

SPINAL CORD INJURY AND MALE INFERTILITY: A REVIEW

TRAUMATISMO RAQUIMEDULAR E INFERTILIDADE MASCULINA: REVISÃO

LESIÓN DE LA MÉDULA ESPINAL E INFERTILIDAD MASCULINA: UNA REVISION

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ABSTRACT

Spinal cord injuries remain an important factor of morbimortality in current society, involving mainly males from adolescence to adulthood. Among the sequelae caused by spinal cord injuries, the impairment of the sexual system is highly relevant since it affects the quality of sexual life and paternity. Infertility is secondary to multiple events such as erectile dysfunction, anejaculation, seminal biochemical modification and morphology of spermatozoa. Current therapies for the infertile spinal cord injured patient focus on the ejaculation stimulus followed by intrauterine insemination, leaving seminal low quality as the major factor of infertility in these patients. In this scenario, therapy with hyperbaric oxygenation, which is still being studied, represents an alternative treatment since it focuses on the central nervous system injured by the trauma and the testicular tissue in order to decrease spinal damage and to preserve the physiological regulation of the urogenital system as a form of avoiding infertility.

Keywords: Spinal cord injuries; Infertility; Hyperbaric oxygenation; Erectile dysfunction; Trauma to the nervous system.

RESUMO

O trauma raquimedular (TRM) é uma importante causa de morbimortalidade na sociedade atual, principalmente por acometer adultos jovens. Dentre as diversas sequelas decorrentes da lesão medular encontram-se as alterações na qualidade de vida sexual e na paternidade. A infertilidade decorre de diversas alterações como: disfunção erétil, anejaculação, alterações bioquímicas no sêmen e estruturais nos espermatozoides. As terapias para a infertilidade pós-TRM, em geral, objetivam o estímulo à ejaculação e posterior inseminação, sendo a baixa qualidade do sêmen o fator determinante para infertilidade. A terapia hiperbárica representa uma possibilidade de atuar diretamente no tecido lesado, seja ele medular ou testicular, diminuindo o dano.

Descritores: Traumatismos da coluna vertebral; Infertilidade; Oxigenação hiperbárica; Disfunção erétil; Traumatismo do sistema nervoso.

RESUMEN

La lesión de la médula espinal sigue siendo una causa importante de morbilidad y mortalidad en la sociedad actual, que afecta principalmente a hombres en la adolescencia a la edad adulta. Entre las varias secuelas resultantes de lesiones de la médula espinal, el deterioro del sistema sexual es de gran relevancia una vez que afectan la calidad de la vida sexual y la paternidad. La infertilidad es secundaria a varios eventos, tales como la disfunción erétil, aneyaculación, modificación bioquímica seminal y la morfología de los espermatozoides. Los tratamientos para la infertilidad post-TRM, en general, tienen por objeto estimular la eyaculación seguida de inseminación in vitro, siendo la baja calidad seminal el factor determinante de la infertilidad de estos pacientes. En este escenario, la terapia con oxigenación hiperbárica, aún en estudio, representa un tratamiento alternativo ya que actúa sobre el sistema nervioso central lesionado por el trauma y sobre el tejido testicular para reducir el daño espinal y preservar la regulación fisiológica del sistema genital como una forma de evitar la infertilidad.

Descriptores: Traumatismos vertebrales; Infertilidad; Oxigenación hiperbárica; Disfunción erétil, Traumatismos del sistema nervioso.

INTRODUCTION

Spinal Cord injury (SCI) has become a social epidemic of major proportions in the public health system^{1,2}, since it is a frequent cause of severe incapacity and death after trauma. Traumatic lesions of the spinal cord occur more often in young males (80%)^{3,4} aged 16 to 35^{2,5,6}, and therefore it has a high financial impact^{7,8}.

SCI is an incapacitating clinical condition with permanent and debilitating effects on the patient's quality of life, since 70% remain paraplegic and 30% remain tetraplegic. Besides, other body systems are affected, of which the endocrine and reproductive apparatus play an important role⁹.

When young males with SCI are analyzed, it is found that only 30% are married and also 30% have children at the time trauma occurs⁵. After the SCI, the possibility of having children depends on the spinal trauma severity (complete or incomplete) and its

repercussion on the reproductive system. Among patients with no offspring with complete spinal lesions, only 10% will be able to achieve paternity with medical aid^{10,11}. Under these circumstances, reproductive capacity is found to be of great relevance after SCI, making sexual rehabilitation the main priority to be considered^{3,10}.

The loss of encephalic control over the male reproductive apparatus determines an inability to have an erection and ejaculate, associated with worse seminal quality. Male sexual dysfunction occurs in 75% of patients with SCI¹², contrasting with the general population in whom the prevalence of male sexual dysfunction is 7%¹³. Although most men with spinal cord injury may have some sort of erection (reflexogenic, psychogenic or pharmacological), many can not ejaculate during sex. Besides, these patients have decreased quality and formation of the sperm, secondary to loss of autonomic regulation due to SCI.

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The objective of this article is to review the factors involved in male sexual dysfunction after SCI, also analyzing current treatment and potential therapeutic targets studied.

Physiology of male sexual function

Sexual function depends on the spinal cord reflexes and on the cortical control. Reflexogenic erections involve the parasympathetic autonomous nervous system and sacral spinal cord. However, psychogenical erection depends on adequate cerebral cortical functioning, including the limbic system, visual and hearing cortex, and the connections of these centers to the autonomic spinal cord centers¹⁴.

The parasympathetic system sends efferent fibers from the second to the fourth sacral spinal cord segment, which performs synapses with the pelvic plexus using acetylcholine as the neurotransmitter. Acetylcholine promotes erection and stimulates a secretory response of the urethral and bulbourethral glands. Erection can also be mediated by nitric oxid, since it has a relaxing effect on arterial and arteriolar smooth muscles represented by vasodilatation¹⁴.

The sympathetic system has the reflexogenic center located in the spinal cord between the second thoracic segment (T2) and the second lumbar segment (L2), and is responsible for ejaculation during sex. The information leaves these spinal segments reaching the pelvic plexus by the hypogastric and pelvic nerves. The first synapse of the sympathetic system is cholinergic, while the second is mediated by norepinephrine^{5,15}. Ejaculation is obtained by the contraction of the prostate and seminal vesicle, associated with constriction of the internal urethral sphincter.

Somatic stimulus is also important for penile erection, since it is important for sensibility and for bulbocavernosus and ischiocavernosus muscle contractions in the final stages of erection and ejaculation. Somatic nerves originate from the second to the fourth sacral spinal segment¹⁴.

Infertility on the SCI patient

After the primary mechanical lesion on the spinal cord, a cascade of events leads to secondary degeneration and death of the potentially viable neuronal tissue¹⁶⁻¹⁸. Among the components of the secondary lesion, hypoxia/ischemia is considered of utmost importance to spinal tissue injury, impairing the physiological medullar mechanism and its encephalic connections. Consequently, a motor and sensitive dysfunction develops on the somatic and visceral musculature, resulting in the high rates of sexual dysfunction and anejaculation¹⁹.

The effects over sexual physiology depend on kind, level and intensity of trauma²⁰. Patients with complete spinal cord lesion of the higher motor neuron are able to achieve reflex erections, but not intentional cortical erections. On the other hand, patients with incomplete higher motor neuron lesion can have reflex and psychogenic or intentional erections, although they are often not sufficient for intercourse.

Among patients with complete SCI, ejaculation is obtained in 5% of males. Comparatively, erection is achieved in 90% and ejaculation in 70% of patients with incomplete SCI^{14,17}. When patients with complete lesion of the lower motor neuron are analyzed, 25% of males with SCI at the sacral level are able to have psychogenic erection and can ejaculate, but reflex erections are unusual^{14,20} (Table 1).

SCI patients exhibit hormonal alterations on thyroid, hypothalamic and gonadal glands. Serum concentration of thyroxine and triiodothyronine are low^{9,21}. Abnormalities involving the diminishing levels of luteinizing and follicle stimulating hormone indicate alterations on the hypothalamic-pituitary-gonadal axis. The most accepted hypothesis for this condition is that the chronic post-traumatic stress of the post-traumatic state prevents pulsatile secretion of gonadotropins²¹. Lastly, serum testosterone levels diminish after SCI, although it is not understood if this situation results from the neurologic insult or if it is secondary to physical and emotional stress triggered by the trauma⁹.

Table 1. Rates of erection and ejaculation according to the spinal cord injury severity.

	Complete SCI*	Incomplete SCI*	References
Psychogenic erection UMN ^o	9%	48-79%	Monga, 1999. Linsenmeyer, 1991.
Reflexogenic erection UMN ^o	95%	90-93%	Monga, 1999.
Psychogenic erection LMN ^a	24-25%	-	Monga, 1999. Ricciardi, 2007.
Reflexogenic erection LMN ^a	12%	-	Monga, 1999.
Ejaculation	5%	70%	Monga, 1999. Linsenmeyer, 1991.

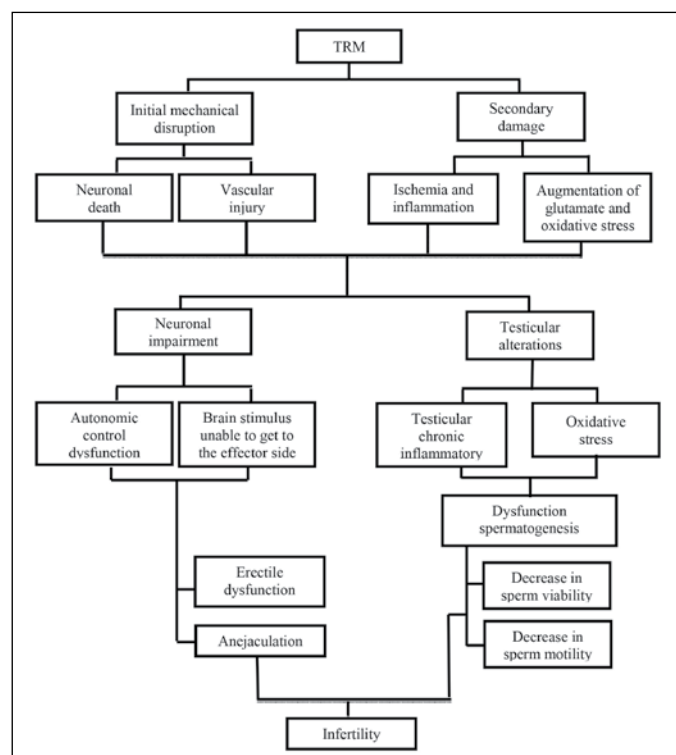
*SCI- Spinal cord injury; ^oUMN= upper motor neuron; ^aLMN= lower motor neuron.

Causes of infertility after spinal cord injury

According to current medical literature, fertility impairment in patients with SCI is the result of the neuronal damage represented by erectile dysfunction and anejaculation associated with testicular alterations, evidenced by spermatogenesis deficit^{5,20,22,23} (Flowchart 1). Moreover, contributing factors in these patients include repetitive urinary tract infection, scrotal loss of thermoregulation, medicines, retrograde ejaculation, and changes in seminal fluid³ (Table 2).

It is believed that autonomic alterations trigger the loss of homeostasis in the central nervous system (CNS). SCI with complete medular lesion prevents cortical stimulus from reaching the spinal cord at the appropriate level. Besides, the high leucospermia and DNA fragmentation of sperm are characteristic findings in this population, suggesting the presence of constant inflammatory process, producing cytotoxic factors in semen such as reactive oxygen species (ROS)²²⁻²⁴.

Physiological and controlled production of ROS are of utmost importance for sperm function and reactions, such as tyrosin kinase phosphorylation, hyperactivation, capacitation and acrosome reaction. The control of ROS production is also performed by the synthesis of antioxidant substances²⁵. Superoxide dismutase and catalase are important antioxidant enzymes extinguishing, respectively, the excess of free radicals superoxide and hydrogen peroxide²⁶. The seminal fluid also has other enzymatic antioxidant substances such



Flowchart 1. Events after spinal cord injury that lead to infertility.

Table 2. Causes of anejaculation, erection and spermatogenesis dysfunction after spinal cord injury.

Features	Causes	References
Erectile dysfunction and anejaculation	Neurologic injury that causes autonomic control dysfunction Brain stimulus unable to get to the effector side	Iremashvili, 2010. Ricciardi, 2007. Kathiresan, 2011. Brackett, 2010.
Dysfunction spermatogenesis	Testicular chronic inflammatory process Detectable levels of reactive oxygen species Oxidative stress Increase in midpiece morphologic defects. Decrease in energetic cellular production DNA fragmentation	Kathiresan, 2011. Brackett, 2010. Ibrahim, 2009. Pasqualotto, 2008. Moustafa, 2004. Agarwal, 2003. Griveau, 1995.
Other factors	Retrograde ejaculation Loss of scrotal thermoregulation Drugs Recurrent infections of the genitourinary tract Changes in seminal constituents	Brackett, 1998.

as glutathione peroxidase, and a variety of non-enzymatic antioxidants such as ascorbic acid, α -tocopherol, pyruvate and carnitine²⁶.

However, when ROS levels are greater than the antioxidant system of seminal fluid, a reaction known as oxidative stress (OS) occurs²⁷. The OS promotes fatty acid degradation by ROS, in a process called lipid peroxidation²⁸. Sperm are vulnerable to lipid peroxidation because they contain polyunsaturated fatty acids on cell membrane, substances that maintain fluidity for membrane fusion during fertilization.

There are two sources of the ROS found in seminal fluid: leucocytes and immature or defective sperm. Leucocytes, especially neutrophils and macrophages, are considered the primary source while the uncontrolled production of ROS by sperm depends on defective cell development, represented by retention of cytoplasmic organelles^{25,26}.

OS diminishes sperm motility and viability, increasing the prevalence of morphological abnormalities, all factors that impair sperm maturation and acrosome reaction²⁷. Motility impairment is secondary to the destabilization and reduction of the cell control over the membrane selective permeable property, associated with alteration of the mitochondrial potential membrane. A mitochondrial dysfunction damages the cell functioning, evidenced by the lower cellular energy production²⁹⁻³¹.

The production and amount of ROS are increased in infertile patients. When an analysis was performed to find out whether the concentration of ROS in infertile SCI patients was higher than in infertile patients for other reasons except SCI, studies showed discordant results. Results from a study conducted by Brackett³², showed no difference in ROS seminal concentration in infertile patients with SCI compared with infertile patients with no history of SCI. However, Padron et. al.³³ found that the concentration of ROS is substantially higher in SCI patients.

Different forms of sperm DNA damage are caused by ROS, such as intersection of chromatin, chromosome deletion and oxidation²⁷. OS also promotes DNA nuclear fragmentation³⁴, which impairs fertilization, genetic information passage and the correct embryological development³⁵⁻³⁷.

Although a few patients, especially those with incomplete spinal lesion, are able to achieve psychogenic or reflex erection, most of them can not ejaculate during intercourse³. Besides, even in those patients that have erection and ejaculation, the infertility index is elevated because semen quality is poor. It is believed that low seminal quality is a result of: stasis of prostatic fluid, testicular hyperthermia, abnormal testicular histology and sperm contact with urine or sperm antibodies²³. These events will result in a decreased sperm count, progressive impairment of mobility and viability, and an increasing percentage of morphological spermatozoa alterations, such as the presence of two heads or abnormal tails³².

According to Iremashvili et al, there is effective treatment for

erectile and ejaculation dysfunction, which makes sperm quality the major factor in the prospect of fatherhood for these patients⁴.

Infertility therapy

Most men with SCI requires medical treatment in order to achieve fatherhood²². The type of intervention depends on the patient's capacity of erection and on the seminal sperm status (Table 3).

Table 3. Treatment for erectile dysfunction, anejaculation and sperm viability.

Dysfunction	Treatment options	Action mechanism	References
Erectile Dysfunction	Pills Injection Topical medication and intraurethral prostaglandin suppositories Prosthesis	Vasodilatation Vasodilatation Vasodilatation Penile prosthesis	Monga, 1999. Maddox, 2011.
Ejaculation Dysfunction	Electroejaculation External vibratory stimulation Testicular microsurgery	Induce ejaculation Induce ejaculation Sperm collection from testicles.	Iremashvili, 2010. Kathiresan, 2011. Maddox, 2011. Elliott, 2000.
Sperm viability	Hyperbaric oxygen therapy	Decrease reactive oxygen species production	Hillard, 2007. Falavigna, 2009. Ibrahim2009. Brackett, 2010. Kathiresan, 2011.
Sperm quality	Artificial insemination	Introduction of the sperm in the ovule	Iremashvili, 2010.

Hyperbaric oxygenation therapy

In the scenario described above, it becomes relevant to research the effects of hyperbaric oxygenation therapy not only as a treatment for SCI, but also to evaluate the influence over the physiological mechanisms involved in male fertility, such as the testicular inflammatory process that creates cytotoxic seminal factors (ROS)²²⁻²⁴.

The healing process of the tissues damaged by trauma is divided into three phases: inflammatory, proliferative and remodeling. It is important to note that oxygen is an indispensable component of the repairing process¹⁶.

The action mechanism of the hyperbaric oxygenation therapy is to increase the oxygen supply in the injured tissues, since the higher oxygen tension promotes collagen synthesis, angiogenesis and epithelization^{16,38}.

Treatment of sexual dysfunction

For patients unable to achieve an effective erection for intercourse, defined erectile dysfunction, there are different therapies and products such as pills, injections, tablets and implants. Vasodilator drugs such as Viagra[®], Cialis[®] and Levitra[®] significantly improve sexual life and satisfaction of the patients with SCI between T6 and L5. The injection of papaverina or alprostadil in the lateral penis region promotes a vasodilatation and, consequently, an effective erection for almost 2 hours. The use of alprostadil tablets introduced in the urethra of the patient, in order to be absorbed by the mucosa, results in a relaxation of the penile vessels with consequent blood filling. A penile prosthesis is a therapeutic option for erectile dysfunction, requiring the implantation of a synthetic material inside the cavernous body of the penis³⁹.

Management of ejaculatory dysfunction

There are two current therapies to obtain semen in patients with SCI: electroejaculation by transrectal stimulus and vibro-stimulation over the glans^{5,23,29}. Therapeutic algorithms that guide treatment of anejaculatory patients recommend a penile vibratory stimulus as the first choice therapy, followed by rectal stimulus^{22,23}. The preference for electroejaculation is due to the possibility that this method can be performed at home, differently from the transrectal stimulus, which requires

a specialized clinic to be accomplished, since the method involves implantation of an electric probe in the rectum. In cases in which sperm is not obtained either by glans or by rectal stimulus, it is necessary to perform microsurgies in order to remove sperm from the testicle³⁹.

Enhancement of seminal quality

Even though there are therapeutic possibilities to obtain sperm samples, the low sperm quality remains the main factor responsible for infertility in SCI patients. The management of this condition requires high technology artificial insemination methods, characterized by ovule intracytoplasmic injection of spermatozoa⁵.

However, even with all these therapeutic options, some couples fail in the attempt to form offspring biologically. In these cases, they can use sperm obtained from a sperm bank or the couple is advised to think about adoption.

FINAL CONSIDERATIONS

SCI is a pathology with elevated morbidity for patients who survive trauma. Besides motor and sensitive impairments, the neurological deficit implies disability of many other biological systems, including the reproductive system. The prevalence of erectile dysfunction in males after SCI is almost ten times greater than in the

regular population, and this fact, associated with anejaculation and poor seminal quality, results in a high percentage of infertility.

The treatment for males with SCI depends on the capacity of the patient to achieve erection and ejaculation. For males unable to sustain an effective erection there are different therapies that may be imposed, including pills, injections, tablets and penile implant. However, many patients with adequate erection and even ejaculation remain infertile because seminal quality is low.

This fact is a consequence of the spinal cord damage, which impairs the medular reflex and cortical control over the reproductive apparatus involved in intercourse. Therefore a patient with low sperm quality requires specialized methods in order to obtain offspring, such as insemination methods in human reproduction clinics.

According to this concept hyperbaric oxygenation therapy is a promising therapeutic goal that is still being studied. High oxygen tension in injured tissues promotes collagen synthesis, angiogenesis and local epithelization, events that are essential to neuronal and testicular repair, diminishing the involvement of the reproductive system and, consequently, infertility rates.

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