mollii elektrodress

Electro-therapy as a feasible method to treat spasticity

Electro-Therapy (ES) is a minimally invasive method with high potential in the treatment of motor impairment pathologies first used as therapeutic treatment in 1997[1, 2] although it use as a therapy strategy began in patients with motor function impairment of the upper extremity in 1979[3]. It is based in the application of electrical currents to the muscles and/or tendons in order to elicit muscle contraction or afferent fibers stimulation reactivating the spinal cord circuits and its neurons. There are several modalities depending on the length and intensity of stimulation. We will focus mainly in two out of the three modalities of Electro-Therapy (TES and NMES also mentioned in some works as TENS). Distinctions between these modalities is worth of mention including protocols of stimulations and studies (either open or Random Control Trials-RCTs-) supporting the efficacy of this methods.

Methods mentioned here are used to modify impairments and activity limitations as a consequence of spasticity in children with CP, adults with some kind of spinal cord injury and stroke. The following table describes the main three different modalities of ES used in many open studies and RCTs.

There are a huge number of reports and research articles in the literature supporting the use of one of these modalities in the treatment of spasticity in different UMN syndromes. We will focus in some of them pointing out the major differences and agreement between reports, as well as how these modalities have been using in different disease, especially in CP, stroke and Spinal Cord Injury (SCI). Last, all the data present in this sections comes from different review and meta-analysis performed among several hundreds of reports on ES as a therapy against spasticity, among the reviews the reader will find meta-analysis in ES in children with CP[4-6], Patients with Spinal Cord Injury (SCI) (http://www.bu.edu/drrk/research-syntheses/spinal-cord-injuries/spasticity)[6] and in stroke patients[6, 7].

Children with CP: Kerr and colleagues (2004)[4] classified the different studies in 5 different levels of empirical research, having the level I or RCT, level II or non-RCT, level III Case-control study (comparison of a study with a historical control group), level IV Before and after the case and a level V or non-empirical research level (Anecdotes and/or experts´ opinions).

Authors	Study Design	Type of CP	Intervention	Control	Outcome measures	Results
[8]	Matched groups RCT	Hemiplegia, diplegia and quadriplegia	NMES (plus physiotherapy)	Usual physiotherapy	Gait analysis, muscle strength, ROM, GMFM, parent questionnaire	ns (all measures)
[9]	RCT	Diplegia	TES (plus physiotherapy)	Usual physiotherapy	GMFM, seat postural control, MMT, muscle tone, ROM, PCI	GMFM ($p=0.001$), other measures ns
[10]	Matched groups RCT	Hemiplegia	NMES (plus physiotherapy)	Usual physiotherapy	ROM, MMT, gait analysis	Active and passive ROM and strength ($p<0.05$)
[11]	RCT	Diplegia	NMES (plus physiotherapy)	Physiotherapy	Radiographic measurement of kyphotic, Cobb´s and lumbrosacral	Kyphonic angle, GMFM sitting score

					angle, GMFM sitting score	(p<0.05) other measures ns
[12]	Crossover RCT	Diplegia	TES (physiotherapy and stretching program)	physiotherapy and stretching program	Gait and LL function, MMt, PDMS	ns (all measures)
[13]	RCT	Hemiplegia, diplegia	TES (plus physiotherapy)	Placebo and usual physiotherapy	Quantitative motor-function test, ROM, Ashworth, muscle bulk	ns (all measures)

Table 8. Summarize of all level I and II empirical research performed using one type of ES in children with CP.

Authors	Type CP	Intervention	Outcome measure	Results
[14]	Hemiplegia	NMES	Hand function, active ROM, wrist movement	Hand function and active ROM (p<0.05)
[15]	Diplegia, hemiplegia	EMG-triggered NMES	Gait, UL videography, goniometry, PDMS	ns (all measures)
[1]	Diplegia, hemiplegia	TES (own controls)	PDMS	All test significant (p<0.01)
[16]	Diplegia, hemiplegia	NMES	Gait	P=0.001

Table 9. Level III and IV of empirical research studies performed on children with CP

Continuing with the review all the level V studies (n=8) reported an improvement in one of the functions and parameters studied[17-22]. We will not mention level VI studies as they are only observations with no quantifications. As we can see the effects of ES in open studies (level III and IV) are greater than those expose in the RCT (level I and II). Summing up, the results from ES as a therapy method in children with CP are very promising, although it is argued the need of increasing the number of RCT and standardized protocols[23, 24].

Note: as we will see in the next chapter inervention´s method is based in level IV studies through the assessment of the mobility and spasticity level in patients before and after using Molli® for a 1 hour's session.

Cauraugh and colleagues (2010)[5] performed a meta-analysis of few selected reports divided in two different groups (n=14 for impairment and n=15 for activity limitations) with a total of 238 patients treated with ES and 224 as control. After performing a heterogeneity test the results showed a positive effect in ES therapy improving the walking impairment and activity limitations of children with cerebral palsy (see Figure 6). Regarding to the studies included in the impairment meta-analysis several of them were performed using NMES[10, 16, 25-28] while others reports differences in the effect size using TES[9, 12, 25]. Regarding to the activity limitation, effectiveness several of the studies addressing walking impairment also are cited in this analysis, and here we can point out that the results were positive using any of the forms of ES available[9, 13, 25, 27, 29, 30].

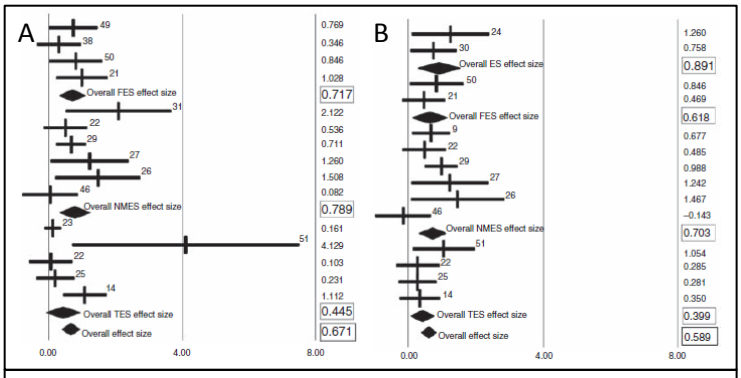

Figure 6. Forest pots showing the individual effect sizes of the 15 (A) and 14 (B) studies based on the impairment and activity limitations respectively. *Modified from Cauraugh et al., 2010*

Summarizing the results presented in ES therapy for the treatment of Cerebral Palsy, we could say that the effects of any type of ES on the spasticity level, as well as in the function improvements are generally positive. Furthermore we have pointed out here that due to these meta-analysis studies, it would be safe to assume the validity of this positive effect, as the heterogeneity or variability of the results among all these kind of studies is low, or said in other words the correlation of the effect of ES is high and reproducible among children suffering of CP.

SCI patients: Spasticity after spinal cord injury (SCI) is a common, complicated, and often frustrating impairment that is generally considered both a "health" problem[31]and a deterrent to function and quality of life[32]. The amount of reports describing effects of ES in the spasticity generated upon SCI are less compare with children with CP. Nevertheless, all the studies here review show positive results of ES treatment in spasticity level and functional recovery. Moreover some of the articles here cited attribute these therapeutically effects to the activation of reciprocal inhibition. Various methods have been employed to treat spasticity of SCI origin among them we can cite: stimulation to the antagonist muscle, application of tetanic contraction to the spastic muscle, functional electrical stimulation (FES), and transcutaneous electrical nerve stimulation (TENS), reporting beneficial effects up to 3 hours after the treatment[33-36]. The mechanism suggested for these positive effects vary among the reports, level of spasticity and muscle groups reported: Stimulation of the antagonist muscle: augmentation of reciprocal inhibition of the spastic muscle[33] Repetitive tetanic stimulation of spastic muscle: fatigue of the muscle due to repetitive tetanic stimulation[33] FES: change the mechanical properties of a spastic joint by strengthening the antagonists of the spastic muscle or might decrease the hyperactivity of spastic muscles through reciprocal inhibition[37] TENS: may involve the stimulation of large diameter afferent fibers that travel from mechanoreceptors to the spinal cord[33]. Other reports have empathized the positive effects only in the spasticity and clonus level[38, 39]. Overall these reports indicated the positive effect of ES in the treatment of spasticity in SCI patients.

Stroke patients: Spasticity upon stroke is been reported to be treated using ES in all its modalities. One of the most notable reviews is done by Quandt and colleagues (2014)[7]. These authors state the obvious benefits of FES in the treatment of spasticity in stroke patient. Although this review is about FES, which is not the electrical therapy modality exerted by Molli®, it does however bring clear and solid evidences of the benefits of the ES treatments from a numerous amount of reports. On the other hand, other reports have been published stating the benefits of other modalities of ES in stroke patients[40]. The overall results from all these studies are that either NMES or FENS are valid and solid therapies to treat spasticity in stroke patients[6, 41-45]. However as we will see in the next chapter, one of the most exciting observations coming out of the application of ES in stroke patients is the possibility that this therapy may affect processes of neuroplasticity, helping the CNS to keep the uninjured cells and support the compensation mechanism exerted by other brain areas upon damage after a ischemic episode in the brain.

Summary

The inervention´s method is based in the application of electrical stimuli onto the muscles in order to facilitate the process of reciprocal inhibition exerted naturally by the central nervous system at the spinal cord level. As we have discussed before ES is a non-invasive, feasible and relatively cheap effective method that helps the body to "train neuronal circuits" in order to reduce spasticity. Most of the reports presented in clinical research are open studies, that is, not so "rigorous" controlled studies. This is true in all cases and therapies proposed to treat spasticity, in many of the reviews and meta-analysis performed in each single of the therapies available two main conclusion can be drawn out of them: **Necessity of more RCT and the combination of therapies in order to achieve the best results.** Summarizing all articles and research reports here presented, there is no an infallible method, but these methods should be considered depending on the type of disease, outcome, type of patient, degree of the symptoms and severity. All other methods here mentioned have also been proven to help in spasticity and most notably as many authors have claimed a therapy approach based in the combination of two or even three of these methods, which could add an additive effect and better and faster positive outcomes in the spasticity´s therapy. Nevertheless ES is the only method available to date that promoters training at different levels (muscle contraction, neuronal synapsis, information transmission…) making possible to train neuronal circuits to achieve an improved outcome in the treatment of spasticity.

References.

[1]. Pape KE, Kirsch SE, Galil A, Boulton JE, White MA, Chipman M. Neuromuscular approach to the motor deficits of cerebral palsy: a pilot study. *J Pediatr Orthop*. 1993 **13:** 628-633.

[2]. Pape KE. Caution urged for NMES use. *Phys Ther*. 1994 **74:** 265-267.

[3]. Baker LL, Yeh C, Wilson D, Waters RL. Electrical stimulation of wrist and fingers for hemiplegic patients. *Phys Ther*. 1979 **59:** 1495-1499.

[4]. Kerr C, McDowell B, McDonough S. Electrical stimulation in cerebral palsy: a review of effects on strength and motor function. *Dev Med Child Neurol*. 2004 **46:** 205-213.

[5]. Cauraugh JH, Naik SK, Hsu WH, Coombes SA, Holt KG. Children with cerebral palsy: a systematic review and meta-analysis on gait and electrical stimulation. *Clin Rehabil*. 2010 **24:** 963-978.

[6]. Schuhfried O, Crevenna R, Fialka-Moser V, Paternostro-Sluga T. Non-invasive neuromuscular electrical stimulation in patients with central nervous system lesions: an educational review. *J Rehabil Med*. 2012 **44:** 99-105.

[7]. Quandt F, Hummel FC. The influence of functional electrical stimulation on hand motor recovery in stroke patients: a review. *Exp Transl Stroke Med*. **6:** 9.

[8]. van der Linden ML, Hazlewood ME, Aitchison AM, Hillman SJ, Robb JE. Electrical stimulation of gluteus maximus in children with cerebral palsy: effects on gait characteristics and muscle strength. *Dev Med Child Neurol*. 2003 **45:** 385-390.

[9]. Steinbok P, Reiner A, Kestle JR. Therapeutic electrical stimulation following selective posterior rhizotomy in children with spastic diplegic cerebral palsy: a randomized clinical trial. *Dev Med Child Neurol*. 1997 **39:** 515-520.

[10]. Hazlewood ME, Brown JK, Rowe PJ, Salter PM. The use of therapeutic electrical stimulation in the treatment of hemiplegic cerebral palsy. *Dev Med Child Neurol*. 1994 **36:** 661-673.

[11]. Park ES, Park CI, Lee HJ, Cho YS. The effect of electrical stimulation on the trunk control in young children with spastic diplegic cerebral palsy. *J Korean Med Sci*. 2001 **16:** 347-350.

[12]. Sommerfelt K, Markestad T, Berg K, Saetesdal I. Therapeutic electrical stimulation in cerebral palsy: a randomized, controlled, crossover trial. *Dev Med Child Neurol*. 2001 **43:** 609-613.

[13]. Dali C, Hansen FJ, Pedersen SA*, et al.* Threshold electrical stimulation (TES) in ambulant children with CP: a randomized double-blind placebo-controlled clinical trial. *Dev Med Child Neurol*. 2002 **44:** 364-369.

[14]. Wright PA, Granat MH. Therapeutic effect of functional electrical stimulation of the upper limb of eight children with cerebral palsy. *Dev Med Child Neurol*. 2000 **42:** 724-727.

[15]. Atwater SW, Tatarka ME, Kathrein JE, Shapiro S. Electromyography-triggered electrical muscle stimulation for children with cerebral palsy: a pilot study. *Pediatr Phys Ther*. 1991 **3:** 190-199.

[16]. Comeaux P, Patterson Nö, Rubin M, Meiner R. Effect of neuromuscular electrical stimulation during gait in children with cerebral palsy. *Pediatr Phys Ther*. 1997 **9:** 103-109.

[17]. Carmick J. Comments on a recent study of therapeutic electrical stimulation in cerebral palsy. *Dev Med Child Neurol*. 2002 **44:** 212.

[18]. Carmick J. Use of neuromuscular electrical stimulation and [corrected] dorsal wrist splint to improve the hand function of a child with spastic hemiparesis. *Phys Ther*. 1997 **77:** 661-671.

[19]. Carmick J. Clinical use of neuromuscular electrical stimulation for children with cerebral palsy, Part 2: Upper extremity. *Phys Ther*. 1993 **73:** 514-522; discussion 523-517.

[20]. Pape KE, Kirsch SE, Bugaresti JM. New therapies in spastic cerebral palsy. *Contemp Pediatr*. 1990 **3:** 6-13.

[21]. Dubowitz L, Finnie N, Hyde SA, Scott OM, Vrbova G. Improvement of muscle performance by chronic electrical stimulation in children with cerebral palsy. *Lancet*. 1988 **1:** 587-588.

[22]. Beck S. Use of sensory level electrical stimulation in the physical therapy management of a child with cerebral palsy. *Pediatr Phys Ther*. 1997 **9:** 137-138.

[23]. Prescott RJ, Counsell CE, Gillespie WJ*, et al.* Factors that limit the quality, number and progress of randomised controlled trials. *Health Technol Assess*. 1999 **3:** 1-143.

[24]. Barton S. Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *BMJ*. 2000 **321:** 255-256.
[25]. Kerr C, McDowell B, Cosgrove A, Walsh D, Bradbury I, McDonough S. Electrical stimulation in cerebral palsy: a randomized controlled trial. *Dev Med Child Neurol*. 2006 **48:** 870-876.
[26]. Katz A, Tirosh E, Marmur R, Mizrahi J. Enhancement of muscle activity by electrical stimulation in cerebral palsy: a case-control study. *J Child Neurol*. 2008 **23:** 259-267.
[27]. Maenpaa H, Jaakkola R, Sandstrom M, Airi T, von Wendt L. Electrostimulation at sensory level improves function of the upper extremities in children with cerebral palsy: a pilot study. *Dev Med Child Neurol*. 2004 **46:** 84-90.
[28]. Nunes LCBG, Quevedo AAF, Magdalon EC. Effects of neuromuscular electrical stimulation on tibilialis anterior muscle os spastic diplegic cerebral palsy: a preliminary study. *Rev Bras Fisiother*. 2008 **12:** 317-323.
[29]. van der Linden ML, Hazlewood ME, Hillman SJ, Robb JE. Functional electrical stimulation to the dorsiflexors and quadriceps in children with cerebral palsy. *Pediatr Phys Ther*. 2008 **20:** 23-29.
[30]. Ho CL, Holt KG, Saltzman E, Wagenaar RC. Functional electrical stimulation changes dynamic resources in children with spastic cerebral palsy. *Phys Ther*. 2006 **86:** 987-1000.
[31]. Taricco M, Pagliacci MC, Telaro E, Adone R. Pharmacological interventions for spasticity following spinal cord injury: results of a Cochrane systematic review. *Eura Medicophys*. 2006 **42:** 5-15.
[32]. Adams MM, Hicks AL. Spasticity after spinal cord injury. *Spinal Cord*. 2005 **43:** 577-586.
[33]. Jozefczyk PB. The management of focal spasticity. *Clin Neuropharmacol*. 2002 **25:** 158-173.
[34]. Kirshblum S. Treatment alternatives for spinal cord injury related spasticity. *J Spinal Cord Med*. 1999 **22:** 199-217.
[35]. Parziale JR, Akelman E, Herz DA. Spasticity: pathophysiology and management. *Orthopedics*. 1993 **16:** 801-811.
[36]. Albert T, Yelnik A. [Physiotherapy for spasticity]. *Neurochirurgie*. 2003 **49:** 239-246.
[37]. Emery E. [Intrathecal baclofen. Literature review of the results and complications]. *Neurochirurgie*. 2003 **49:** 276-288.
[38]. Ping Ho Chung B, Kam Kwan Cheng B. Immediate effect of transcutaneous electrical nerve stimulation on spasticity in patients with spinal cord injury. *Clin Rehabil*. **24:** 202-210.
[39]. Krause P, Szecsi J, Straube A. Changes in spastic muscle tone increase in patients with spinal cord injury using functional electrical stimulation and passive leg movements. *Clin Rehabil*. 2008 **22:** 627-634.
[40]. Lisa LP, Jughters A, Kerckhofs E. The effectiveness of different treatment modalities for the rehabilitation of unilateral neglect in stroke patients: a systematic review. *NeuroRehabilitation*. **33:** 611-620.
[41]. Sabut SK, Sikdar C, Kumar R, Mahadevappa M. Functional electrical stimulation of dorsiflexor muscle: effects on dorsiflexor strength, plantarflexor spasticity, and motor recovery in stroke patients. *NeuroRehabilitation*. **29:** 393-400.
[42]. Peurala SH, Pitkanen K, Sivenius J, Tarkka IM. Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clin Rehabil*. 2002 **16:** 709-716.
[43]. Dewald JP, Given JD, Rymer WZ. Long-lasting reductions of spasticity induced by skin electrical stimulation. *IEEE Trans Rehabil Eng*. 1996 **4:** 231-242.
[44]. Hines AE, Crago PE, Billian C. Functional electrical stimulation for the reduction of spasticity in the hemiplegic hand. *Biomed Sci Instrum*. 1993 **29:** 259-266.
[45]. Wang RY, Tsai MW, Chan RC. Effects of surface spinal cord stimulation on spasticity and quantitative assessment of muscle tone in hemiplegic patients. *Am J Phys Med Rehabil*. 1998 **77:** 282-287.

Common Questions

How do I know that the Inerventions method on which Mollii is based works?
The Inerventions method utilises the principle of antagonist inhibition to reduce spasticity through electrical stimulation. The principle is scientifically proven and clarified in a number of studies. Read more about antagonist inhibition under the Research tab on our website.

What are the contraindications for Mollii?
Mollii should not be used together with electrical implanted devices or devices that can get damaged by magnets, i.e. magnetic shunts. Do not use Mollii without consulting a doctor in connection with: epilepsy, heart disease, malignancy (cancer), infectious disease, fever, pregnancy, abnormal blood pressure, skin problems/damaged skins or other medical treatments.

Is it possible to test the method and observe the effect?
Yes! A free of charge-trial of the Inerventions method is available at our premises in Solna, Sweden. Mail or phone us to schedule an appointment.

At what age can you start using the Interventions method?
The Inerventions method with electrodes can be used from 6 months old. Mollii can be used from when the child fits clothes size 104 CL and upwards, and by adults.

Who can use Mollii?
Mollii can be used by people with spasticity or other motor impairment that have arisen as a result of upper motor neuron damage; for example people who have cerebral palsy, hereditary spastic paralysis, dystonia, stroke, acquired brain damage, spinal injury, MS and Parkinson's disease.

Does it hurt?
No. It can tingle slightly, or not at all, it is often pain-relieving and pleasant.

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