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The Role of Spasticity in Functional Neurorehabilitation-Part II: Non-pharmacological and Pharmacological Management: A Multidisciplinary Approach

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Abstract

The symptom/clinical sign of spasticity constitutes a negative factor when considering FNR for both the quadruped animal and the human biped. The existence of multidisciplinary protocols, based on neuroscience, is essential for patients to develop a coordinated motor function. Thus, a multi-modal approach to spastic movement disorder is required.

In the quadruped animal an association between thermotherapy, transcutaneous eletrical stimulation (TENS) (50 Hz for 30 minutes) and resistance training in the under water treadmill (UWTM), followed by passive stretches, for 5 days a week during the initial stages of spasticity, has a significant and positive impact in patients' motor coordination and functionality. It is possible to assume, through clinical evidence, that, by neuroanatomical comparison, similar protocols will reveal the same level of success if applied to the human biped.

An early intervention, associated to a multimodal approach of stretching, thermotherapy, TENS and UWTM allows for a successful FNR. To complete the multidisciplinary approach, in the more severe cases it is possible to provide pharmacological support for the management of neuropathic pain and muscular relaxation. This support can be either local (botulinum toxin) or systemic.

Keywords: Thermotherapy; Underwater treadmill; Botulinum toxin

Introduction

Throughout this review, the article seeks to address spasticity as a concept of multimodal clinical treatment, with an association between FNR modalities and pharmacological management (either local or systemic). With this multimodal approach it is important to note the relevance of neuropathic pain and its multimodal management which is obtained through an association between pharmacological and non-pharmacological interventions.

Finally, through the clinical evidence observed in the quadruped's FNR, the noble role of water locomotor training (underwater treadmill-UWTM) stands out as a multidisciplinary modality for the treatment of spasticity and spastic movement disorder (SMD).

Rehabilitation Procedures in the Management of Spasticity

Spasticity management includes a non-pharmacological management and a pharmacological approach. The non-pharmacological management covers functional neuro-rehabilitation (FNR) modalities such as: stretches, resistance training, shock wave therapy, ultrasound therapy, cryotherapy and thermotherapy, which will be described below.

Non-pharmacological Management

Stretching contributes to the normalization of muscle tone, stimulates the maintenance and excitability of the connective, tendinous and ligamentous tissues, reduces muscular contractures and promotes an independent function [1-3].

Stretches should be performed after the modality of thermotherapy, either passively or actively, depending on the progress of the biped or quadruped patient [1]. To stretching exercises, we should associate passive kinesotherapy exercises, such as PROM and endfeel, to allow for an increase in the ROM, as well as a greater flexibility of the tendino-ligamentous system [1-3].

When prescribing sretches, it is essential to provide information regarding the kind of tension that must be applied to the skeletal muscle, the type of speed, duration of each stretch and the amount of repetitions performed per day [1,2]. To promote an extended stretch, splints and orthoses can be used, since these are thought to reduce the excitatory input of intrafusal fibers and, thereby, controlling the α and γ co-contraction [1,2,4].

Several studies have shown that stretching after eccentric exercises, can decrease the excitability of motoneurons [1]. In order to avoid contractures it is necessary to reduce the use of extension immobilizations, since these will lead to a decrease in the elasticity of the antagonist muscles [1,5]. Prolonged stretches for an hour a day were found to be the most effective in human medicine (MH) [2].

Stretches associated with immobilization should not last for longer than six hours per day, so as to avoid contractures [1].

Concerning the resisatance training, several studies have demonstrated that progressive resistence strengh training (PRST) is a therapeutic option for the human biped with spasticity. The PRST promotes an increase in muscle resistance during training, allowing for a greater sustentation capacity and muscular fortification [1].

In the quadruped animal, the PRST is performed in the under water treadmill (UWTM). Oscilating velocities are used in order to perform exercises, such as squats, balance, and gait in the UWTM, since the resistance to movement in water is greater than the attenuation caused by buoyancy [6,7].

Another FNR modality that as been aplied is shock wave therapy. A clear explanation for the mechanism behind the use of shock wave therapy in the treatment of spasticity has yet to be found. However, it is thought that this therapy stimulates the synthesis of nitrous oxide, which promotes vasodilation and, therefore, an increase in blood supply to the area and muscular hydration, besides it possibly being a central nervous system neurotransmitter [1] with the capacity to reduce muscle spasms. It is also known that it stimulates the production of angiogenesis growth factors, leading to an increase in blood flow [8].

Ultrasound therapy, is a rehabilitation modality that should be used in association with static stretches, since its effects of thermal vasodilation, allow for a greater flexibility and range of motion (ROM) due an increase in cellular metabolism, circulation and hydration of muscle fibers [1,8,9].

The programs that last for 10 to 15 minutes per session in a continuous mode with a frequency of 1 MHz and intensity of 1.5 W/cm , reduce the excitability of the α motoneuron by raising the tissue's temperature and modifying the viscoelastic properties of spastic muscles [1,8,9].

Another FNR modality that is often used is cryotherapy, which reduces the excitability of the α-LMN by activating its inhibition and, therefore, inhibiting the contraction of extrafusal fibers during the γ and α co-contraction [1].

The combination between cryotherapy and air pressure, used in the intermittent pneumatic cryotherapy technique, yields better results, leading to a reduction in spasm for up to 6 hours. Studies have shown that, on post-surgical and polytraumatized quadruped patients, reduced levels of pain make it difficult for spasticity to develop, since these allow mobility a and muscular functionality [10].

The application of heat possesses a mechanism similar to that seen in ultrasound therapy, eventhough its anti-spastic effect is due to a decrease in the activity of gamma-afferent fibers [11], which might lead to a reduction of impulses provenient from the mechanoreceptors present in the intrafusal fibers , leading to a reduction in the amount of impulses at the level of extrafusal fibers mediated by theα-LMN [1].

The application of heat results in local vasodilation secondary to histamine and bradiquine release via the dorsal root ganglia, allowing a decrease in local sympathetic activity and, thus, reducing muscular contraction and facilitating vasodilation [10,12,13].

The relaxation observed is due to the activation of the mechanism of inhibition of theα-LMN in the extrafusal fibers [12,14] and it promotes flexibility as well as an increase in ROM [10].

To complement the management of spastic disorders, it is associated the locomotor training and eletromyostimulation (TENS). The locomotor training [LT] can be in through an aquatic metod or by a terrestrial metod, which will be described below.

A study performed by Houg in 2014, using the rat as an experimental model, regarding the association between locomotor training and transcranial magnetic stimulation has shown that there is a higher amount of beta-hydroxylase dopamine, glutamic acid decarboxylase 67, gamma-aminobutyric acid B receptor, and brain-derived neutrophilic factor in the lumbar spinal cord segments of the animals belonging to the group receiving treatment when compared to the control group. Consequently, it has been suggested that this type of treatment enables the self-regulation of neuroplasticity in the spinal cord [13,15,16], and, as a result, the use of a combined treatment may lead to a decrease in spasticity and an increase in locomotor control. Certain studies indicate that the terrestrial treadmill, with or without weight bearing, can and will be used as part of FNR programs with the purpose of promoting a functional gait [13,15,17-20], but not as part of programs aimed towards the resolution of spasticity.

The LT can also be done in the underwatter treadmill (UWT). Hydrotherapy plays a key role in FNR, even in UMN syndromes, where spasticity occurs. The unique properties water possesses, such as density, buoyancy, viscosity, surface tension, temperature and resistance [6,21], allow all active or active assisted kinesotherapy exercises to act more effectively. While buoyancy aids in the development of voluntary movement, facilitating the process, water temperature leads to a decrease in activation of gama fibers combined with the inhibition of the α- LMN in extrafusal fibers, which results in muscle relaxation and, therefore, in a decrease in muscle spasm, limiting the vicious cycle of pain-spasm-pain [6,22,23].

The rhythmic bycicle movements performed by the technician, in the water, will allow a relief in muscle tension while promoting stretching, thus, stimulating a differentiated approach to the treatment of spasticity [6,22]. In veterinary medicine, quadruped FNR uses this modality within the UWTM, which, besides reducing spasticity in several ways, makes use of the advantages of underwater locomotor training

in order to stimulate the neuroplasticity of the central pattern generators while simultaneously reducing the negative effects of neuroplasticity, such as neuropathic pain and spasticity. There are several protocols for FNR in the UWTM, but the most frequently used in quadrupeds initially has a duration of 10 minutes at a speed of 2 km/h, for 6 days a week. This protocol is altered every 3 to 5 days according to the patient's evolution in neurological terms while taking into consideration its cardio-respiratory capacity and it can reach 60 minute sessions at a speed of 2.5 km/h, for the same 6 days per week. These protocols also take into account the number of repetitions of the same movement, intended to stimulate memorization at a spinal level. The hydrotherapy protocols in the UWTM should be associated to other FNR modalities and to pharmacologic management, with it being either local or systemic.

In the UWTM, body weight is supported, leading to a decrease in the compressive forces acting at the joint level. As a result, this therapy prepares the connective and ligamentous tissues for stretching while reducing the algic state [11]. This way, an increase in AAROM and ROM occurs whenever the water line is above the joint where the range of motion was measured. This increase also allows for an increase in coordination and balance during locomotor training, which is achieved through the the viscosity, buoyancy and resistance of water [6,21]. It is also known that, in the UWTM, all fortification exercises are more effectively performed, since the viscosity and water resistance stimulate muscle fortification [6].

To the LT we should associate transcutaneous eletromyostimulation (TENS), since the application of TENS reduces muscle tone in patients who suffered a stroke, spinal cord injuries and cerebral palsy. It is believed that there is a release of endorphins leading to a decrease in the excitability of motoneurons as well as a reduction in nocieceptive inputs [1].

The multimodal management of neuropathic pain, should be one of the goals in FNR, therefore, the combination of pharmacological management with TENS is an option for the management of spasticity. This way, in daily practice, associating an anticonvulsant, like pregabalin, to TENS therapy, allows the multidisciplinary management of neuropathic pain and spasticity [24,25].

Several studies have proven that transcutaneous eletromyostimulation possesses an effect on muscle spasticity, eventhough its effect of inhibition of the excitability of motoneurons only lasts for a short period of time. A study performed in hemiplegic biped patients following a stroke, showed that a TENS protocol at 100 Hz, with 20 minute duration, acts for 45 minutes in spasticity [26]. Within this period of time it is possible to perform passive or active stretches. The latter can be achieved through locomotor training in the UWTM, as it will be mentioned later on.

In 2014 Ursula S. Hofsloetter, achieved excellent results with transcutaneous eletrical spinal cord stimulation [TSCS], proving the occurence of a decrease in γ andα co-activation in spastic muscles, while stimulating an increase in ROM in the adjacent joints and, in addition, certain patients showed an increase in speed consistency during movement [27]. This way, while the TENS therapy used in clinical practice stimulates superficial neural structures, which allows an approach to pain management [10,28,29], TSCS is able to stimulate deep neural structures, promoting a bilateral and multi-segmental stimulation of inputs to the spinal cord as well as a modification of the circuits responsible for the excitability of motoneurons [27].

During TSCS, 1a afferent fibers possessing large diameters form synaptic connections with Ia inibitory interneurons. By stimulating the 1a afferent fibers and, consequently, Ia inibitory interneurons it is possible to stimulate the inhibition of the brain stem's descending pathways, supporting the idea that the loop spinal-brainstem-spinal mechanisms might be involved in the supression of segmental excitability, thus, controlling spasticity [27,28,30].

Ursula concludes that TSCS at 50 Hz for 30 minutes, leads to a reduction in the pathophysiology of spasticity, promoting, instead, a normal physiology (voluntary motor control), which allows a better resistance and fortification training, for example, in the UWTM.

Pharmacological Management

As it as been told, we should associate in the multidisciplinary protocols of spastic disorders treatments, the pharmacological management.

The pharmacological management aims to increase the patient's quality of life by reducing contractures and painful spasms [18]. This management reduces the hyperexcitability of motoneurons and/or of interneuronal spinal mechanisms [18].

For pharmacological management, a systemic route of administration may be used, such as the oral prescription of baclofen, diazepam, dantrolene sodium, tizanidine as well as other not so commonly used drugs, such as cannabis and clonidine. Considering neuropathic pain, it is also possible to associate an anticonvulsant [15], such as pregabalin [2] or gabapentin to the therapy [1,4,31,32].

Diazepam is an anti-spastic agent that acts by increasing the gaba presynaptic inhibition in the spinal cord, possessing, however, clinical limitations due to its secondary effects of fatigue and lethargy associated with drowsiness and, therefore, it should be administered at night in both the biped and the quadruped [1,3,4,18].

The same group of benzodiazepines includes clonazepam, which can be used in the biped overnight. It operates by attenuating hyperreflexia, decreasing the excitability of motoneurons by the activation of GABA B receptos [18,33].

Baclofen is the most commonly used anti-spastic agent, it is a GABA analogue and, as such, it binds at the GABA B receptor site. When prescribing it, especially in the quadruped it is important to consider its secundary effects, which include

muscle weakness, fatigue, ataxia, disorientation, hallucinations and psychosis [1,3,4,33,34].

Baclofen acts by reducing PICS in the motoneurons, which support reflexes and are associated with muscle spasm [35]. PICs are composed of a persistent sodium current (NaPIC) and a persistent calcium current (CaPIC), and baclofen reduces the CaPIC, which is an antagonist of the excitatory post synaptic potential (EPSP) [1,36]. A good anti-spastic agent is one that manages to inhibit PICs motoneurons involved in spasticity, without blocking the release of the presynaptic neurotransmitter, since this leads to a superior effect [1,35,37,38].

Studies indicate that the power of baclofen, as an anti-spastic agent, is enhanced when combined with stretching exercises [1] and, ideally, each session should last for 30 minutes and the program should have duration of 4 weeks. [1].

Dantrolene sodium is an anti-spastic effect due to the suppression of the release of Ca^{2+} ions at the level of the sarcoplasmic reticulum, thus, acting peripherally in intrafusal and extrafusal muscle fibers. It's side effects are similar to those of baclofen and, if prescribed, it should be in association with a hepatic biochemical profile [18,35].

Tiazidine is a central α-adrenergic agonist and, similarly to dantrolene, its side effects include fatigue and muscle weakness. The hepatic parameters should be monitored as well [35]. As an anti-spastic drug, it as shown a reduction in spasticity, promoting a voluntary activation in the human biped [20].

Clonidine is an α2-adrenergic agonist, which reduces the excitability of the motoneurons, proven in studies with rats with chronic spinal cord injury [12].

Gabapentin is an antiepileptic which inhibits the release of glutamate in the pre-synapse, therefore decreasing spasticity [12].

The administration of drugs for the treatment of local spasticity is made through focal treatment which resorts to nerve block techniques [through the use of alcohol or phenol] and/or to the administration of botulinum toxin, leading to a decrease in spasticity in the affected muscles [1,4].

Concerning focal management we are going to expand Botulinum toxin, since the results are positive in the daily practice.

It was the biggest advance happening in the past few years regarding the management of spasticity. It acts by enabling the presinaptical release of acetylcholin, producing neuromuscular blockade [35,39], meaning the inhibition of release of acetylcholine [34]. The botulinum toxin is a natural neurotoxin [40] which allows for a selective and reversible chemodenervation [41]. The botulinum toxin is used in the management of spasticity, which occurs in several neurological conditions and, therefore, it is essential to understand the etiology of spasticity [42] In the biped, the botulinum toxin can be used in children with cerebral palsy [11,43,44], in cases of multiple sclerosis, in ischemic/hemorrhagic stroke, in spinal cord injuries and brain injuries [45], etc. In the quadruped animal this toxin is used in situations of spasticity like those observed in polyradiculoneuropaties secondary to Toxoplasma spp. or Neospora spp., in spinal cord lesions in young dogs and cats and in ischemic stroke, however, further studies regarding its application are required.

In order for the toxin to act certain guidelines must be followed:

1-The number of toxin units used should be enough to neutralize neuromuscular function activity;

2-The quantity of volume should be adequate;

3-The process of placing the needle beyond the muscle fascia should be performed with resort to eletromyography, ultrasonography or palpation of the muscle belly through the use of landmarks [46].

In the biped, as well as in the quadruped, the dosage varies according to the inherent etiology. In the human biped, multiple sclerosis processes are the ones which require more toxin units, followed by cerebral palsy and, lastly, strokes [42]. The dosage also varies depending on the severity and location of spasticity [47].

The focal management using the botulinum toxin can be performed, either in an isolated way, or in association with anti-spastic oral medications and other FNR modalities [40] Besides it being used in the treatment of spasticity, this toxin is also effective in the treatment of neuropathic pain [11,44,45], since its been proven that it inhibits the release of P substance and other pain neuromodulators, therefore, explaining its analgesic properties [40].

The botulinum toxin acts at the level of the neuromuscular junction by inhibiting acetylcholine release [3], as cited above and it is effective in reducing pain and muscle spasm, however, it possesses an adverse side effect since it can lead to excessive muscle weakness and to a decrease in muscle mass [18,44]. Due to this effect, functional rehabilitation protocols must be associated to this therapy, since these possess activities which allow mobility [23].

There is a synergistic effect between locomotor training and the use of botulinum toxin for the treatment of spasticity.

The average time necessary for the observation of the clinical effect caused by the treatment with botulinum toxin is at around four days since its administration, with it being perfectly visible within seven days. It reaches its maximum effect at around a month following its administration and it lasts for three months [3]. The final result translates into muscle weakness and relaxation.

In conclusion, a multidisciplinary treatment must be implemented by combining the use of botulinum toxin with functional rehabilitation [3].

Pharmacological Management of Neuropathic Pain

If, in all multidisciplinary spasticity protocols, with an associated non-pharmacological and pharmacological management [local or systemic], hyperesthesia or allodinia persist, a specific pharmacological management can be implemented [31,32,48,49]. Many patients in FNR, in the biped and quadruped, previously underwent surgical procedures. In these cases, the administration of a perioperative multimodal pharmacological analgesic combined with afferent neural blockade may prevent central neuroplasticity [32].

Pharmacological treatment consists in the administration of anticonvulsants; anti-depressants, opioids, NMDA blockade and topical agents, this way, it is possible to associate an opioid to a co-analgesic or to use it by itself [32].

The most commonly used antidepressants are tricyclic antidepressants (amitriptyline, chlormipramine, etc). As for anticonvulsants, the most frequently used are second-generation anti-epileptic drugs (AED) which include gabapentin, pregabalin and lamotrigine ([31,47]. Finally, the topical agents of choice are lignocain, capsaicin and ketamine [32].

In the future, the application of neurotrophic factors [such as the glial-derived neurotrophic factor] is expected to lead to a reduction in sensory pathways, while preventing microglial activation (with minocycline), thus, acting as a support to the multidisciplinary approach [32].

Discussion

In case of a CNS injury, the alterations in muscle tone can limit the execution of an efficient movement, thus, reducing motor functionality. This is where the spastic movement disorder comes into play, and, as such, the rehabilitator must be able to differentiate whether it is a result caused by neural factors [35,41,43,44,50-54] directly related to causes of α-LMN hyperexcitability, or by non-neural factors [43,44,51] like the viscoelastic properties of tissues (especially in the muscle). Thus, advances in FNR are mandatory, in order to prevent, control and reduce the symptom/clinical sign of spasticity and, indirectly, neuropathic pain. Manual methods such as passive and active muscle stretching are essential, as well as kinesiotherapy exercises, particularly the PROM and endfeel, which are the most effective when it comes to promoting an increase in ROM [1-3,5]. Whenever stretches are performed after thermotherapy or ultrasound (US) protocols, which will lead to an increase in vasodilation and, consequently an increase in blood supply as well as contributing to muscle nutrition and hydration, an increase in effectiveness is also verified. This way, initially, a protocol of thermotherapy/ continuous US at 1 MHz 10 for 15 minutes [1,8,9] followed by passive stretching should be prescribed. Then, a TENS modality, lasting 30 minutes at 50 Hz is performed [27,55], making it possible to take advantage of the following 45 minutes [26] to perform the locomotor training in the UWTM. The latter can be considered the big push towards the promotion of functionality, since it directly leads to the reduction of the vicious cycle of pain-spasm-pain [3,10,52]. This modality maintains vasodilation while also allowing training to alternate between resistance and fortification training. This way, it is possible to benefit from the intrinsic neuromodulation of locomotor training [56,57] as well as from the properties of the water, which lead to a decrease in high impact.

The exact mechanism, and its explanation through neuroanatomy, as to why hydrotherapy in the UWTM leads to a reduction in muscle spasm and an increase in ROM is not yet clear, but, on the other hand, it is known that a decrease in spasticity and neuropathic pain is possible through the use of botulinum toxin, since, besides causing a decrease in muscle tone, it inhibits the release of neurotransmitter and pain neuromodulators, such as the P substance [40].

Conclusion

It was possible to conclude that, an early and multidisciplinary approach to spasticity is essential in order to obtain successful results in its treatment. In this multidisciplinary approach diversified FNR protocols are available, including manual methods, FNR modalities and assisted and passive assisted kinesiotherapy exercises in the aquatic environment, especially in the UWTM. As a result, the human biped may benefit from the development of FNR, which will promote neuroplasticity, corrected by neuromodulation, as a way of stimulating the CNS's memory, to the point of rehabilitating the patient without the development of compensatory signs.

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