

Clinical Effect of Leuprolide Acetate, an Agonist of GnRH, on Sensitive and Motor Function in a Patient With Chronic Spinal Cord Injury

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Abstract

The spinal cord is the major conduct through which sensory and motor signals pass between brain and body. Spinal cord injury (SCI) results in a disruption of these pathways and dramatic functional losses. There are different experimental approaches to counteracting the effects of SCI, such as the use of neurotrophic factors. It has been demonstrated that GnRH and its agonist leuprolide acetate (LA) have neurotrophic properties in SCI experimental model animals. Here, we report our findings from a patient suffering chronic SCI, who had undergone treatment with LA therapy. Treatment consisted of intramuscular injection of LA each month during 12 months. An important improvement in sensitive and motor functions was seen in the patient after treatment with LA. Further research is necessary to elucidate the mechanism of action of LA in SCI patients.

Keywords: Sensitive and motor functions; GnRH; Leuprolide acetate; Spinal cord injury; Neurotrophic factor; ASIA score

Introduction

Spinal cord injury (SCI) causes different and long-term neurological disorders and even morbidity in humans. The main types of neurological disorders after SCI include motor and sensory deficits, bladder, bowel and sexual dysfunction, chronic pain, and autonomic dysreflexia. The first approach in SCI is through surgical methods in conjunction with anti-inflammatory treatment as methylprednisolone [1]. There are different experimental approaches to counteracting the effects of SCI,

such as the use of neurotrophic factors, Nogo neutralizing antibodies and N-methyl-D-aspartate receptor modulators [2, 3].

Recently, it has been demonstrated that GnRH and its agonist leuprolide acetate (LA) have neurotrophic properties. *In vitro*, GnRH incubation induced changes in outgrowth, number and length of neurites in rat spinal cord neurons [4]. *In vivo*, GnRH treatment improved locomotor activity and bladder function, and increased the expression of neurofilaments in spinal cords in rats with SCI [5]. Likewise, LA administration partially improves locomotor activity, gait, micturition reflex, and spinal cord morphology in a rat model of SCI [6]. LA is less susceptible to proteolysis than GnRH and has a greater binding affinity to receptors than the natural hormone, increasing its biological activity [7]. Currently, LA is used in patients for diverse clinical applications, including the treatment of prostate cancer, endometriosis, uterine fibroids, central precocious puberty and *in vitro* fertilization techniques [8]. LA administered via intramuscular is a non-invasive treatment and it is able to cross the blood-spinal cord barrier. It is safe for use and with few side effects, meaning a potential alternative for SCI treatment. Here, we report our findings from a patient suffering chronic SCI, who had undergone treatment with LA therapy.

Case Report

A 64-year-old male was admitted at rehabilitation clinic of the Autonomous University of Aguascalientes with complaints of being unable to walk, using wheelchair and with spasticity of lower limbs muscles since 3 years ago.

The subject was invited to voluntarily participate in the study. Before the initial assessment, he signed an informed consent, and all his questions or doubts about the study were clarified. This research was approved by the local Bioethical Committee of the Universidad Autonoma de Aguascalientes. All procedures used here were non-invasive and posed no hazard to the patient's health.

The patient was diagnosed with incomplete lesion in T-9 with paralysis in lower limbs type C according to American Spinal American Association (ASIA) posterior to a vertebral column surgery. Physical examination revealed tightness in lower limbs and his lower limbs muscles were weak. He experienced difficulty in standing up without support. A detailed examination of the patient was done before and after the treat-

Manuscript accepted for publication November 23, 2016

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doi: <https://doi.org/10.14740/jnr403w>

Table 1. Bilateral and Atypical Sensitivity of Patient Treated With LA (3.75 mg) Each Month During 12 Months

Level	ASIA Sensorial							
	Initial				12 months of treatment			
	Light touch		Pin prick		Light touch		Pin prick	
	Right	Left	Right	Left	Right	Left	Right	Left
Normal	T9	T9	T9	T9	T11	T10	T11	T10
Atypical	T10-S5	T10-S5	T10-S5	T10-S5	T12-S5	T11-S5	T12-S5	T11-S5

ment. This treatment consisted of intramuscular injection of LA (3.75 mg) each month during 12 months. The patient has received rehabilitation from his lesion (3 years ago) and it was maintained during treatment with LA.

Before to LA administration, normal bilateral sensitivity was to T-9 and atypical sensitivity from T-10 to S-5 (Table 1). Changes in the level of sensitivity after treatment were observed (Table 1).

Regarding the analysis of motor activity in hip flexors, knee extensors, ankle dorsiflexors, long toe extensors and ankle plantar flexors, results show a significant improvement (approximately 30%) at the end of 12 months of treatment with LA (Fig. 1). After treatment, spasticity was decreased assessed in heel reflex. At first of treatment, this reflex was absent, but at the final evaluation, it was presented with a hyporeflexia.

In spinal cord independence measure, initially the patient was traveling in conventional wheelchair and can keep standing for seconds. However, 12 months after treatment with LA, he could walk slowly until 28 steps with the help of instruments and supervision.

Discussion

There are few reports on the administration of neurotrophic factors in patients with acute and chronic traumatic SCI. It has been reported that in patient with chronic SCI, there were significant improvements in ASIA motor and sensory scale scores and functional independence measure at 24 months after treatment with acidic fibroblast growth factor (aFGF) [9]. A difficulty of the procedure is that surgery is required for the administration of aFGF.

Similar results were found in patients with traumatic SCI who received treatment with thyrotropin-releasing hormone (TRH). In these patients, an intravenous dose of TRH was administered 12 h after SCI and sensory and motor functions were evaluated 4 months after treatment. The results of this study indicated a significantly higher sensory and motor recovery compared to placebo. In this case, TRH was injected acutely [10].

The present study provides a novel non-invasive treatment with LA, a GnRH agonist, to a patient with chronic SCI. Sensitive and motor functions were partially recovered with 12 months of treatment.

In SCIs, drug therapy for neurological recovery is a complex multifactorial process. Thus, according to the experimental models on neuroregeneration, LA administration could improve the conditions in patients with SCI through different mechanisms. It is possible that LA can induce: 1) an increase in the synthesis of protein basic of myelin, likewise a decrease in the factor NF-kB activation and mRNA expression levels of proinflammatory cytokines IL-1β, IL-17A and TNF-α as occurs in spinal cord of rats with experimental autoimmune encephalomyelitis [11, 12]; and 2) improvement in spinal cord morphology, locomotor behavior, gait, micturition reflex and reduction of microglial immunological reaction in spinal cord as it has been observed in a rat model of SCI [6].

LA injections were well tolerated. Furthermore, the administration of this agonist does not require a surgical procedure as in the case of aFGF, which is a great advantage for its use.

Conclusion

A significant sensitive and motor functions improvement was

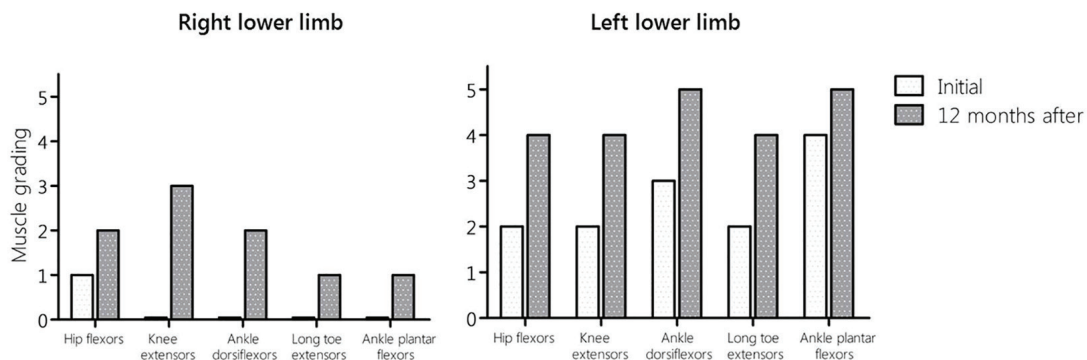


Figure 1. ASIA score results of motor activity in lower limbs before and after of 12 months of treatment with LA.

seen in a chronic SCI patient after LA therapy. The results must be interpreted with considerable caution because only a patient with chronic SCI was treated with LA, but together with several experimental animal studies, they support the need for a large multicenter clinical trial of LA.

Acknowledgments

The authors acknowledge Dr. Andres Quintanar Stephano for his medical assistance, Lic. Luis Ernesto Munoz for his support in the Physical Rehabilitation Clinic of the Universidad Autonoma de Aguascalientes and Dr. Ernesto Ruiz Esparza Padilla and Ing. Victor Masaaki Ono Yoshikawa for their support in the Medical Center Medica Norte.

Conflicts of Interest

The authors do not have any conflicts of interest.

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