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Spinal cord injury models in non human primates: Are lesions created by sharp instruments relevant to human injuries?

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ABSTRACT

The worldwide incidence of traumatic spinal cord injury (SCI) is approximated at 180,000 new cases per year. Experiments using nonhuman primates (NHP) are often used to replicate the human condition in order to advance the understanding of SCI and to assist in the development of new treatments. Experimental spinal cord lesions in NHP have been created by a number of methods including blunt trauma, epidural balloons, circumferential cuffs, and dropping a precision weight over the spinal cord. As well, experimental lesions have been created with sharp instruments after opening the dura mater. However, spinal cord lesions that are created with a sharp instrument in NHP experiments may not replicate the clinical and pathological features of human spinal cord injury. Researchers should recognize the challenges associated with making clinical inferences in human SCIs based on NHP experiments that created experimental lesions with a sharp surgical instrument.

Traumatic spinal cord injury is a devastating clinical condition. Worldwide, it is estimated that there are approximately 180,000 per year [1]. In order to advance the understanding of spinal cord injury (SCI) and to assist in the development of new treatments, many recently published studies utilized nonhuman primates (NHP) [2–4] supplementing the research that has been conducted in a number of species including mice, rats, cats, dogs, and rabbits [5–8]. In general, a great deal has been learned from these experiments involving animals.

Over the past 30 years, investigators have created experimental spinal cord lesions in NHPs by causing blunt trauma over the intact skin, dropping a weight over the exposed spinal cord, expanding a balloon in epidural space, and inflating a circumferential cuff over the intact dura [5,6,10]. With regards to more recent research completed in nonhuman primates, a subset of the experimental spinal cord lesions have been created by laminectomy, followed by opening the dura and subsequent transection of part of the spinal cord [9]. These experimental lesions may be created with a sharp instrument, which may be a scalpel blade or a specialized sharp device [2,3,9].

The primary goal of NHP models is to replicate the human condition in order to develop effective treatments. Considering there is a wide range of experimental model designs in NHPs, it would be advantageous to develop and devote resources to models most relevant to the types of human SCI. In this context, it is worthwhile to review the relevance of NHP experiments that create spinal cord lesions with a sharp instrument.

Most human spinal cord injuries, in fact, are not related to sharp penetrating injuries. The mechanism of these injuries results in opening of the dura mater. Of note, less than 1% of all spinal cord injuries in the United States are caused by knife injuries [15]. Most human traumatic spinal cord injuries are the result of blunt trauma such as a motor vehicle collision (MVC) and falls. In most blunt injuries, the dura mater is not opened or transected. Clinically, knife injuries result in compromise of the dura with leakage of the cerebral spinal fluid predisposing to infection [12]. In contrast, infections of the spinal cord secondary to blunt trauma are extremely rare.

From a pathomechanistic perspective, an analysis of the physical science suggests that MVC injuries are distinct from knife injuries. Consider the theoretical case in which a car collides with a stationary structure. The car has a mass of 1700 kg, and the single occupant has a mass of 80 kg. Furthermore, the car is traveling 50 km/hour. Based on MVC safety research data, the approximate amount of force experienced by the car would be approximately 530,000 newton, and the occupant would experience approximately

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26,000 newton. In a typical MVC, the multidirectional field of forces is disproportionally applied to the upper part of the human body. The force components are distributed to various organ systems with a theoretical epicenter of force transfer. This is in contrast to an experimental injury in NHP where a sharp surgical instrument creates a lesion in the spinal cord. A typical force generated by creating a surgical lesion is less than 10 newton. As well, this force is applied in a focal unidirectional manner.

As articulated by Guttman [16], the cascade of pathophysiological and clinical events that follow a knife injury is different from blunt trauma, such as MVC. In human beings, blunt SCI is associated with typical pathologic changes including petechial hemorrhages, which coalesce into larger hemorrhages with time [11]. These hemorrhages are more noticeable in the grey matter. Over a period of time, there is the formation of cavitations and fibrotic scars. The pathologic findings suggest that blunt injuries disrupt large vascular structures at the epicenter of the lesion as well as distally. This vascular disruption likely causes an inflammatory cascade and activation of thrombotic factors, including von willebrand factor, tissue factor, and tissue plasminogen activator [14]. It is reasonable to anticipate that this inflammatory cascade occurs with a greater magnitude with blunt trauma as opposed to a sharp transection.

Another complexity of establishing a relevant experimental model of human SCI is whether a lesion created by opening the dura confounds the evaluation of recovery. Opening the dura, by relieving pressure, has been shown to be improve the outcome in blunt traumatic spinal cord injury models in NHP. This observation is relevant to experimental injuries created with a sharp instrument in NHPs, in which, by necessity, the dura is opened [17]. This observation further suggests that experimental lesions created by a sharp instrument are distinct from the human experience in which the dura largely remains intact.

In addition, the physical impairments associated with a sharp cord transection in NHPs are different from those expected from a similar lesion in human beings. NHP studies show that sharp transections on one half of the cervical spinal cord primarily result in loss of hand dexterity [13]. There are also reports of stereotyped scratching of the back with the affected limb, which may be attributed to pain [9]. This is distinct from what would be expected in a human being, where a hemicord cervical lesion would be anticipated to result in substantive paralysis of both the arm and leg. Of note, in one experimental model, only 20% of NHP developed spasticity after an extensive cervical hemicord lesion. In human beings, virtually every patient with extensive cervical lesions would have some component of spasticity.

Intuitively, it can be argued that an experimental lesion created by sharp transection creates more predictable and standardized clinical impairments and histopathological abnormalities, when compared to other methods such as an impacter device or epidural catheter. However, the evidence does not necessarily support this inference. Specifically, sharp transections cannot fully control for the biological variations in the anatomy or location of motor neuron pools between subjects. A standardized 7th cervical lesion in one NHP does not necessarily cause the same level of pathological disruption or impairment in another NHP. Histologically, sharp transections, utilizing a standardized protocol for lesion creation, have resulted in disparate cross sectional lesion size [13,6]. In one group of experiments, the surface area of the lesion varied extensively, ranging from 38% to 95% of the cross sectional area [13]. As Wu remarked, "a clean hemisection is not easy and has been rarely documented in the literature" [18].

Clearly, a great deal has been learned from research involving animals. Experimental models in NHP that create experimental lesions with a sharp device have served to advance our understanding of the basic mechanisms of SCI. In addition, some of metrics of recovery are innovative and relevant to human SCI. Moving forward, however, researchers should also be cognizant of the challenges associated with making clinical inferences in human beings based on NHP experiments that create experimental lesions with a sharp surgical instrument.

Footnote

Of interest, this stereotyped scratching was treated with haloperidol or gabapentin. Theoretically, these medications can adversely affect neuronal recovery, which may further confound interpretation of results [9]. Q2

Summary

1. Penetrating spinal cord injuries are relatively rare in human beings.
2. The amount of energy transferred with an experimental lesion caused by a sharp instrument is substantially less than with a blunt injury.
3. The pathological manifestations of human spinal cord lesions caused by sharp objects is dissimilar to blunt trauma.
4. The clinical manifestations of experimental spinal cord injury created with sharp instruments is different that the clinical manifestations of a similar injury in human beings.
5. Experimental spinal cord lesions created with a sharp instrument are not more "standardized"; in fact, there is significant variability among subjects.
6. A great deal has been learned from experiments with NHP.

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