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The pig model of chronic paraplegia: A challenge for experimental studies in spinal cord injury

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ABSTRACT

The regenerative medicine techniques that are beginning to be applied to the nervous system have led to increased hope in the treatment of diseases that have been considered incurable and that require experimental models on which to test new therapeutic strategies. We present our experience with adult pigs (minipigs) that have undergone a traumatic spinal cord injury (SCI) experimental model, and that have been followed for 1 year. We describe the surgical aspects of our SCI model by acute compression and also describe protocols for daily care and rehabilitation that are necessary to maintain the paraplegic pigs in good health during the months following the injury. Furthermore, we provide in detail the main complications that arise with this experimental model and the treatments used to address these complications. Suitable housing conditions, daily rehabilitation and prevention of complications (i.e., taking the same care applied to patients following SCI) are essential for achieving the absence of mortality and long-term maintenance of the animals. We consider the model that is described here to be feasible and useful for preliminary testing of novel therapeutic strategies aimed at regeneration of the injured spinal cord in paraplegic patients.

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Abbreviations: BP, blood pressue; CNS, central nervous system; ECG, electrocardiogram; MEPs, motor evoked potentials; MRI, magnetic resonance imaging; ROM, range of motion; SCI, spinal cord injury; SSEPs, somatosensory evoked potentials.

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1. Introduction

Spinal cord injury (SCI) is a clinical entity that has been known since antiquity. SCI has great importance both medically and socially, as it represents a major cause of disability with serious personal and family consequences. Trauma causes 70% of SCI cases. Each year, there are 50 new SCI cases per million people. SCI mostly affects people under 40 years of age and is associated with mortality rates that vary between 5% and 20%, depending on the spinal cord level of the lesion (Rodríguez-Boto and Vaquero, 2009).

In recent decades there has been a breakthrough in the treatment of patients with SCI, mainly in regard to the prevention of complications. However, although there are many open lines of research in this field, there is still no effective treatment that leads to the full functional recovery of patients, whose deficits are generally permanent and irreversible (Ridet et al., 1997; Silver and Miller, 2004; Esclarin de Ruz, 2010).

It is therefore understandable that one of the most important challenges in the field of neurosurgery is the search for new strategies for the treatment of traumatic SCI. This requires the development of animal models in which to test possible treatments that will subsequently be applied to humans (Blesch and Tuszynski, 2009). In these animal studies, the initial aim is to demonstrate safety and then efficacy.

There is a large body of literature on SCI, from the studies of Ramón y Cajal (1914) to the present day. These studies of experimental animals, mainly rodents, have been mostly aimed at increasing the low capacity of the central nervous system (CNS) to regenerate after damage. In upper mammals, this low capacity for regeneration is due in part to the apparent inability of the CNS to induce spontaneous axonal regeneration in the area of injury (Ramón y Cajal, 1991; Goldberg and Barres, 2000). This is possibly due to an inhibitory microenvironment that is partly attributed to glial cells (Schwab et al., 1993; Ridet et al., 1997; Fournier and Strittmatter, 2001; Morgenstern et al., 2002; Zhao and Liu, 2004).

Since 1940, some publications have described transplants of various neural tissues, such as the peripheral nerve, nodosum ganglia or brain tissue, in attempts to restore anatomical continuity in the sectioned spinal cord (Brown and McCough, 1947; Barnard and Carpenter, 1950; Kao et al., 1977; David and Aguayo, 1981). In recent years, despite the technical difficulties of such models, there has been increasing interest in this field of research. This increased interest coincides with the hope that is offered by modern techniques of cell therapy (Chopp et al., 2000; Hofstetter et al., 2002; Fraidakis et al., 2004; Ohta et al., 2004; Parr et al., 2007; Zurita et al., 2008; Vaquero and Zurita, 2011).

2. Models of SCI

Most research on traumatic SCI has been performed on adult rats because these animals are easy to handle. With regard to the severity of the injury, numerous studies have been done on models of incomplete SCI. In studies of incomplete lesions there are fewer problems with achieving the survival of the animals. However, the effectiveness of different treatments is more difficult to determine because spontaneous recovery can occur in rats with incomplete lesions (Li et al., 1998; Takami et al., 2002; Verdú et al., 2003; Bravo et al., 2004; Gorska et al., 2007, 2009). Therefore, some researchers study complete SCI. These studies generally focus on the thoracic level because it is an area where experimental and clinical studies showed that the possibility of some degree of spontaneous functional recovery is poor (Ramsey et al., 2010; Harrop et al., 2011). However, complete paraplegia models are clearly much more complex, especially with regard to postoperative care and monitoring of animal evolution.

To advance our understanding and to uncover possible cures of SCI, it is important to develop an experimental model that is able to reproduce the effects of acute and chronic SCI in humans. The literature shows different experimental models of traumatic SCI that differ in the nature of the injury-causing agent. The contusion model, in which a weight generates a measurable and reproducible acute compressive force on the spinal cord, is one of the most widely used (Allen, 1911). This model is applicable to human clinical practice, because contusion is the underlying cause in 49% of paraplegic patients (Potter and Saifuddin, 2003).

The compression model of SCI is used as an alternative to the contusion model. In the compression model, a continuous force is applied to the spinal cord over a period of time. This model, originally described by Tarlov (1957), involves placing an inflatable balloon in the extradural space; the balloon is inflated acutely or at set intervals of time. One variation on this model is the application of an aneurysm clip to the spinal cord, which produces an acute compression injury of varying severity, depending on the time that the clip is applied and the force applied by the clip (Rivlin and Tator, 1978; Joshi and Fehlings, 2002a,b).

When a researcher aims to work with an experimental model of SCI, it is important to establish the time period from when the injury takes place until when the treatment in question is applied. Therefore, we must distinguish chronic phase studies (Zurita and Vaquero, 2004, 2006; Fraidakis et al., 2004; Lu et al., 2007; Muñoz-Quiles et al., 2009; Hu et al., 2010; Gelain et al., 2011; Dulin et al., 2011), in which the spinal cord lesion is chronically established, from acute phase studies (Carvalho et al., 2008; Lutton et al., 2012;