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Botox applications in patients with neurological symptoms following Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) is defined as damage to the spinal cord causing temporary or permanent changes in patient's major functions. The main type of SCI occurs from direct trauma, as in accidents, and is called traumatic. Despite scientific and therapeutic progress, traumatic SCI remains a major cause of morbidity and mortality. Its long-term medical complications have serious consequences for patients and their families; therefore, finding effective therapeutic interventions is very important. This study is a review of the existing literature on the therapeutic effects of botulinum toxin (Botox) as an intervention for the treatment of neurological complications occurring in patients after SCI, with emphasis on chronic complications. Botox is produced by the bacterium Clostridium botulinum, which causes botulism in humans. There are seven immunogenic toxins, however, the most used formula is BoNT-A. Botox treatment in patients with SCI is effective against spasticity, bladder dysfunction and chronic pain.

Key Words: Spinal Cord Injury, Botox, Spasticity, Urinary system, Pain

Introduction

Spinal cord injury (SCI) is defined as damage to the spinal cord causing temporary or permanent changes in patients' main functions as various degrees of motor and/or sensory deficits, paralysis, paraplegia, and quadriplegia [1,2].

Based on the etiology, SCI can be categorized into traumatic and non-traumatic. Traumatic SCI can occur from external physical factors that directly damage the spinal cord as in car accidents, falls and injuries during sports activities or cases of violence. Non-traumatic SCI is caused by an acute or chronic disease, such as tumor or infection [3].

Traumatic SCI occurs more often in men (79.8%) than in women (20.2%). Regarding the age profile, people with traumatic SCI are mainly between 15-29 years old [3]. Despite scientific and therapeutic progress, traumatic SCI remains a major cause of morbidity and mortality. Acute hospital mortality is estimated to range from 4% to 17%, while post-discharge annual mortality rates remain consistently high [1].

The pathophysiology of SCI is classified into two phases of injury, the "primary" and the "secondary". "Primary injury" results from direct physical injury to the spinal cord, where cell lysis begins. Then, a complex process of "secondary injury" takes place, which through a cyclical process promotes neuronal and glial cell death, causing inflammation. "Secondary injury"

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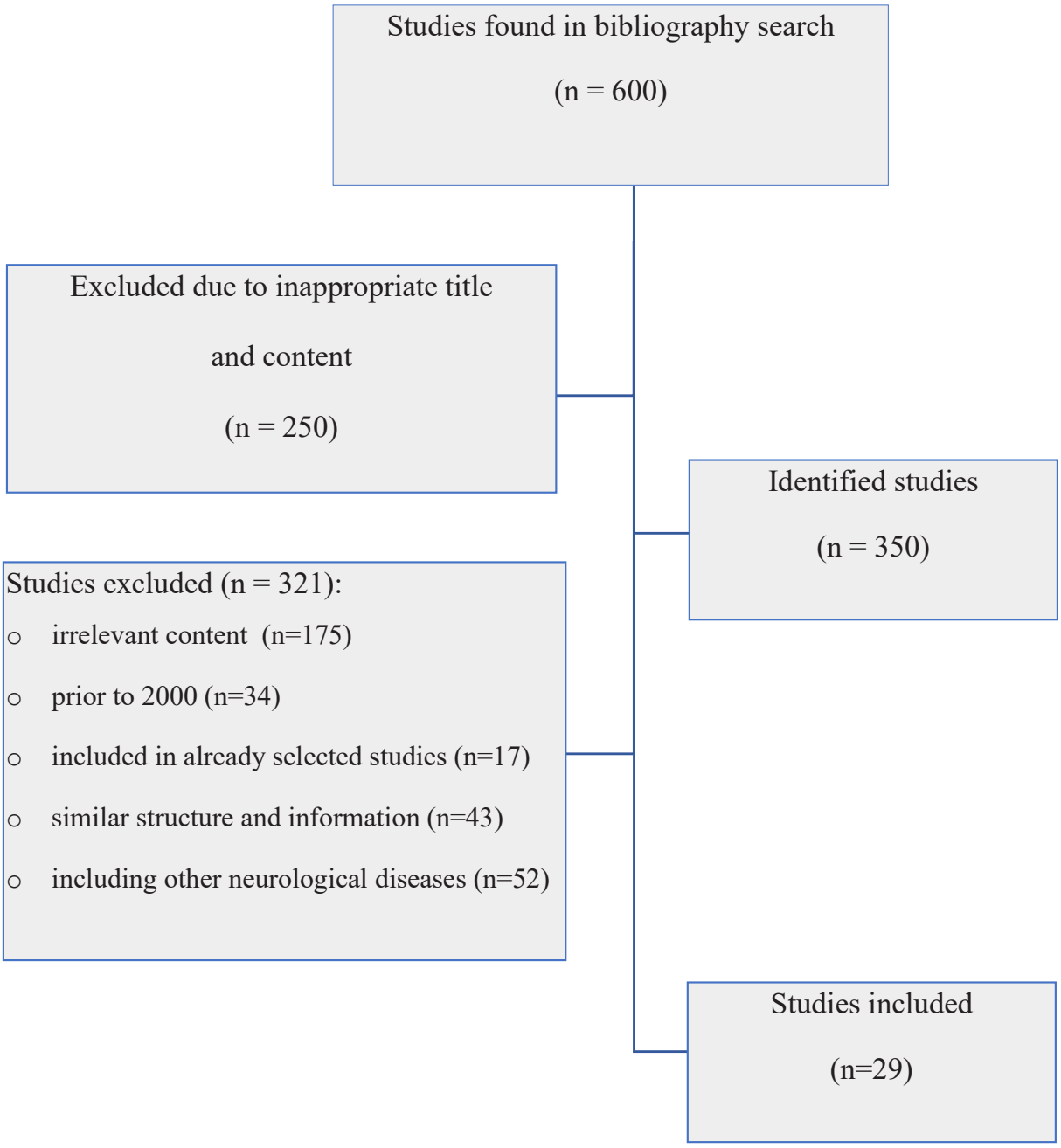

Figure 1: Flowchart

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is divided into the following phases: (i) acute (<48 hours), (ii) subacute (48 hours to 14 days), (iii) intermediate (14 days to 6 months) and (v) chronic (> 6 months) phases [1,3].

A serious condition like this entails long-term medical complications, which have devastating consequences, physical, social, as well as occupational, for the patients and their families. The main features are loss of independence, increased rates of hospitalization and mortality, loss of employability and quality of life [2,4]. Chronic complications of SCI vary and include musculoskeletal, respiratory, cardiovascular, gastrointestinal and urinary disorders, as well as spasticity and chronic pain. Musculoskeletal complications include "Charcot" neuropathic arthropathy, osteoporosis, and bone fractures [3,4]. Respiratory complications, mainly respiratory failure, are the most important cause of morbidity and mortality both in the acute and in the chronic phase. Cardiovascular complications include orthostatic hypotension, autonomic dysreflexia, and thromboembolism [4]. Gastrointestinal and urinary tract disorders, such as neurogenic bladder and neurogenic bowel, are a significant source of social and psychological stress for patients with SCI [1,4]. Incontinence, kidney failure, and urinary tract infection are some of the complications of this condition [5]. Spasticity is a common secondary complication of SCI, resulting from injury to the upper motor neurons in the central nervous system, and is characterized by hypertension, intermittent or prolonged involuntary physical reflexes (hyperreflexia), clone and muscle spasms [6]. Spasticity affects 70% of patients with SCI and causes significant disability in many patients [4]. Chronic pain is distinguished to algebraic (musculoskeletal) and neuropathic pain, and is one of the common secondary complications, affecting up to 80% of patients with SCI [7]. It is therefore understandable that patients with SCI display significant acute and chronic complications, which negatively affect their functional independence and quality of life. The development of effective therapeutic approaches, aiming at the improvement of patients' functional level and quality of life, as well as in reducing secondary morbidity is becoming extremely important [3,4].

Clinical applications of Botox have proven to be a useful tool for managing different complications following SCI, such as spasticity, chronic pain and bladder dysfunction. Botulinum toxin (BoNT) is one of the most potent natural neurotoxins, which has emerged in recent decades [8,9]. This study is a review of the applications of Botox as a therapeutic tool for the rehabilitation of long-term complications in patients with SCI. The research for the suitable literature took place using the Google Scholar database, where 600 articles were initially collected, and then were limited to 29 as they were considered more appropriate for the present study (Figure 1).

Discussion

Botulinum toxin (BoNT) is a neurotoxin produced by the anaerobic bacterium Clostridium botulinum and is one of the most poisonous substances that causes botulism in humans. Botox is characterized by four genetic groups with seven different immunogenic toxins (A - G), which are produced during the formation of spores of Clostridium Botulinum [10]. Types A, B and E are more commonly involved in cases of botulism in humans, while types A (BoNT-A) and B have been used with clinically beneficial effects in various neurological disorders and are available for treatment. Although types A and B are available in medicine, the most used type is BoNT-A [11].

Chemical structure and Mechanism of action of Botox

The toxins have a molecular weight of ≈ 150 kDa, and despite having many serotypes, all BoNTs have structurally similar characteristics, consisting of two chains linked by a disulfide bond: a light chain and a heavy chain [12]. The light chain is the toxic unit, while the heavy chain provides protection to the molecule from digestive enzymes, allowing the bacterium to act as a food poison [10]. The heavy chain of BoNT binds to the vesicular synaptic protein (SV2) and enters the presynaptic end of the nerve cell via endocytosis. The disulfide bond then breaks down, and the light chain that is now the active part of the molecule breaks down a protein called SNAP-25 in the presynaptic membrane. Subsequently, the fusion of acetylcholine-containing vesicles into the plasma membrane is stopped [9]. As a result, the release of acetylcholine is inhibited, causing the affected neuromuscular con-

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nections to become paralyzed and the muscle contraction to decrease. Clinical effects occur 24-72 hours after injection, while the reason for this delay is unknown [10]. BoNT-A inhibits the release of acetylcholine and other neurotransmitters into the neuromuscular junction in human striated muscle. Intravesical administration of BoNT-A results in the cleavage of SNAP-25, inhibiting the release of vesicular noradrenaline and preventing the activation of α- and β3-adrenoceptors. This affects the contraction of the bladder and allows the detrusor to relax [9].

BoNT-A applications in SCI

Spasticity

Spasticity is a common complication of SCI that can significantly increase dysfunction, as spastic involuntary muscle contraction competes with voluntary muscle action, and as a result function is inhibited. This can cause pain and lead to contractions, reduced mobility and cause various problems in patient's daily activities [13]. Botox has been reported to inhibit the release of acetylcholine from the nerve cell end. Botox, when injected intramuscularly, spreads approximately 30 mm through muscle and fascia, binding presynaptic cholinergic nerve cells [14]. The reduction of muscle fiber contraction begins in 24 to 72 hours after administration, while the maximum effect is observed in 5 to 14 days. The duration of its action varies from 2 to 6 months depending on the dosage [15]. By injecting BoNT-A into certain muscles, local muscle hyperactivity can be reduced without affecting other muscles, thus improving function, and preventing deformities, so its use is indicated in local spasticity [16]. The treatment is effective in reducing pain and muscle spasm. The main side effect is the excessive weakness of the treated muscle [6]. It may be necessary to locate specific muscles with electromyographic guidance to produce optimal results [13]. Palazón-García *et al*, studied the effect of BoNT-A in 90 patients with SCI. The authors reported a significant improvement in muscle tone, increased range of motion, and reduced pain, with no adverse side effects. Patients with the slightest injury showed greater improvement. In addition, significantly greater improvement in muscle tone was observed in patients with local spasticity and with immediate administration of BoNT-A after injury [16]. In another study, Ma *et al*, injected BoNT-A into rats to investigate the inhibition of muscle spasticity by blocking calcium channels. The results showed that Botox may reduce SCI-induced muscle spasticity by affecting the expression of the Cav3.2 calcium channel subunit in rats [17]. In a different study, Marciniak, Rader, & Gagnon injected BoNT-A into 28 adults, showing 56% improvement in movement, 71% improvement in maintenance of positioning, 78% improvement in upper limb function, and 83.3% reduction in pain. BoNT-A appeared to be an effective treatment for reducing local spasticity and increasing function in patients with SCI [18]. In a similar study, Opara, Hordyńska, & Swoboda administered BoNT-A infusion to 20 paraplegic patients with SCI with moderate to severe lower extremity spasticity. The injection was given in the thigh adductors and knee and leg flexors. There was improvement in most patients who experienced reduction or relief of pain [19].

Urinary system

The most common urological complications in SCI are urinary tract infection and bladder dysfunction [5]. Bladder dysfunction is associated with overactivity of the detrusor [11]. People with an overactive bladder often complain of one or more of the following problems: incontinence, frequent urination and nocturia. The neurogenic hyperactive detrusor is used to describe a urodynamic finding characterized by involuntary contractions of the detrusor during the filling phase [20].

The exact way that Botox affects the bladder is still unclear. According to initial findings, relaxation of the detrusor was observed [10]. Injection of BoNT-A to the detrusor has been found to affect the adrenergic nerves and sensory fibers, blocking the presynaptic release of acetylcholine from the parasympathetic active nerve, promoting paralysis of the motor neurons of the bladder, similar to the way it acts on the striated muscle [12,20]. Kuo studied the effect of BoNT-A in patients with SCI, who had difficulty in urinating and incontinence, by injection into the urethral sphincter and into the detrusor, respectively. Urodynamic parameters showed significant improvement in both groups, with better results in patients injected into the detrusor. However, a discrepancy was observed between

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the objective urodynamic results and actual patient satisfaction [21]. In another study, Chen, Chang & Kuo investigated changes in proteins of urothelial connection and suburothelial inflammation before and after BoNT-A injection into the detrusor in 26 patients with SCI. Urinary dysfunction and protein concentrations in patients' bladders were recovered after treatment with BoNT-A. However, this effect decreased over time [22]. Chen, Xie, & Jiang investigated the efficiency of BoNT-A injections at the detrusor in patients with urinary incontinence and bladder compliance secondary to SCI. The duration of the study was 12 weeks, where a significant reduction in cystourethral regression was observed, incontinence was improved as the pressure exerted on the bladder decreased, and urine volume increased [23]. Chen *et al*, applied directed peripheral BoNT-A infusion to 18 SCI patients in the external urethral sphincter to treat external sphincter detrusor dysfunction. The followings were observed: a) significant reduction in static urethral pressure and bladder contractions, b) significant reduction in urine residues, in the first and second months after treatment, c) contractions and pressure exerted on the detrusor did not decrease sufficiently [24]. Jia *et al*, investigated the effect of BoNT-A on urinary tract infection in 41 men with neurogenic extrinsic hyperactivity following SCI. The study lasted 6 months and the injection was performed in the detrusor. BoNT-A significantly reduced urinary tract infection, possibly associated with decreased urine residues and decreased detrusor contractions [25].

Neuropathic Pain

Pain is one of the most common SCI complications, with pain prevalence rates ranging between 75% and 81%. The most common subtype of chronic pain in SCI patients is neuropathic pain, which is defined as "pain caused by a damage or disease of the somatosensory system" [8, 26].

Although BoNT-A is commonly used to treat spasticity and urinary tract complications, studies have shown that it is effective in treating chronic pain conditions such as chronic migraine, mesothermal neuralgia, post-traumatic neuralgia or diabetic neuropathy [27]. It has been suggested that BoNT-A may inhibit neurogenic inflammation and peripheral sensitization of nicotine fibers by inhibiting the release of local neuropeptides, thereby reducing pain [26]. Li *et al*, studied the effect of Botox against neuropathic pain in 44 patients with SCI who were divided into two groups. In one group BoNT-A was injected into the area of pain, while in the second group placebo (saline solution) was injected. Individuals in both groups were treated daily for 8 weeks. BoNT-A intervention was more effective than placebo in significantly reducing neuropathic pain in patients with SCI [28]. In a similar study, Han *et al*, studied the analgesic effect of BoNT-A on neuropathic pain in 40 patients with SCI. The study lasted 8 weeks with patients divided into two groups, where one group received placebo and the other group was injected with BoNT-A. Among the participants in the BoNT-A group, 55% reported pain relief of 20% or more, while in the placebo group only 10-15% reported a similar level of pain relief [29].

In conclusion, SCI remains a serious medical condition that causes acute and long-term secondary medical complications. Patients' autonomy and quality of life are adversely affected by chronic complications, which is why early prevention and treatment are essential. The use of BoNT-A as a therapeutic intervention is applied to chronic complications, such as spasticity, urinary tract disorders and neuropathic pain. Its mechanism of action and its effectiveness in reducing spasticity have been adequately studied and the findings suggest that reducing muscle spasms significantly increases patients' range of motion. The findings from the application of BoNT-A in the urinary system are positive, although its mechanism of action is still under study. Regarding the application of Botox to reduce neuropathic pain, which is a relatively new subject of study, the results are optimistic. However, the mechanism of action has also not yet been clarified. Further studies regarding the use of Botox in patients with traumatic SCI and its mechanism of action are needed to improve its clinical outcome and improve patients' quality of life.

Conflict of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Hachem LD, Ahuja CS, Fehlings MG. Assessment and management of acute spinal cord injury: From point of injury to rehabilitation. The Journal of Spinal Cord Medicine 2017;40(6):665–75.
2. Dumont RJ, Okonkwo DO, Verma S, et al. Acute spinal cord injury, part I: pathophysiologic mechanisms. Clinical neuropharmacology 2001;24(5):254-64.
3. Ahuja CS., Wilson JR., Nori S, et al. Traumatic spinal cord injury. Nature reviews Disease primers 2017;3(1):1-21.
4. Sezer N, Akkuş S, Uğurlu FG. Chronic complications of spinal cord injury. World journal of orthopedics 2015;6(1):24-43.
5. Al Taweel W, Seyam R. Neurogenic bladder in spinal cord injury patients. Research and reports in urology 2015;7:85-99.
6. Adams MM, Hicks AL. Spasticity after spinal cord injury. Spinal cord 2005;43(10):577-86.
7. Hagen EM, Rekand T. Management of neuropathic pain associated with spinal cord injury. Pain and therapy 2015;4(1):51-65.
8. Hashemi-Zonouz T, Jabbari B. The Role of Botulinum Toxins in Treatment of Brain and Spinal Cord Injury Symptoms. In: Jabbari B. (ed). Botulinum Toxin in Treatment in Clinical Medicine. Springer-Cham. 2018, pp 193-211.
9. Lin YH, Chiang BJ, Liao CH. Mechanism of action of botulinum toxin A in treatment of functional urological disorders. Toxins 2020;12(2):129.
10. Harper M, Fowler CJ, Dasgupta P. Botulinum toxin and its applications in the lower urinary tract. BJU international 2004;93(6):702-06.
11. Cho YS, Kim KH. Botulinum toxin in spinal cord injury patients with neurogenic detrusor overactivity. Journal of exercise rehabilitation 2016;12(6):624-31.
12. Jiang YH, Chen SF, Kuo HC. Frontiers in the Clinical Applications of Botulinum Toxin A as Treatment for Neurogenic Lower Urinary Tract Dysfunction. International Neurourology Journal 2020;24(4):301-12.
13. Fried GW, Fried KM. Spinal cord injury and use of botulinum toxin in reducing spasticity. Physical Medicine and Rehabilitation Clinics 2003;14(4):901-10.
14. Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine 2001;26(24S):S146-60.
15. Elbasiouny SM, Moroz D, Bakr MM, et al. Management of Spasticity After Spinal Cord Injury: Current Techniques and Future Directions. Neurorehabilitation and Neural Repair 2009;24(1):23–33.
16. Palazón-García R, Alcobendas-Maestro M, Esclarin-de Ruz A, et al. Treatment of spasticity in spinal cord injury with botulinum toxin. The Journal of Spinal Cord Medicine 2019;42(3):281-87.
17. Ma K, Zhu D, Zhang C, et al. Botulinum Toxin Type A Possibly Affects Cav3. 2 Calcium Channel Subunit in Rats with Spinal Cord Injury-Induced Muscle Spasticity. Drug Design, Development and Therapy 2020;14:3029-41.
18. Marciniak C, Rader L, Gagnon C. The use of botulinum toxin for spasticity after spinal cord injury. American journal of physical medicine & rehabilitation 2008;87(4):312-17.
19. Opara J, Hordyńska E, Swoboda A. Effectiveness of botulinum toxin A in the treatment of spasticity of the lower extremities in adults-preliminary report. Ortopedia, traumatologia, rehabilitacja 2007;9(3):277-85.
20. Linsenmeyer TA. Use of botulinum toxin in individuals with neurogenic detrusor overactivity: state of the art review. The journal of spinal cord medicine 2013;36(5):402-19.
21. Kuo HC. Therapeutic outcome and quality of life between urethral and detrusor botulinum toxin treatment for patients with spinal cord lesions and detrusor sphincter dyssynergia. International journal of clinical practice 2013;67(10):1044-49.
22. Chen SF, Chang CH, Kuo HC. Effect of detrusor botulinum toxin an injection on urothelial dysfunction in patients with chronic spinal cord injury: a clinical and immunohistochemistry study before and after treatment. Spinal Cord 2016;54(10):889-94.
23. Chen H, Xie K, Jiang C. A single-blind randomized control trial of trigonal versus nontrigonal Botulinum toxin-A injections for patients with urinary incontinence and poor bladder compliance secondary to spi-

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nal cord injury. The journal of spinal cord medicine 2020:1-8.
24. Chen S., Bih LI, Chen GD, et al. Transrectal Ultrasound–Guided Transperineal Botulinum Toxin A Injection to the External Urethral Sphincter for Treatment of Detrusor External Sphincter Dyssynergia in Patients With Spinal Cord Injury. Archives of physical medicine and rehabilitation 2010;91(3):340-44.
25. Jia C, Liao LM, Chen G, et al. Detrusor botulinum toxin A injection significantly decreased urinary tract infection in patients with traumatic spinal cord injury. Spinal Cord 2013;51(6):487-90.
26. Han ZA, Song DH, Oh HM, et al. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Annals of neurology 2016;79(4):569-78.
27. Ma L, Nagai J, Sekino Y, et al. Single Application of A2 NTX, a Botulinum Toxin A2 Subunit, Prevents Chronic Pain Over Long Periods in Both Diabetic and Spinal Cord Injury–Induced Neuropathic Pain Models. Journal of pharmacological sciences 2012;119(3):282-86
28. Li G, Lv CA, Tian L, et al. A randomized controlled trial of botulinum toxin A for treating neuropathic pain in patients with spinal cord injury. Medicine 2017;96(20):e6919.
29. Han ZA, Song DH, Oh HM, et al. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Annals of neurology 2016;79(4):569-78.

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