The effect of botulinum toxin on gait analysis of paraplegic patients with lower limb spasticity

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ABSTRACT

Often, people who have suffered spinal cord injury or stroke present spasticity in the lower extremities, due to uncontrolled muscle spasms, walking is completely prevented. Thus, to treat spasticity and regain walking, existing treatments include medications with substances that act on the central nervous system, such as baclofen, and substances whose infusion causes muscle denervation, such as botulinum toxin. The purpose of this study is to analyze the effect of botulinum toxin on lower extremity spasticity in paraplegic patients, and its contribution, when injected into selected muscle areas, to reduce focal hyperactivity. Research is also made, to determine the role of botulinum toxin in rehabilitation programs, when combined with other means, to improve quality of life in patients with spinal cord injury. For this review, research was made in Pubmed and Medline databases. The use of botulinum toxin issafe and effective, to reduce spasticity after spinal cord injury and other upper motor neuron damage. As for the improvements offered by botulinum toxin on walking,in patients with spinal cord injury, the results are indirect and related to the level of injury damage.In database, there are some articles with small sample of patients or case reports, so further research is needed to establish botulinum toxin's ability to regain gait,on population that has suffered from spinal cord injury.

KEY WORDS: Botulinum Toxin, Spasticity, Spinal Cord Injury

Introduction

Botulinum toxin improves walking ability in patients with lower limb spasticity following spinal cord injury [1]. Inhalation with botulinum toxin appears to be an effective additional therapy in the management of paraplegic spasticity, as spasticity is one of the most common complications following spinal cord injury [2,3]. However, the sample in most studies examining the effect of botulinum toxin on population who suffer a spinal cord injury and its contribution to gait analysis consists of a small number.

Botulinum Toxin – BT

Botulinum toxin belongs to a class of proteins with toxic action [4]. Produced by anaerobic bacteria *(Clostridium botulinum)*, its chemical formula is as follows: $C_{6760}H_{10447}N_{1743}O_{2010}S_{32}$. There are 8 different types of toxin; however only one, type A, is often applied in the field of medicine mainly for hyperactivity syndromes. The toxin acts in a bimodular way. On one hand, it suspends the secretion of acetylcholine during neuromuscular contraction resulting in muscular chemical denervation while on the other hand it affects the neurosis

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of several glands, through acetylcholine action on the parasympathetic nervous system [5]. Therefore, it is also used for the treatment of hyperhidrosis and salivation. It causes focal, dose-dependent and reversible muscle denervation that lasts from 12 to 16 weeks, while the degradation of the toxin and its pathological factors begins after a 4-week period.

Botulinum Toxin in Motor disorders

Botulinum toxin mainly affects neuromuscular synapses, preventing the release of acetylcholine. As a result, the toxin is capable of controlling spasticity, an abnormal increase in muscle contraction often caused by damage to central motor pathways that control voluntary movement. Treatment with botulinum toxin has shown to reduce spasticity due to spinal cord and brain injury, multiple sclerosis, cerebral palsy, stroke, and other neurodegenerative pathologies [6]. Botulinum toxin is considered as a milestone in the treatment of mobility disorders, such as dystonia, myoclonus, tremor, and is the mainstay of treatment for certain mobility disorders in neurological diseases. The toxin exerts its action through balancing the abnormal equilibrium between agonists and muscle competitors, highly affected by SCI's increase in muscle tone and spasticity [7]. Spastic muscle overactivity may be encountered in one or more limbs and is then referred as "focal". In focal spasticity, the intramuscular chemical attenuation caused by botulinum neurotoxin is an important therapeutic technique that has been shown to be effective and safe when administered under certain conditions (dosage, intramuscular injection, specialized physicians) [8]. Richardson et al reported that selective use of botulinum toxin to weaken muscles can reduce resistance to passive movement around a distant joint, thus improving passive range of motion and focal spasticity [9].

The purpose of this review is to evaluate the role of botulinum toxin in paraplegic patients with lower extremity spasticity and investigate its contribution to reducing pain and recovering and facilitating gait ability, thus affecting patients' quality of life.

It also discusses the application of botulinum toxin in rehabilitation programs and its proper combination with other medications and treatments in a multi-factor approach to treating people with lower limb spasticity.

The authors performed a comprehensive search of the published medical literature, using the following electronic databases Medline and Pubmed. An extensive search was conducted, from which 100 articles were found. Following the removal of duplicate articles, articles that had limited access and articles that were not entirely relevant to the subject being investigated, the number used to compile the paper was limited to 59. (Table 1)

Discussion

Botulinum Toxin in Spinal Cord Injury – BT in SCI

Bravo-Esteban Eet al, in a descriptive study of 66 people with spinal cord injury, reported lower limb hypertension and spasticity, during subacute and chronic phase, that affected their daily activities [10]. Losing voluntary bending and hypertension of extensors, seemed to contribute strongly to the loss of gait activity. Botulinum toxin appears to be an effective treatment for focal spasticity and disabilityrestriction in people with spinal cord injury [11]. According to the diagrams of 28 adults who received toxin injection, 56% reported improvement in movement and 71% better placement, while in total, upper limb function improved at 78%, hygiene at 66.6% and pain decreased at 83,3%. Botulinum toxin is effective in focal spasticity and is also recommended as a good additional therapy for oral medication to spasticity in people with spinal cord injury and generalized spasticity, according to a study with 90 patients with incomplete spinal cord injuries treated with BT for the first time. Therapy lasted for at least 1 year, and patients showed improvement in pain levels by 38.9% and improved muscle tone. ASIA D injuries showed the greatest improvement as far as muscle tone was concerned [3]. Subjective and objective improvement in spasticity was recorded following selective injections of botulinum toxin, in a patient with incomplete damage to the twelfth thoracic vertebra accompanied with strong and painful spasms in lower limbs, who was unwilling to receive intrathecal baclofen treatment, at two years follow-up [12].

Gait Analysis in Spinal Cord Injuries

Kinematics in gait analysis, via video, is a sensitive tool for quantifying gait abnormalities, while spasticity and injury level determine the pattern of gait anomaly following spinal cord injury [13]. In a study of 27 people with spinal cord injury who had retained the ability to walk (Frankel D), a statistically significant difference was found between people with thoracic injuries demonstrating a decrease in rhythm, frontal and angular knee speed, and those who suffered from injuries to the lumbar spine, showing reduced stride length and velocity in the ankle joint. People with neck injuries did not have a statistically significant difference in gait analysis.

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Patrick JH suggests that the prognosis for gait depends on factors such as loss of muscle strength, degree of spasticity, type of deformity in lower limbs joints and the availability of treatment [14]. Incomplete spinal cord injuries, especially ASIA D injuries, often lead to walking retraining efforts, which can be performed after proper understanding and assessment of kinematics and forces exerted on the hip, knee and ankle. In addition, the analysis of muscle synergies during cycling can provide a detailed quantitative assessment of functional motor impairments caused by abnormal activation of agonist and antagonist muscles following incomplete spinal cord injury, as cycling shares similar synergistic control with that observed in walking [15].

Assisted Gait in Spinal Cord Injury

Robotic devices are making a significant progress, as an innovative and effective treatment for people with spinal cord injury. Among the promising results recorded using robotic gait are reduction in pain perception and spasticity, increase of proprioception, sensitivity to temperature, vibration, pressure, reflexive behavior, gait speed, step length, distance traveled and body placement [16]. Robot walking is well accepted by people with spinal cord injuries and has shown positive results in reducing pain and spasticity. More specifically, in a study with 21 individuals performing a walking session with a powered exoskeleton robotic machine, results demonstrated high scores on positive senses and low scores on unpleasant sensations [17]. Exercising with robotic assistance, in patients following spinal cord injury, seems to have a positive effect on restoring functional gait and improving motor ability, thus allowing patients to maintain a healthy lifestyle and increase their level of physical activity. A review analysis, on 502 participants, reported significant improvements in walking distance, foot strength and functional mobility level from robot-trained groups compared to conventionally-trained groups, in the acute phase, and significantly greater improvement in walking speed, in the chronic phase, for the robot-assisted group [18]. A pilot study describes the use of a voluntary driven exoskeleton system as a new tool for rehabilitation in chronic spinal cord injury and supports that exercising in an electric treadmill using a hybrid assisted exoskeletal limb improved gait, leading to the conclusion that hybrid assisted exoskeletal limb facilitate walking ability [19]. In a study of 8 subjects, improvement in walking time, distance and speed were found with the use of the hybrid exoskeleton. Additionally, improvement was demonstrated in functional abilities, without the use of the exoskeleton, while total muscle strength was increased. Among many exoskeletons created to support walking in people with spinal cord injury, a novel system is required that would detect onset and cessation of gait via electroencephalographic signals, with the aim to control extracorporeal lower limb, thus assisting walking ability of paraplegic patients [20].

Botulinum Toxin on Gait Analysis

The spastic activity of the rectus femoris and the abnormal movement of the knee, impede the activity of walking and the ability to stand upright, in people with SCI. These factors can be reversed after a motor nerve block of the rectus femoris [21]. Injection of botulinum toxin into the spastic rectus, inhemiplegic patients, may improve muscle kinematics during walking but does not reach normal values in maximum muscle length [22]. However, a study reports significant increase in muscle length as well as muscle lengthening speed, following the injection of botulinum toxin into ten patients with knee stiffness and rectus femoris spasticity. The toxin also improved muscle tone, spasm rate and joint mobility. Although statistical significance for these parameters was not encountered, gait rate was improved [1]. According to Cioncoloni D. et al, significant improvement in gait performance can be achieved in chronic patients with lower extremity spasticity following injection of botulinum toxin into several muscles, especially the hip adductors [23]. Botulinum toxin seems to be effective and safe for focal spasticity of the lower extremities in paraplegic adult patients following cervical or thoracic spinal cord injury or patients with multiple sclerosis. Patients who have been administered toxin into the hip adductors, knee flexors and ankle flexors have experienced a reduction or resolution of pain [24].

Botulinum Toxin for Neuropathic Pain

In addition to botulinum toxin use in muscles with hyperactivity to reduce spasticity, there are evidence showing the toxin's contribution to neuropathic pain treatment. Botulinum toxin can be applied effectively in disorders based on both muscular (dystonia, spasticity) and non-muscular pain (neuropathic pain). However, no significant difference on pain relief was detected, thus implying the presence of independent mechanisms of toxin-induced pain relief [25]. Moreover, the effects of botulinum toxin on neuropathic pain associated with spinal cord injury, post-stroke pain,

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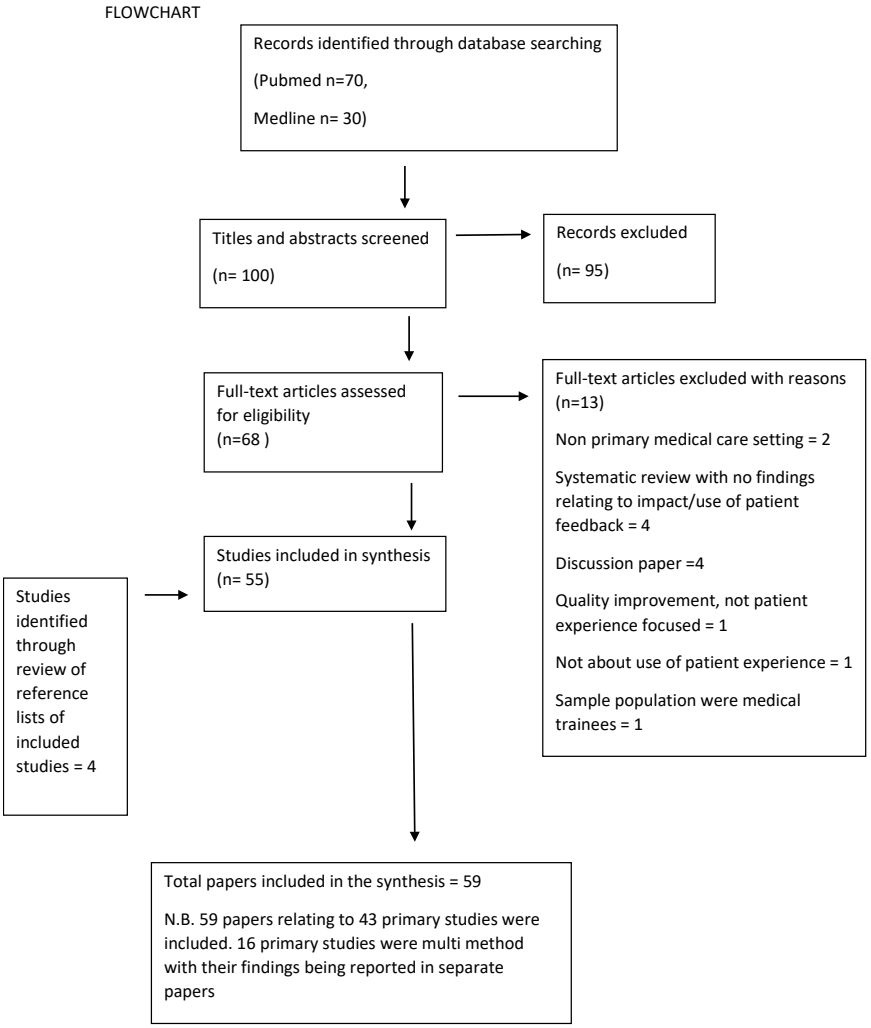
Table 1



and multiple sclerosis have been shown to be beneficial [26]. According to Jung Hyun Park and Hue Jung Park, the mechanism by which botulinum toxin acts on neuropathic pain involves inhibiting the release of inflammatory mediators and peripheral neurotransmitters from the sensory nerves. Thus, botulinum toxin injections are useful in managing a variety of disorders such as in treating post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia and intractable neuropathic pain such as post-stroke pain and spinal cord injury [27].

Combined Therapies

Spasticity occurs as a symptom of upper motor neuron damage in patients with central nervous system pathology resulting in significant pain and limited mobility, leading to reduced quality of life and difficulty in maintaining personal care. Therefore, available treatment options for spasticity include oral medications, with centrally acting agents such as baclofen, clonidine, tizanidine, and anticonvulsants such as benzodiazepines, gabapentin and peripherally actingdantrolene. As far as interventional procedures are concerned, botulinum toxin, phenol or alcohol injections and intrathecal baclofen pump may be applied, together with surgical treatments such as selective dorsal rhizotomy and neurectomy [28]. Since oral medications can cause side effects in the central nervous system, a multidisciplinary ap-

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proach combined with medication and physiotherapy to treat spasticity should be considered. Vogt T. and Urban P. suggested that combining intrathecal baclofen and botulinum toxin may improve clinical benefits and reduce side effects [29]. Spasticity following spinal cord injury should be evaluated regularly, and treatment strategy should depend on the state of functional insufficiency. Active exercise, physical therapy and oral medication are the simplest and most affordable options, although the use of tablets may be accompanied by severe side effects. International guidelines recommend a combination of botulinum toxin, physiotherapy injections and intrathecal baclofen pump in cases of peripheral spasticity as well as and orthopedic surgery or neurosurgery in selected patients with ineffective spasticity [30]. In their study, Yan X. et al. testing the efficacy and safety of botulinum toxin in spinal cord injuries, showed that the group receiving baclofen tablets was significantly improved compared to the group treated with botulinum toxin injections, while the botulinum toxin also showed steady improvement. Taking into consideration the addiction caused by the continued use of baclofen, botulinum toxin is being suggested as an effective treatment for spasticity following spinal cord injury [31]. However, instead of comparing botulinum toxin with baclofen, many studies speak of their combination, as the use of botulinum toxin can be an important adjunct in increasing the therapeutic effect of intrathecal baclofen pump, thus facilitating the use of gait orthoses and improving performance of rehabilitation programs. In a case study of a patient treated with intrathecal baclofen pump, unable to wear orthoses due painful muscle spasms, the situation resolved when bilateral injections of botulinum toxin were administered into the flexor digitorum brevis muscles [32]. Since there has been a significant reduction in patients with focal spasticity who received botulinum toxin, it is suggested that combination of botulinum toxin injections with proper orthoses may provide better results for SCI patients following rehabilitation programs [33]. Based on literature guidelines (level 1b), botulinum toxin injections reduce patients' lower extremity spasticity compared to physiotherapy alone, and when additional treatment is applied through a lower extremity cast, the results seem to improve [34]. Alongside, there is suggestion of combinate electroacupuncture and botulinum toxin injections to treat muscle spasticity following spinal cord injury, claiming that a safe and complete treatment can be achieved by reducing pain and improving quality of life faster [35].

Conclusion

Literature data support that botulinum toxin causes a decrease in muscle tone [9]. This is particularly useful for spasticity management of SCI and other upper motor neuron diseases, where there is an abnormal increase in muscle tone. More specifically, its infusion is ideal in cases where focal spasticity is detected, since it allows a better control of lower limb movements and improved walking ability. Paraplegic patients with lower limb spasticity, when injected with botulinum toxin into appropriate muscle groups, will be able to perform rehabilitation programs, maintain their functional ability and keep up their physical status. In addition, several studies report that botulinum toxin demonstrates an analgesic action; however, the exact mechanism has not been documented. The fact that the use of botulinum toxin decreases pain sensation expands its use to treat pain in clinical practice. Literature data reports additional advantages of botulinum toxin application. The healing of pressure ulcers through muscle spasm control assists medical stuff to provide better trauma care and higher patients' compliance for the rehabilitation programs. Still, botulinum toxin, in most of the available resources, has not been shown to directly improve the gait of paraplegic patients, but apparently acts indirectly, by reducing muscle spasms and regulating spasticity at certain points. In conclusion, optimum results following botulinum toxin administration are more likely to be observed in comprehensive rehabilitation programs, when combined with other medical treatments and assisted by orthoses, casts and exoskeleton systems. However, further evidence is needed to establish treatment protocols that will accurately determine the infusion criteria, frequency and dose of toxin, area of injection, appropriate rehabilitation programs and the application of orthoses to assist patients suffering from spinal cord injuries [18,22,36].

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