Clip Impact-Compression Model

Charles H. Tator, Peter Poon, and Andrea J. Mothe

Abstract In human spinal cord injury, the most common mechanism is the combination of acute impact and continuing compression. To simulate combined impact-compression, we developed in the 1970s the acute clip impact-compression model, one of the first non-transection models in the rodent. Subsequently, we characterized the relationships between clip strength, duration of compression and neurological recovery, and established dose-response relationships between the forces of clip compression injury, axon evoked potentials, spinal cord blood flow, neurological function, axon counts and retrograde labeling of supraspinal neurons with axonal tracers. In this review, we discuss the defining features of the acute clip impact-compression model of spinal cord injury and outline its advantages and disadvantages. We also briefly discuss other impact-compression/contusion models and non-impact models of spinal cord injury. The method for performing acute impact-compression injury in rats is included. Clip injury is useful for *in vitro* and *in vivo* spinal cord injury studies in rats and mice for cervical, thoracic and lumbar injuries, and is consistent, reliable and relatively inexpensive.

Keywords Spinal cord injury · Injury mechanisms · Rodent models · Impact-compression · Contusion

C. H. Tator (✉)
Krembil Brain Institute, Toronto Western Hospital, University Health Network, Toronto, ON, Canada

Department of Surgery, Division of Neurosurgery, University of Toronto, Toronto, ON, Canada
e-mail: charles.tator@uhn.ca

P. Poon · A. J. Mothe
Krembil Brain Institute, Toronto Western Hospital, University Health Network, Toronto, ON, Canada
e-mail: ppoon@uhnres.utoronto.ca; amothe@uhnres.utoronto.ca

J. Chen et al. (eds.), *Animal Models of Acute Neurological Injury*, Springer Series in Translational Stroke Research, https://doi.org/10.1007/978-3-030-16082-1_33

Introduction

There are many mechanisms involved in producing spinal cord injury (SCI) in humans, although the most common are impact-compression, contusion, laceration, transection and traction of the spinal cord [1]. No single experimental model can simulate all these diverse mechanisms, and therefore, there is a need for more than one model of SCI, especially for screening potential therapies for use in human SCI [2, 3]. There have been several informative reviews of experimental models for SCI [4–6], and in our view, there are several reliable and consistent animal models some of which replicate human injuries reasonably well [6, 7].

The most common mechanism of SCI in humans is a combination of acute impact followed by persisting compression [1, 8], and this combination occurs in fracture-dislocations and burst fractures of the spine, the two most common mechanisms in human SCI. In anterior fracture-dislocation, the most common type, the anterior surface of the spinal cord is compressed between the posterior aspect of the rostral vertebra while the posterior surface of the spinal cord is compressed by the anterior aspect of the lamina of the caudal vertebra. In burst fractures the anterior surface of the spinal cord is compressed by the posterior aspect of the vertebral body while the posterior surface of the spinal cord is compressed by the anterior aspect of the lamina of the same vertebra. To simulate these mechanisms of combined impact-compression, the senior author developed in the 1970s the acute clip impact-compression model, one of the first to simulate the sequence of acute impact followed by persisting compression [9]. Sudden impact is produced by rapid release of the clip. The clip closes rapidly producing bilateral, dorsal and ventral impact followed by persisting compression injury with severity related to the closing force of the clip and the duration of compression. This model was one of the first non-transection models in the rodent [7]. Subsequently, in my laboratory, we characterized the relationships between clip strength, duration of compression and neurological recovery [10, 11]. We also established dose response-curves for the relationships between the force of clip compression injury, axon evoked potentials, and spinal cord blood flow [12], and for the relationships between the force of clip compression injury, neurological function, axon counts and retrograde labeling of supraspinal neurons with retrograde axonal tracers [13]. Since then, most of the studies in the Tator and Fehlings laboratories at the University of Toronto have utilized this model in *in vitro* and *in vivo* SCI studies in rats and mice in cervical, thoracic and lumbar injuries.

In the initial phase of the development of this model of experimental SCI, we found that a 1-min duration of clip compression was the minimum time required to produce a consistent pathological and clinical effect in rats with clips varying in force from 2 to 178 g. With clips of this range of forces, we varied the duration of compression from 3 s to as long as 4 h, and found a complex correlation between both the force and duration of compression in rats at C7-T1 or T7-8 and several histopathological and clinical outcome measures. We also showed similar findings in injuries at T2-3 and L1-2 in the rat [14]. Recently, we characterized acute clip impact-compression injury at the lumbar spinal cord level L1-2 showing neurological

and histological correlation with clip strength [15]. The range of clip forces can be varied to represent the range of injury severities associated with incomplete injuries in humans graded by the system of the American Spinal Injury Association (ASIA) as ASIA grades B to D [16]. More severe injuries such as a 50 g injury at T4 in the rat produces the clinical and histological features of a complete SCI [17], graded as ASIA A in the human. An incomplete bilateral clip-compression injury to the cervical cord in the rat can be achieved with an 18 g clip at C6 [18]. Of major importance is that the clip impact-compression SCI can be used to model injuries at all levels of the spinal cord, at a range of severities, and also acute, subacute and chronic SCI [14, 15, 19–22].

In the Fehlings laboratory, the clip was adapted for producing SCI in the mouse, and the mouse clip was found to produce consistent SCI of graded severity similar to what had been previously established in the rat [23, 24]. However, the pathological changes in the mouse spinal cord differ significantly from what has been established in rats and humans. In both rats and humans, major SCI causes ischemia, necrosis and cavitation whereas in the mouse the lesions are generally without cavitation.

It should be noted that many other investigators have used clip compression SCI, some with the same modified Kerr-Lougheed aneurysm clip that we have used [17, 25]. However, many other types of clips have been used in experimental SCI [26]. For example, von Euler et al. used bulldog clips of varying forces, and placed them on the cord vertically, so that the compression force was from side-to-side or lateral rather than in the antero-posterior direction [27]. Similarly, a vascular clip was placed vertically to achieve lateral compression of the mouse spinal cord at thoracic level T9 [28]. In many reports, the authors did not state whether the clips were slowly released to produce compression or rapidly released to produce impact-compression.

Advantages and Disadvantages of the Clip Impact-Compression Model

The main advantages and disadvantages of the clip impact-compression model are as follows:

Advantages

1. Inexpensive.
2. Durable. The same clip can be used for an infinite number of times, although the springs will weaken after multiple openings and closings.

3. Useful for injuries at all levels of the spinal cord-cervical, thoracic and lumbar.
4. Useful for modeling acute, subacute and chronic injuries.
5. Useful in both rats and mice.
6. Does not require opening of the dura.
7. Produces anterior-posterior compression of the spinal cord.
8. Rapid release of the clip produces sudden impact of the spinal cord.
9. Control of time and force of application.
10. Consistent graded injuries can be produced. Both the force and duration of compression can be altered to model injuries of low to high severity, and reliable dose-response curves can be generated for both force and duration of compression.
11. Stabilization and precise positioning of the spine during injury is not required.
12. The same clip can be mounted with different rings to produce injuries of varying severity.
13. Very low mortality and morbidity rates.

Disadvantages

1. After hundreds of openings and closings the springs upon which the force of the clips depends will weaken. Thus, it is wise to calibrate the force of compression before and after each experiment. Calibration is not very complicated and the method of calibration, including a description of the calibration device has been published [29]. Alternatively, the clips can be sent to the Tator or Fehlings laboratories for calibration.
2. Practice and some surgical expertise are required for optimal and consistent placement of the clip around the cord with minimal cord trauma.
3. Laminectomy is required for clip placement.

Other Impact-Compression or Contusion Models

Several other impact-compression models were developed after the acute clip impact-compression model. Although the New York University (NYU) weight-drop impactor [30] is an improvement over the original Allen [31] weight-drop model, none of the weight-drop models produce persisting compression, and thus, they do not simulate the impact-compression of the most common human SCIs. Also, there is inherent variation and wide standard deviations in the results probably because of the randomness with which the weight contacts the walls of the cylinder and the impounder placed on the surface of the cord. The Ohio State University electromagnetic spinal cord injury device [32] is based on cord displacement which can be

accurately measured. The same is true of the Infinite Horizons impactor [33, 34], but it is expensive, impacts the spinal cord from the dorsal surface only, has limited dwell-times (i.e. persisting compression for only up to 60 s), and requires both stabilization by forceps and horizontal positioning of the spinal column at the time of SCI. However, the Infinite Horizons device has the advantages of being able to produce SCI of varying displacement and force in rats [34] and mice [35]. The clip compression model is easily adaptable for use at the cervical level, which is not true for several of the contusion models where the adjacent and overlying spinal musculature can interfere with lesion making [36]. Recently, the Ohio State electromagnetic SCI device was modified to produce a consistent and graded hemi-contusion injury at cervical level C4 [37]. In this model, the electromagnetic probe is lowered to the surface of the cord with the same starting force and then a high velocity spinal contusion is produced [37]. Establishing a common starting point for the injury probe reduces variability in impact force.

The temporal effect of impact-compression injury is not achieved in most other contusion or compression models, including the Infinite Horizons model which has a limited dwell time. In our previous studies with the clips, we examined these temporal effects after cervical cord SCI in the rat [10, 11]. The ability to study varying compression times is an advantage of the clip technique as it can be used to examine the duration of cord compression and the value of early decompression which are important issues in human SCI [2]. The clip can remain in place compressing the spinal cord for clinically relevant durations of compression.

Non-impact and Non-contusion Models of SCI

There are many non-impact and non-contusion models, and only a fraction of them will be discussed. A large number of complete and incomplete transection models have been used to great advantage to examine finite pathophysiological events, but laceration and transection are rare in human SCI. Photochemical injury delivered by irradiation of the spinal cord after intravenous administration of the photosensitive rose bengal dye [38–40] produces ischemia and graded infarction of the spinal cord and is useful to examine post-traumatic ischemia and infarction which are common secondary mechanisms after SCI [1, 41, 42]. Also, this model is less invasive because irradiation can reach the spinal cord without laminectomy. Some compression models involve “placement” of a static weight on the cord, and thus do not cause sudden impact [43], and therefore, these have been considered non-impact.

Balloon compression models were first introduced by Tarlov [44] in the 1950s and there have been many subsequent versions. Most are slowly compressing, and non-impact, although the more recent balloon materials can be rapidly inflated without bursting. In general, balloon compression models suffer from a lack of reproducibility due to the uncertainty of the balloon-cord interface.

Forceps compression of specific tracts can be achieved with forceps blades that are inserted into the cord and slowly closed. Most common is forceps compression of the dorsal columns resulting in damage to the ascending sensory axons and descending corticospinal tract [45]. If the forceps blades are rapidly closed, impact-compression can be achieved, although closing force is not consistent or calibrated. These partial lesions are also difficult to produce reliably and consistently, and are dependent on proper placement of the forceps blades.

Methods for Clip Impact-Compression Injury

The following description applies specifically to rats.

Anesthesia

Rats can be anesthetized with a variety of techniques. We have found that the combination of 1.5–2% isofluorane and oxygen produces rapid induction, good analgesia, and lack of movement during SCI. Rats are placed on a heating pad at 36 °C during surgery.

Microscopy

After the skin incision is made the entire dissection, clip placement and removal are performed with a surgical operating microscope.

Laminectomy

A laminectomy is performed at the desired cervical, thoracic or lumbar level. To facilitate the laminectomy a self-retaining retractor is essential for holding laterally the paraspinal muscles (Fig. 1a). Failure to retract the muscles sufficiently far laterally impairs accurate and atraumatic clip placement. We usually remove two laminae to facilitate dissection of the extradural plane. The laminae are removed as far laterally as possible (Fig. 1b). Usually, this involves removal of the pedicles as far anteriorly as possible so that the stumps of the pedicles will not obstruct the passage of the clip (Fig. 1b). Bone removal is performed with a small bone-cutting instrument or rongeur with slender tapering ends (Fig. 2). A nail cutting instrument is ideal. Rongeurs with larger blades work better for laminectomy in the cervical region.

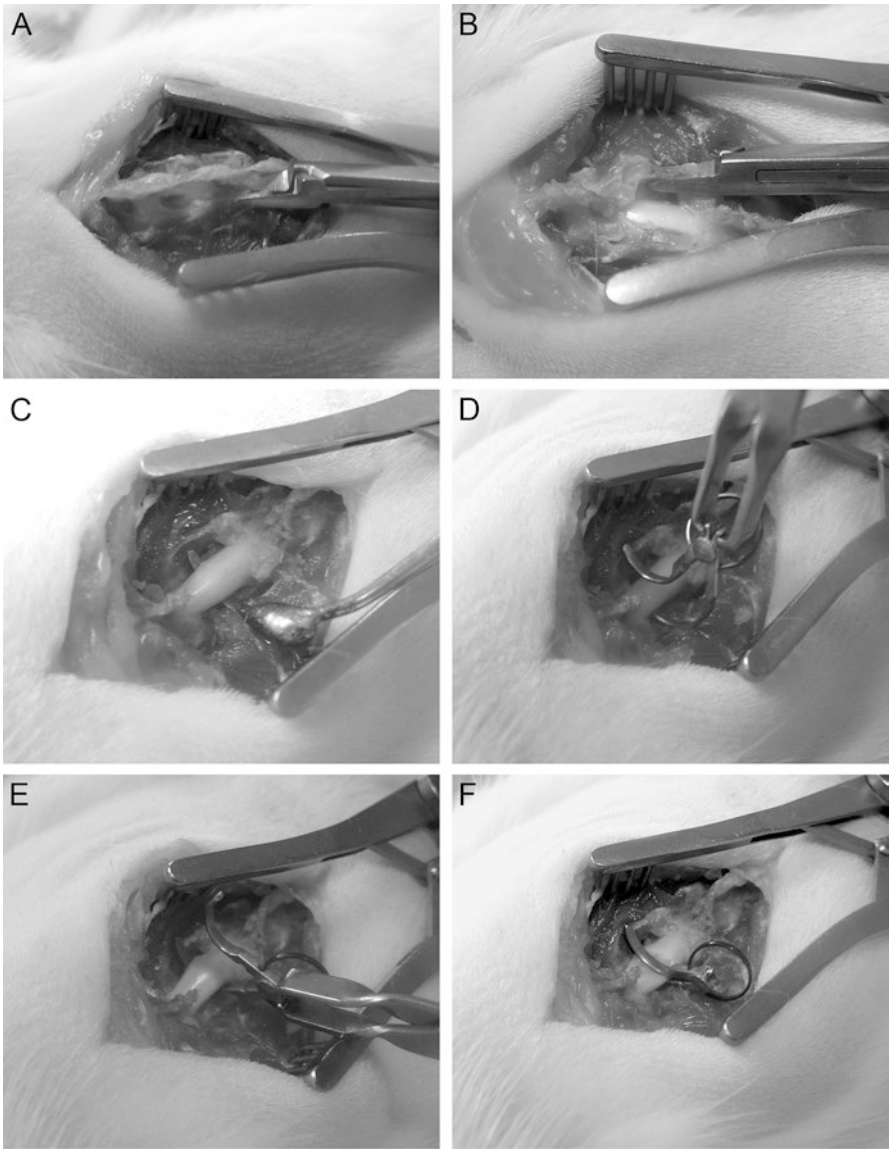

Fig. 1 The operative procedure. The steps are shown in a rat that has been perfused. (**a**) shows the self-retaining retractor in place holding back the paraspinal muscles. (**b**) shows the rongeur removing portions of the pedicle far laterally and anteriorly. (**c**) shows the cord exposed after the two-level laminectomy, and with the passage of the probe anteriorly and extradurally. (**d**) shows the clip held in the clip applicator, with the clip in the fully opened position, just prior to passage of the blade of the clip extradurally. (**e**) shows the blades of the clip anterior and posterior to the cord in the extradural space just prior to release of the clip from the applicator. The clip is still in the fully opened position. (**f**) the clip has been released from the applicator and is compressing the cord

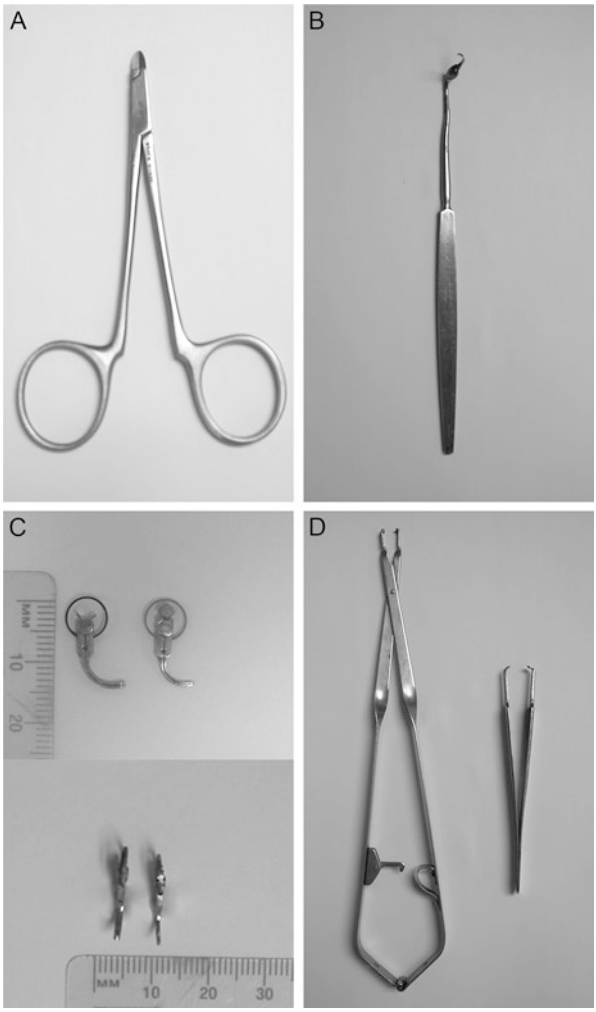

Fig. 2 The instruments for performing clip compression and the clips. (**a**) The bone cutting instrument (rongeur) for removing the laminae and pedicles. (**b**) The probe for exploring the extradural plane is a dental hook bent to conform to the shape of a clip blade. (**c**) The upper panel is a side view of the clips and the lower panel is a top view. In both the upper and lower panels, a rat clip is on the left and a mouse clip is on the right. The length of the blades of the mouse clip is smaller, and the blades and spring of the mouse clip are thinner. (**d**) Two styles of clip applicators. The applicators have ledges at the ends that fit into the grooves at the end of the clip blades to permit firm grasping of the clips

Exploration of the Extradural Plane

A dissecting hook, (Figs. 1c and 2) with similar curvature and thickness as the clip, is used to dissect the extradural plane between the dura and the adjacent vertebrae. The clips, dissecting hook, and clip applicators are manufactured to specification (Fig. 2). The hook is especially important for locating the nerve roots, and for clearing away any extradural adhesions at the optimal site for clip placement which is at the mid-point between adjacent roots. It is important to pass the hook extradurally from both the right and left sides to determine the optimal trajectory for clip

placement. Bleeding will often occur at this stage from the epidural veins and can be controlled with application of small cotton pledgets and with gelfoam sponge. Bleeding must be controlled in order to have optimal visualization of the cord during clip placement.

Placement of the Clip

With the clip held in the applicator in its fully opened position (Fig. 1e), the anterior blade of the clip is passed extradurally anterior to the cord with avoidance of damage to the adjacent nerve roots, and with as little cord displacement as possible (Fig. 1e). Some displacement is necessary, but it should be done very slowly to avoid any traction or impact of the cord. The clip held in the applicator can be used to clear away any remaining adhesions that are encountered, but only minimal force can be used, otherwise the clip will be unintentionally and prematurely released from the applicator.

Rapid Release of the Clip to Deliver the Impact-Compression Injury

The clip is then rapidly released from the applicator to produce the acute impact-compression injury (Fig. 1f). This is done by allowing the blades of the applicator to spring open at maximum velocity. The clip is then left compressing the spinal cord for the desired duration of compression.

Removal of the Clip with the Applicator

After the desired interval, the applicator is re-introduced and used to grasp and then open the clip maximally without any further manipulation of the cord. The clip is then removed with as little cord displacement as possible.

Suturing of the Wound

After injury, the muscles are sutured in one layer using 3-0 sutures and the skin closed with either sutures or Michel clips (Fine Science Tool, B.C., Canada). Buprenorphine (0.03 mg/kg, Temgesic, Schering-Plough, U.K.) is given subcutaneously before the animals awake, and then every 12 h for 48 h.

Post-operative Care

The rats are housed singly in a temperature-controlled room at 26 °C for the duration of the experiment with a 12 h light/dark cycle. Bladders are expressed three times daily until spontaneous voiding occurs, and Clavamox is added to the drinking water to prevent urinary tract infection. Water and food are provided *ad libitum*.

Ordering Information

The clips and applicators for rats and mice can be ordered directly from the Tator or Fehlings laboratories. The rat clips are approximately $2000 each and the mouse clips are approximately $1300 each. They can be supplied in a variety of forces of clip closing strength.

The clips for mice known as Fejota (Fehlings-Joshi-Tator) clips and can be ordered from the Fehlings laboratory, and a signed Research Agreement is required. The University Health Network, the group of hospitals in which the Tator and Fehlings laboratories are located is the holder of the patent and trademark on the mouse clip.

Calibration of Clips

Investigators can perform their own force of clip closure calibrations or can request this service from the Tator or Fehlings laboratories.

Outcome Evaluations

A full range of histological (Fig. 3), imaging and functional outcome measures has been used successfully after clip impact-compression injury.

Summary

Our group has used the clip impact-compression injury model to injure the spinal cord at the cervical [46–48], thoracic [19, 20–22, 49, 50], and lumbar [15, 51] levels since the 1970s, and this model has given reliable and consistent results for studying acute, subacute and chronic SCI in rodents. Other groups have also successfully

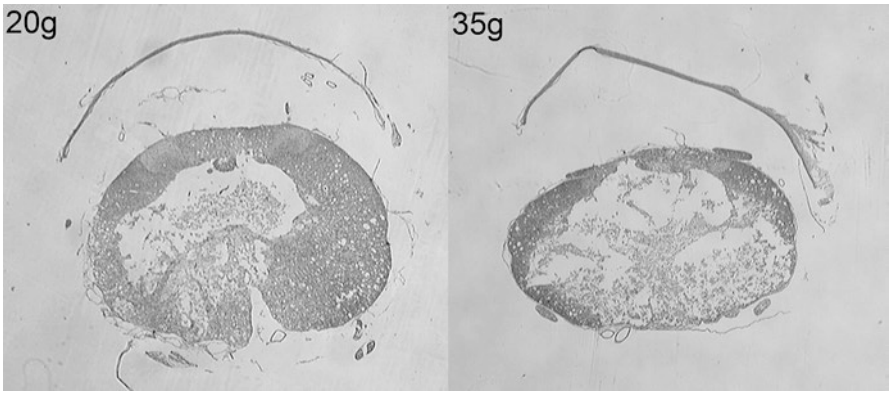

Fig. 3 Histological sections of the rat thoracic cord several weeks after clip compression injury. Hematoxylin and eosin and luxol fast blue staining. The central necrosis and cavitation are much greater after 35 g injury than after 20 g injury

used our clips for experimental SCI in rodents [17, 25, 52]. Several other clip designs were subsequently published and appear to give reliable results [53–56]. The clips have been used for examining a variety of injury mechanisms including inflammatory cytokines [57], secondary injury antagonists [26], and ischemia [12]. The clips have also been used for studying axonal physiology and morphology [58], and neuroprotective and regenerative measures with various agents including localized drug delivery [59–62], biomaterials and scaffolds [20, 63], and cell transplantation [19, 22, 49, 54, 64, 65].

Acknowledgments We thank the following sources for funding: Conquer Paralysis Now and the Sam Schmidt Foundation, Ontario Ministry of Research and Innovation and Medicine by Design, Ontario-China Research and Innovation Fund, Krembil Foundation, Toronto General and Western Hospital Foundation, and Spinal Cord Injury Ontario.

References

1. De Girolami U, Frosch MP, Tator CH. Regional neuropathology: diseases of the spinal cord and vertebral column. In: Greenfield's neuropathology. 7th edn. London: Arnold; 2002.
2. Tator CH. Review of treatment trials in human spinal cord injury: issues, difficulties, and recommendations. Neurosurgery. 2006;59:957–82.
3. Anderson TE, Stokes BT. Experimental models for spinal cord injury research: physical and physiological considerations. J Neurotrauma. 1992;9(Suppl 1):S135–42.
4. Kwon BK, Oxland TR, Tetzlaff W. Animal models used in spinal cord regeneration research. Spine. 2002;27(14):1504–10.
5. Grill RJ. User-defined variables that affect outcome in spinal cord contusion/compression models. Exp Neurol. 2005;196:1–5.
6. Fehlings MG, Tator CH. A review of experimental models of acute spinal cord injury. In: Spinal cord dysfunction: assessment. Oxford: Oxford University; 1988.

7. Wrathall JR. Spinal cord injury models. J Neurotrauma. 1992;9(Suppl 1):S129–34.
8. Tator CH. Spine-spinal cord relationships in spinal cord trauma. Clin Neurosurg. 1983;30: 479–94.
9. Rivlin AS, Tator CH. Effect of duration of acute spinal cord compression in a new acute cord injury model in the rat. Surg Neurol. 1978;10:38–43.
10. Dolan EJ, Tator CH, Endrenyi L. The value of decompression for acute experimental spinal cord compression injury. J Neurosurg. 1980;53:749–55.
11. Guha A, Tator CH, Endrenyi L, Piper I. Decompression of the spinal cord improves recovery after acute experimental spinal cord compression injury. Paraplegia. 1987;25:324–39.
12. Fehlings MG, Tator CH, Linden RD. The relationships among the severity of spinal cord injury, motor and somatosensory evoked potentials and spinal cord blood flow. Electroencephalogr Clin Neurophysiol. 1989;74:241–59.
13. Fehlings MG, Tator CH. The relationships among the severity of spinal cord injury, residual neurological function, axon counts, and counts of retrogradely labeled neurons after experimental spinal cord injury. Exp Neurol. 1995;132:220–8.
14. Poon PC, Gupta D, Shoichet MS, Tator CH. Clip compression model is useful for thoracic spinal cord injuries: histologic and functional correlates. Spine (Phila Pa 1976). 2007;32:2853–9. https://doi.org/10.1097/BRS.0b013e31815b7e6b.
15. Moonen G, Satkunendrarajah K, Wilcox JT, Badner A, Mothe A, Foltz W, Fehlings MG, Tator CH. A new acute impact-compression lumbar spinal cord injury model in the rodent. J Neurotrauma. 2016;33(3):278–89. https://doi.org/10.1089/neu.2015.3937.
16. Geisler FH, Coleman WP, Grieco G, Poonian D. Measurements and recovery patterns in a multicenter study of acute spinal cord injury. Spine. 2001;26(24 Suppl):S68–86.
17. Weaver LC, Verghese P, Bruce JC, Fehlings MG, Krenz NR, Marsh DR. Autonomic dysreflexia and primary afferent sprouting after clip-compression injury of the rat spinal cord. J Neurotrauma. 2001;18:1107–19.
18. Forgione N, Karadimas SK, Foltz WD, Satkunendrarajah K, Lip A, Fehlings MG. Bilateral contusion-compression model of incomplete traumatic cervical spinal cord injury. J Neurotrauma. 2014;31:1776–88. https://doi.org/10.1089/neu.2014.3388.
19. Mothe AJ, Bozkurt G, Catapano J, Zabojova J, Wang X, Keating A, Tator CH. Intrathecal transplantation of stem cells by lumbar puncture for thoracic spinal cord injury in the rat. Spinal Cord. 2011;49:967–73. https://doi.org/10.1038/sc.2011.46.
20. Mothe AJ, Tam RY, Zahir T, Tator CH, Shoichet MS. Repair of the injured spinal cord by transplantation of neural stem cells in a hyaluronan-based hydrogel. Biomaterials. 2013;34:3775–83. https://doi.org/10.1016/j.biomaterials.2013.02.002.
21. Parr AM, Kulbatski I, Tator CH. Transplantation of adult rat spinal cord stem/progenitor cells for spinal cord injury. J Neurotrauma. 2007;24:835–45.
22. Parr AM, Kulbatski I, Zahir T, Wang X, Yue C, Keating A, Tator CH. Transplanted adult spinal cord-derived neural stem/progenitor cells promote early functional recovery after rat spinal cord injury. Neuroscience. 2008;155:760–70. https://doi.org/10.1016/j.neuroscience.2008.05.042.
23. Joshi M, Fehlings MG. Development and characterization of a novel, graded model of clip compressive spinal cord injury in the mouse: part 2. Quantitative neuroanatomical assessment and analysis of the relationships between axonal tracts, residual tissue, and locomotor recovery. J Neurotrauma. 2002;19:191–203.
24. Joshi M, Fehlings MG. Development and characterization of a novel, graded model of clip compressive spinal cord injury in the mouse: part 1. Clip design, behavioral outcomes, and histopathology. J Neurotrauma. 2002;19:175–90.
25. Khan M, Griebel R, Rozdilsky B, Politis M. Hemorrhagic changes in experimental spinal cord injury models. Can J Neurol Sci. 1985;12:259–62.
26. Gorio A, Gokmen N, Erbayraktar S, Yilmaz O, Madaschi L, Cichetti C, Di Giulio AM, Vardar E, Cerami A, Brines M. Recombinant human erythropoietin counteracts secondary injury and markedly enhances neurological recovery from experimental spinal cord trauma. Proc Natl Acad Sci U S A. 2002;99:9450–5.

27. von Euler M, Seiger A, Sundstrom E. Clip compression injury in the spinal cord: a correlative study of neurological and morphological alterations. Exp Neurol. 1997;145:502–10.
28. Marques SA, Garcez VF, Del Bel EA, Martinez AM. A simple, inexpensive and easily reproducible model of spinal cord injury in mice: morphological and functional assessment. J Neurosci Methods. 2009;177:183–93. https://doi.org/10.1016/j.jneumeth.2008.10.015.
29. Dolan EJ, Tator CH. A new method for testing the force of clips for aneurysms or experimental spinal cord compression. J Neurosurg. 1979;51:229–33.
30. Gruner JA. A monitored contusion model of spinal cord injury in the rat. J Neurotrauma. 1992;9:123–6.
31. Allen AR. Surgery of experimental lesions of the spinal cord equivalent to crush injury of fracture dislocation of the spinal column. A preliminary report. JAMA. 1911;57:878–80.
32. Behrmann DL, Bresnahan JC, Beattie MS, Shah BR. Spinal cord injury produced by consistent mechanical displacement of the cord in rats: behavioral and histologic analysis. J Neurotrauma. 1992;9:197–217.
33. Cao Q, Zhang YP, Iannotti C, DeVries WH, Xu XM, Shields CB, Whittemore SR. Functional and electrophysiological changes after graded traumatic spinal cord injury in adult rat. Exp Neurol. 2005;191(Suppl 1):S3–S16.
34. Scheff SW, Rabchevsky AG, Fugaccia I, Main JA, Lumpp JE Jr. Experimental modeling of spinal cord injury: characterization of a force-defined injury device. J Neurotrauma. 2003;20:179–93.
35. Ghasemlou N, Kerr BJ, David S. Tissue displacement and impact force are important contributors to outcome after spinal cord contusion injury. Exp Neurol. 2005;196:9–17.
36. Pearse DD, Lo TP Jr, Cho KS, Lynch MP, Garg MS, Marcillo AE, Sanchez AR, Cruz Y, Dietrich WD. Histopathological and behavioral characterization of a novel cervical spinal cord displacement contusion injury in the rat. J Neurotrauma. 2005;22:680–702.
37. Mondello SE, Sunshine MD, Fischedick AE, Moritz CT, Horner PJ. A cervical hemi-contusion spinal cord injury model for the investigation of novel therapeutics targeting proximal and distal forelimb functional recovery. J Neurotrauma. 2015;32:1994–2007. https://doi.org/10.1089/neu.2014.3792.
38. Watson BD, Prado R, Dietrich WD, Ginsberg MD, Green BA. Photochemically induced spinal cord injury in the rat. Brain Res. 1986;367:296–300.
39. Bunge MB, Holets VR, Bates ML, Clarke TS, Watson BD. Characterization of photochemically induced spinal cord injury in the rat by light and electron microscopy. Exp Neurol. 1994;127:76–93.
40. Verdu E, Garcia-Alias G, Fores J, Vela JM, Cuadras J, Lopez-Vales R, Navarro X. Morphological characterization of photochemical graded spinal cord injury in the rat. J Neurotrauma. 2003;20:483–99.
41. Tator CH. Strategies for recovery and regeneration after brain and spinal cord injury. Inj Prev. 2002;8(Suppl 4):IV33–6.
42. Tator CH. Update on the pathophysiology and pathology of acute spinal cord injury. Brain Pathol. 1995;5:407–13.
43. Koda M, Nishio Y, Hashimoto M, Kamada T, Koshizuka S, Yoshinaga K, Onodera S, Nishihira J, Moriya H, Yamazaki M. Up-regulation of macrophage migration-inhibitory factor expression after compression-induced spinal cord injury in rats. Acta Neuropathol (Berl). 2004;108:31–6.
44. Tarlov IM. Spinal cord compression: mechanisms of paralysis and treatment. Springfield: Thomas; 1957.
45. Gruner JA, Yee AK, Blight AR. Histological and functional evaluation of experimental spinal cord injury: evidence of a stepwise response to graded compression. Brain Res. 1996;729:90–101.
46. Casha S, Yu WR, Fehlings MG. Oligodendroglial apoptosis occurs along degenerating axons and is associated with FAS and p 75 expression following spinal cord injury in the rat. Neuroscience. 2001;103:203–18.

47. Midha R, Fehlings MG, Tator CH, Saint-Cyr JA, Guha A. Assessment of spinal cord injury by counting corticospinal and rubrospinal neurons. Brain Res. 1987;410:299–308.
48. Park YK, Tator CH. Failure of topical DMSO to improve blood flow or evoked potentials in rat spinal cord injury. J Korean Med Sci. 1998;13:638–44.
49. Fan XY, Mothe AJ, Tator CH. Ephrin-B3 decreases the survival of adult rat spinal cord-derived neural stem/progenitor cells in vitro and after transplantation into the injured rat spinal cord. Stem Cells Dev. 2013;22:359–73. https://doi.org/10.1089/scd.2012.0131.
50. Namiki J, Kojima A, Tator CH. Effect of brain-derived neurotrophic factor, nerve growth factor, and neurotrophin-3 on functional recovery and regeneration after spinal cord injury in adult rats. J Neurotrauma. 2000;17:1219–31.
51. Park YK, Tator CH. Prevention of arachnoiditis and postoperative tethering of the spinal cord with Gore-Tex surgical membrane: an experimental study with rats. Neurosurgery. 1998;42:813–23.
52. Schultke E, Kendall E, Kamencic H, Ghong Z, Griebel RW, Juurlink BH. Quercetin promotes functional recovery following acute spinal cord injury. J Neurotrauma. 2003;20:583–91.
53. Baffour R, Achanta K, Kaufman J, Berman J, Garb JL, Rhee S, Friedmann P. Synergistic effect of basic fibroblast growth factor and methylprednisolone on neurological function after experimental spinal cord injury. J Neurosurg. 1995;83:105–10.
54. Boyd JG, Lee J, Skihar V, Doucette R, Kawaja MD. LacZ-expressing olfactory ensheathing cells do not associate with myelinated axons after implantation into the compressed spinal cord. Proc Natl Acad Sci U S A. 2004;101:2162–6.
55. Kureshi IU, Ho SY, Onyiuke HC, Wakefield AE, D'Arrigo JS, Simon RH. The affinity of lipid-coated microbubbles to maturing spinal cord injury sites. Neurosurgery. 1999;44:1047–53.
56. Saporta S, Kim JJ, Willing AE, Fu ES, Davis CD, Sanberg PR. Human umbilical cord blood stem cells infusion in spinal cord injury: engraftment and beneficial influence on behavior. J Hematother Stem Cell Res. 2003;12:271–8.
57. Fu ES, Saporta S. Methylprednisolone inhibits production of interleukin-1beta and interleukin-6 in the spinal cord following compression injury in rats. J Neurosurg Anesthesiol. 2005;17:82–5.
58. Nashmi R, Fehlings MG. Changes in axonal physiology and morphology after chronic compressive injury of the rat thoracic spinal cord. Neuroscience. 2001;104:235–51.
59. Elliott Donaghue I, Tator CH, Shoichet MS. Sustained delivery of bioactive neurotrophin-3 to the injured spinal cord. Biomater Sci. 2015;3:65–72. https://doi.org/10.1039/c4bm00311j.
60. Gupta D, Tator CH, Shoichet MS. Fast-gelling injectable blend of hyaluronan and methylcellulose for intrathecal, localized delivery to the injured spinal cord. Biomaterials. 2006;27:2370–9.
61. Jimenez Hamann MC, Tator CH, Shoichet MS. Injectable intrathecal delivery system for localized administration of EGF and FGF-2 to the injured rat spinal cord. Exp Neurol. 2005;194:106–19.
62. Kang CE, Baumann MD, Tator CH, Shoichet MS. Localized and sustained delivery of fibroblast growth factor-2 from a nanoparticle-hydrogel composite for treatment of spinal cord injury. Cells Tissues Organs. 2013;197:55–63. https://doi.org/10.1159/000339589.
63. Bozkurt G, Mothe AJ, Zahir T, Kim H, Shoichet MS, Tator CH. Chitosan channels containing spinal cord-derived stem/progenitor cells for repair of subacute spinal cord injury in the rat. Neurosurgery. 2010;67:1733–44. https://doi.org/10.1227/NEU.0b013e3181f9af35.
64. Karimi-Abdolrezaee S, Eftekharpour E, Wang J, Morshead CM, Fehlings MG. Delayed transplantation of adult neural precursor cells promotes remyelination and functional neurological recovery after spinal cord injury. J Neurosci. 2006;26:3377–89.
65. Roussos I, Rodriguez M, Villan D, Ariza A, Rodriguez L, Garcia J. Development of a rat model of spinal cord injury and cellular transplantation. Transplant Proc. 2005;37:4127–30.