A review of novel trends in management of canine spinal cord injury

Igor Šulla[1], Slavomír Horňák[2], Valent Ledecký[2], Vladimír Balik[3]

[1]University of Veterinary Medicine and Pharmacy, Department of Anatomy, Histology and Physiology, Košice, Slovakia
[2]University of Veterinary Medicine and Pharmacy, Small Animals Clinic, Košice, Slovakia
[3]Palacky University, Faculty of Medicine and Dentistry, Institute of Molecular and Translational Medicine, Olomouc, Czech Republic

Received January 12, 2019
Accepted April 23, 2019

Abstract

Severe spinal cord injury (SCI) causing significant morbidity and mortality remains one of the most challenging problems in both human and veterinary medicine. Due to the restricted regeneration potential of the central nervous system (CNS) in mammals, the neurological deficit caused by spinal cord (SC) injury is permanent, and no therapeutic measures are able to completely restore neurological functions either in primates or in non-primate animals with traumatic tetraparesis/tetraplegia or paraparesis/paraplegia. The constant progress in the understanding of pathophysiologic events developing after spinal cord trauma constitute an unremitting inspiration for neuroscientists and health care professionals to test novel medicaments and treatment strategies to cope with this situation. Recent experimental studies and preclinical trials have delivered promising results. The aim of this review is a presentation of generally accepted methods of management of dogs with SCI as well as a report on new therapeutic modalities, and comment on their potential for clinical translation. The research strategy involved a search of PubMed, Medline, and ISI Web of Science from January 2010 to December 2018 using the terms "spinal cord injury" and "management of spinal trauma" in the English language literature. References from selected papers were also scanned and evaluated for relevance.

Dog, spinal trauma, new treatment strategies

Spinal cord injury (SCI), or traumatic myelopathy (TM) is an unexpected, catastrophic event, as its consequences often persist for the rest of the patient's life. In dogs it usually occurs abruptly due to an intervertebral disc extrusion, traffic accident, penetrating wound, fall, animal-animal or human-animal interaction (Brison 2010; Ahuja et al. 2017). Lesion of the spinal cord (SC) tissue results in a neurological deficit characterized by impaired motor, sensory, and autonomic functions caudally from the site of injury (Lorenz et al. 2011). The exact incidence of SCIs in domestic animals is unknown, though severe SC damage in dogs, cats, pigs and primates causes death or permanent disability, for which only limited therapeutic measures are available, currently. They include the administration of methylprednisolone sodium succinate (MPSS), early spinal cord decompression, reposition and stabilisation of fractured or luxated vertebrae, and physiotherapy (Nardone et al. 2017; Musselman et al. 2018). Due to unfavourable prognosis and permanent suffering of the severely affected animal, many owners consider euthanasia as a rational option for their pet. Over the last two decades, numerous experimental studies have revealed various therapeutic measures capable of modulating the pathophysiological processes that cause cell death and development of an irreversible SC lesion characteristic for the subacute and chronic phases of TM, as well as of supporting axonal regeneration, especially in rodents. The contemporary effort to translate the promising results of laboratory research into human and veterinary practice inspired the authors to review the current literature dealing with SCI.

Address for correspondence:
MVDr. Igor Šulla, PhD
University of Veterinary Medicine and Pharmacy,
Department of Anatomy, Histology and Physiology
Komenského 73, 041 81 Košice, Slovakia

Phone: +421 903 764 161
E-mail: igor.sulla@uvlf.sk
http://actavet.vfu.cz/

Clinical presentation

Neurological deficit depends on the location, size and development of the SC lesion (Lorenz et al. 2011; Hachem et al. 2017). Clinical symptomatology of TM given by the arrangement of motor and sensitive tracts and spinal cord vessels includes tetra- or paraparesis/tetra- or paraplegia, urinary and faecal incontinence and sexual incompetence (Lorenz et al. 2011; Al Taweel and Sayam 2015). In the event of a partial medullary damage, one of the syndromes of incomplete SCI may develop, such as spinal hemisection syndrome, central SC syndrome, ventral SC syndrome, dorsal SC syndrome, or conus medullaris syndrome (Lorenz et al. 2011).

Management of dogs with spinal trauma

An initial assessment aimed at identification of life-threatening injuries affecting principal arteries, lungs, liver, spleen, kidneys, and long bones is very important (Hachem et al. 2017). A first-line care involves the support of breathing and circulation, followed by an appropriate immobilisation of the vertebral column with the aim to limit further damage of the SC while transporting the patient (Yue et al. 2017). Many animals after SCI present with pulmonary dysfunction, cardiovascular instability, and hypotension/hypovolaemic shock due to the vasodilation of visceral arteries or blood loss. Hypovolaemia and hypoxaemia contribute to secondary spinal cord damage, so rapid correction of SC perfusion, and maintaining oxygenation via hemodynamic support helps to prevent further neurologic deterioration (Yue et al. 2017). In dogs with a mean arterial blood pressure < 90 mmHg, an aggressive fluid resuscitation is needed (Fehlings et al. 2017). Administration of synthetic colloids (e.g. Dextran-70 10–20 ml/kg for 15–20 min, or 4–5 ml/kg of hypertonic saline for 15–20 min) is indicated in the event of hypovolaemia. Dehydrated dogs should receive isotonic crystalloids (e.g. lactated Ringer's solution or 0.9% saline). In animals unresponsive to fluid therapy, vasopressors (e. g. dopamine 5–12 μg/kg/min. or epinephrine infusion 1–10 μg/kg/min.) can boost circulation (Fehlings et al. 2017). Dogs that are able to breathe should be administered supplemental O_2 via nasal catheters. In those with airway obstruction or SCI causing hypoventilation, intratracheal intubation and mechanical ventilation is indicated (Fehlings et al. 2017). Another issue accompanying SCI is a hypotonic bladder with urine retention, causing its distension and serious detrusor damage (Al Taweel and Seyam 2015). So the evacuation of urinary bladder by an indwelling catheter or the Credé maneuvre belongs to the initial therapeutic measures in an acute SCI. Following estimation of diagnosis of the TM, including the location of SCI along with its cause, a decision should be done regarding the type of treatment (Hachem et al. 2017). Generally, it depends on the personal preferences of the veterinarian and the choice of the owner. Vertebral fractures may be treated by a strict rest for 2–6 weeks and/or immobilization using external braces, administration of analgesics, antiinflammatory drugs, and physical therapy (Readdy et al. 2015; Rouanet et al. 2017). However, an early decompression of SC is associated with a more favourable outcome (Saghazadeh and Rezali 2017). An aggressive surgical approach (laminectomy, decompressive duraplasty, reposition of fragments, internal stabilisation of the vertebral column) is indicated in dogs that have preserved at least minimal voluntary motor functions, have unstable vertebral fractures/luxations, magnetic resonance imaging evidence of TM, or progressing neurologic deficit despite a correct conservative therapy (Fehlings et al. 2017).

Pharmacological interventions

Experimental studies and multicentre clinical trials brought positive results after high doses of synthetic corticosteroid MPSS were administered within 8 h following SCI (Bracken 2012). The MPSS mitigates SC swelling, glutamate release, and free-radical accumulation, upregulates antiinflammatory factors, decreases oxidative stress, and induces

neuroprotection (Fehlings et al. 2017). According to the Cochrane review and AOSpine guidelines, the MPSS treatment should be started by a 30 mg/kg bolus as soon as possible (< 8 h after trauma) and continued by 5.4 mg/kg/h for 24 h (Bracken 2012; Fehlings et al. 2017). Still, the systemic MPSS administration can cause serious complications, such as gastric bleeding, development of gastroduodenal ulcers, wound infection or sepsis (Chikuda et al. 2014). A benefit of local delivery of MPSS (e. g. by help of nano-particles) is therefore investigated currently (Kumar et al. 2017).

Rehabilitation (RHB)

Massages, passive motions, and different types of stimulation have positive effects on muscles, contribute to the recovery of motor functions, reduce osteoporosis, improve endurance, as well as cellular, biochemical, and cardiovascular functions (Hachem et al. 2017). Exercise, eventually refilled with additional support of pelvic limbs, elevates the expression of neurotrophic factors, such as neurotrophin-3, nerve growth factor, and insulin-like growth factor (Musselman et al. 2018). In the early phase of SCI, rehabilitation should focus mainly on the prevention of pressure sores, bronchopneumonia, thromboembolism, and catabolism (Shah et al. 2013). Later on, it should concentrate on restoration of functions. Methodical exercise which increases production of the brain-derived neurotrophic factor (BDNF) and cyclic adenosine monophosphate (cAMP), and supports the spinal cord plasticity is considered a particularly appropriate remedy in the subacute stage of TM (Fehlings et al. 2017). Currently, the repetitive treadmill training facilitated by robotic devices and electrical stimulation are gaining increased attention (Shah et al. 2013; Salisbury et al. 2018). The use of equipment combining a brain-computer interface with functional electrical stimulation of peripheral nerves is currently being introduced into human clinical practice (Salisbury et al. 2018). However, so far the machinery is much too complicated, sizeable, and expensive for routine animal use.

Although rehabilitation in canine TM is usually beneficial, the possible negative consequences also should be kept in mind. For example, an active RHB program initiated early after thoracic SCI in cats was not only less efficient than the same type of therapy started two weeks later, but it was accompanied by a significantly increased extravasation in and around the epicentre of injury (Shah et al. 2013). The critical complication roused by training and occurring in patients with TM located cranially from the mid-thoracic level, is autonomic dysreflexia – an episodic, life-threatening hypertonic condition triggered by a spinally-mediated reflex activation of sympathetic vasoconstrictor neurons supplying skeletal muscles and visceral organs (Eldahan and Rabchevsky 2018). Another harmful effect of training is the interaction between recovery in a trained function, which can have a detrimental influence on an untrained task. For example, cats with a complete SC transection trained to walk on a treadmill had difficulties in standing, and cats trained to stand performed worse in walking than untrained ones (Shah et al. 2013).

SCI complications

Neurogenic bladder

An initial bladder flaccidity may be followed by development of a permanent flaccid bladder, or a spastic bladder with reduced capacity; eventually the bladder functions may improve after several days, weeks or month (Al Taweel and Seyam 2015). In the acute stage of SCI when the leading problem is the hypotonic (flaccid and distended) bladder due to a detrusor paralysis, evacuation of urine by help of a permanent catheter or the Credé maneuver is necessary (McMurray et al. 2006). The regular monitoring of urine for infection and prompt antibacterial treatment (if required) is essential (Al Taweel and Seyam 2015). In the chronic stage of TM, two types of neurogenic bladder problems might occur – the upper motor neuron (UMN) and the lower motor neuron (LMN) dysfunction

(Lorenz et al. 2011; Al Taweel and Seyam 2015). The UMN bladder dysfunction in dogs is caused by suprasacral spinal cord lesions, i.e. TM above the S1 spinal cord segment. The main issue in this type of dysfunction is interference between the detrusor reflex and hyperactivity of the urethral musculature (detrusor-sphincter dyssynergia). The bladder fills with urine, its capacity may be normal or smaller, involuntary contractions occur, but sphincter spasm during voiding may prevent the complete emptying of the bladder. When palpated, the bladder is turgid and it is difficult to express the urine manually. The consequences of a UMN bladder are the vesico-urethral reflux, recurrent urinary tract infections, urolithiasis, and in severe cases, development of hydronephrosis, urosepsis, and renal failure (Al Taweel and Seyam 2015). Administration of anticholinergic drugs (e. g. oxybutyrin) blocks the cholinergic transmission at muscarine receptors, ameliorates detrusor hyperreactivity, increases bladder capacity, improves its compliance and reduces intravesical pressure (Al Taweel and Seyam 2015). Intrasphincteric injection of botulinum toxin may also ameliorate hyperreactivity of sphincteric mechanism (Mahfouz and Corcos 2011). Sphincterotomy (in males), converting the bladder into an open system, or S2-S4 rhizotomy, converting the spastic bladder to flaccid one, are indicated when other therapeutic measures fail (Al Taweel and Seyam 2015). The LMN bladder dysfunction accompanies lesions of the sacral micturition centre (S2–S4 SC segments) or nerves of the lumbosacral plexus, resulting in parasympathetic decentralization of the bladder and denervation of the sphincter (McMurray et al. 2006). The situation is characterized by a decreased tone of both the detrusor and urethral musculature, large volume of urine, low intravesical pressure and absent contractions of detrusor. The animal constantly dribbles urine due to decreased or absent perineal reflexes and perianogenital hypesthesia/anaesthesia accompanying the condition. The application of the Credé maneuver 4 times/day helps to solve the problem (McMurray et al. 2006; Al Taweel and Seyam 2015).

Neurogenic colon

Defecation is affected similarly as urination and it can be a serious problem in dogs with TM. The situation is further aggravated by the inability of the animal to maintain a posture, move tail, increase intraabdominal pressure, activate the rectal and urogenital diaphragm, and synchronize the propulsion force with relaxation of the internal anal sphincter (Lorenz et al. 2011; Hughes 2014). The dogs with LMN lesions have areflexic bowel accompanied with relaxed external anal sphincter (EAS), while the internal anal sphincter (IAS) can remain tight. Then the situation results in stagnation of faeces in the colon. On the other hand, the musculature of colon and rectum can be permanently relaxed, unable to move stools in the aboral direction (Hughes 2014). In animals with areflexic bowel, faeces must be removed manually. The insertion of a gloved and lubricated finger into the anal canal and its circular movements stimulate rectum, provoke contractions of the descending colon, improve the aboral movement of stools and enhance internal sphincter relaxation. Digital removal of faeces should be repeated until there is no more palpable stool and the therapist can feel the tightening of the internal anal sphincter (Huges 2014). Dogs with a clinically complete UMN lesion suffer from impaired peristalsis, spastic external anal sphincter, and defective rectal sensation. This type of problem occurs in animals with TM cranially from the medullary cone (Hughes 2014). The best method to initiate defecation in this type of lesion is the application of a suppository, or 125–500 ml warm water enema, which helps to initiate the conus medullaris reflex peristalsis by rectal mucosal stimulation, and a subsequent manual removal of impacted faeces (Hughes 2014).

Pressure ulcers

Dogs with severe paresis or plegia, impaired autonomic innervation, and sensory perception are particularly predisposed to suffer from pressure sores. The primary cause of

decubitus development is the action of pressure resulting in ischaemia-reperfusion damage and subsequent necrosis of tissues situated over bone prominences (Kruger et al. 2013). The bed sores jeopardize all patients following SCI. They occur more often in larger and heavier dogs, especially when they lie on hard or rough surfaces, are immunocompromised, malnourished, or anaemic. The decubitus usually appears in the area of the greater trochanter, the lateral plane of the stiffle joint, the lateral side of the calcanear area, the lateral side of the proximal tarso-metatarsal or metatarso-phalangeal joints or the lateral surface of the elbow joint (Mizokami et al. 2013). Pressure ulcers can be life-threatening as a potential source of serious infection and sepsis. The progression of pressure ulcers can be roughly divided into four stages. Stage 1 is characterized by a hairless, wrinkled, reddish skin area. In stage 2, the lesion forms a shallow ulcer in the skin. The pressure sore of stage 3 expands into the subcutaneous tissue and looks like a shallow crater. Stage 4 decubitus is an extensive, deep necrosis penetrating into the muscles, tendons, bones or joints and is the most serious lesion (Mizokami et al. 2013). Reduction of pressure and exclusion of supportive factors, i. e. shear forces, friction, and/or moisture help to prevent the development of decubital necroses in non-ambulatory dogs (Quaseem et al. 2015). The animal should lie on a dry, soft, thick, well-padded mat and be turned every 2 h. The skin should be cleaned to prevent urine scalding and faecal soiling (Kruger et al. 2013). The sores of stage 1 and 2 positively react to relief of pressure, debridement of necrotic tissues, control of bacterial colonization (by application of disinfectants, administration of antibiotics), sterile bandage, and nutrition supplementation. Ulcers of stage 3 demand surgical excision and tissue reconstruction. In dogs with stage 4 pressure sores, euthanasia is indicated. Generally, the decision upon the therapy of decubital ulcers depends on the attitude of animal's owner (Kruger et al. 2013).

Pain and spasticity

Two thirds of humans after SCI complain of pain; about a third of them perceive their pain as severe (Lui et al. 2015). It is therefore reasonable to assume the same in dogs (Lorenz et al. 2011). Pain can be experienced at the level of the injury, but it can be located in the area of hypaesthesia or anaesthesia (Rouanet et al. 2017). It is supposed that at-level pain results from damage to the SC tissue one or more segments cranially to the epicentre, whereas pain caudally from the lesion is caused by the interruption of axons, the formation of abnormal connections within the SC or functional changes in neurons making them hypersensitive (Lewis and Olby 2017). In the acute stage of SCI, pain is managed with non steroidal anti-inflammatory drugs (NSAID), opioid analgesics or tramadol. It is well known that NSAIDs, especially ketoprofen, can cause gastroduodenal bleeding, development of gastroduodenal ulcers, arterial hypertension, hepatic and/or renal complications. Therefore, drugs with less serious side effects (diclofenac, ibuprofen), are currently preferred (Rouanet et al. 2017). Hyperalgesia in a chronic TM period can be reduced by laser or pulsed radiofrequency stimulation (Chang and Cho 2017; Zielinska et al. 2017). Application of the continuous radiofrequency stimulation (CRFS) to spinal ganglia is less frequently used, as it can induce a permanent lesion of nerve fibres enhancing motor deficit, sometimes leading to dysesthesia or neuralgia (Chang and Cho 2017). Long-term experience shows that 60–80% of humans and animals after SCI suffer from spasticity. It is characterized by hyperreflexia, clonus, paroxysms of muscle contractions, or spasms and cramps. This involuntary motor activity leads to the potentiation of contractures, causing reduction of joint motion and development of deformities (Lewis and Olby 2017). Recent studies show that the principal cause of spasticity is a lesion of descending tracts resulting in the decreased activity of inhibitory interneurons, leading to excessive reactions of motoneurons to excitatory stimuli (Lewis and Olby 2017). In the management of spasticity, administration of baclofen, diazepam or dantrolene,

chemodenervation by botulinum toxin, and laser or pulsed radiofrequency therapy deliver positive results (McIntyre et al. 2014; Lui et al. 2015; Chang and Cho 2017; Zielinska et al. 2017). In spasticity resistant to conservative treatment, the interruption of reflex pathways by selective dorsal rhizotomy or myelotomy is recommended (Enslin and Fieggen 2016).

Sexual incompetence

In dogs with partial spinal cord lesions, sexual functions may be preserved, but tetra- or paraplegia precludes copulatory activities. Severe SCI also disrupts reflexes required for erection in males, vasocongestion of clitoris, vaginal wall, and lubrication of its surface in females. Even if the sympathetically mediated arousal is intact, male dogs suffer from anejaculation or retrograde ejaculation, and decreased vitality of sperm. It is proposed that sperm quality and motility is negatively affected by recurrent urinary infections, prostatic secret stagnation, and testicular denervation (McMurray et al. 2006). While male dogs with severe spinal cord lesions lose their breeding value, equally affected female dogs are capable of conception and delivery of healthy puppies (McMurray et al. 2006).

Neuroprotective and reparative strategies

There are many important differences between the arrangement and function of SC in rodents, non-primate animals and humans. The translation of new therapeutic strategies from laboratories to human and veterinary clinical practice is therefore complicated and results are often frustrating. On the other hand, the principal structure and function of CNS in dogs, cats, pigs, apes, and humans are alike, SCIs occur naturally in these species, regeneration of their neurons is equally limited, symptomatology and outcomes are similar. Hence many scientists consider the use of feline, canine or porcine SCI models as an intermediate between rodent laboratory studies and human clinical trials. Multiple experiments performed with the aim to restore or significantly improve neurological functions after TM, brought at least partially positive results when processes involved in the secondary SCI cascade were modified by hypothermia, administration of neuroprotective drugs (e. g. glyburide, riluzole, cethrin, minocycline, melatonin, statins, curcumin), regeneration enhanced by anti-nogo therapy, and stem/precursor cells transplantation (Yu and He 2015).

Therapeutic hypothermia

Experimental studies as well as clinical experience show that hypothermia can improve the neurological outcome in patients following traumatic and ischaemic brain or SC lesions (Martyrosian et al. 2017). The reduction of body temperature divides hypothermia into profound (< 30 °C), moderate (30–32 °C), modest (32–34 °C) and mild (35 °C) (Wang and Pearse 2015). Hypothermia inhibits cellular metabolism by 5–8% per 1 °C, retards basic enzymatic activity, reduces oxygen consumption, and energy demand (Wang and Pearse 2015). Hypothermia increases adenosine triphosphate (ATP) stores, helps to maintain the normal transmembrane ion and neurotransmitter gradients, preserve the BSCB (blood-spinal cord barrier), ameliorate the local oedema, suppress axonal swelling and development of gliosis, reduce oxidative stress, inflammation, and mitochondrial membrane permeabilization which is the point-of-no-return in apoptosis (Alkabie and Boileau 2016). Interesting results of experimental studies in minipigs showed that local SC cooling by 4 °C solutions administered by a peristaltic pump to the perfusion chamber placed through laminectomy at the epicentre of spinal trauma, starting 30 min after injury and maintained for 5 h, is safe, allows to maintain stable body temperature, does not create adverse reactions, does not need a special rewarming protocol, and improves both, clinical outcome and histopathological features of SC samples (Gedrova et al. 2018). However, the

decelerated function of enzymes can slow the metabolism of medicaments. The decrease of body temperature increases blood viscosity (2% per 1°C), even mild hypothermia (32–34 °C) can cause shivering (causing an excessive oxygen consumption), induce insulin resistance, and suppress leukocyte and phagocyte chemotaxis. It also impairs immune functions and supports the development of life-threatening infection complications in spite of the prophylactic antibiotic administration (Kim et al. 2016). Due to its negative side effects and equivocally positive results, the clinical use of systemic hypothermia in patients with TM is controversial (Alkabie and Boileau 2016). Obviously, systemic hypothermia is a too complex procedure for veterinary practice. On the other hand, local hypothermia applied during a surgical decompression of the SC, and (if appropriate) stabilisation of the vertebral column (eventually supplemented with local administration of MPSS), seems to be a promising therapeutic modality in dogs with TM.

Glyburide

Glyburide (glibenclamide) is an antidiabetic drug which is able to reduce tissue damage, and ameliorate neurological deficit (Jeffery et al. 2018). The mode of its action is via the blockade of S_{UR1}-T_{RMP4} channels, playing an important role in the development of cytotoxic oedema, cell death, blood-brain barrier breakdown, traumatic capillary fragmentation and lesion expansion. Glyburide is also able to trigger an early scavenger activity of microglia, support the removal of dead cells and myelin fragments, block the K_{ATP} channels that are overexpressed in activated microglia, thus alleviating the consequences of TM (Mehta et al. 2015). The data obtained in a group of dogs with acute SCIs confirmed the safety and efficacy of oral glyburide administration. The optimal serum concentrations of the drug were 25–50 ng/ml. These figures were achieved when the treatment started with an initial dose of 150 µg/kg, followed by oral administration of 75 µg/kg of glyburide at 8-h intervals. No negative side-effects were detected in any participating animal (Jeffery et al. 2018).

Riluzole

Riluzole (6-trifluoromethoxy-2-benzothiazolamine) is an anticonvulsant drug with neuroprotective, anti-depressant and anxiolytic effects, and is a Food and Drug Administration (FDA) approved medication for amyotrophic lateral sclerosis (ALS) (Duble 1996). The side-effects observed in humans included blurred vision, sensation of difficult breathing, dizziness, gastrointestinal discomfort. However, they had no significant consequences, and vanished following the termination of therapy (Duble 1996). Several studies showed that riluzole can improve the neurological deficit in patients following SCI (Meshkini et al. 2018). Riluzole modulates glutamate neurotransmission by decreasing glutamate release and postsynaptic glutamate receptor signalling, inhibiting permeability of voltage-gated Na^{+} and Ca^{++} channels, and suppressing astrocytosis. The administration of 8 mg/kg riluzole 1–3 h after SCI, followed by administration of 6 mg/kg every 12 h for 7 d in a rodent cervical SCI model led to functional, histological, and molecular benefits (Wu et al. 2013). Extrapolating from the development of secondary SC injury mechanisms in rats, the authors estimated a therapeutic time window for riluzole in humans to be approximately 12 h (Wu et al. 2013). They initiated oral riluzole treatment in 36 humans (28 with cervical and 8 with thoracic TMs), members of the phase I clinical trial study group, by a dose of 50 mg of the drug within 12 h post injury, and continued by administration of 50 mg every 12 h for 14 d. The total dose of 1400 mg of riluzole did not cause serious complications but increased hepatic enzyme and bilirubin levels, quickly returning them to normal without detrimental after effects. The results showed a significant improvement of motor scores in patients with cervical TM (Grossman et al. 2014).

Cethrin

Cethrin, a recombinant Rho GTP-ase protein antagonist BA-210 with dura mater and cell membrane penetrance, blocks the activation of RhoA (a member of Rho family) and supports axonal growth. The BA-210 is an FDA approved medicament for treatment of patients with SCIs. A I/IIa clinical trial in humans with cervical (n = 32) and thoracic (n = 16) TMs showed that an epidural application of 0.3, 1.0, 3.0, and 9.0 mg of Ba-210 to the epicentre of injury through laminectomy was a simple task. More favourable results following administration of 3.0 mg of cethrin at a single dose were observed in patients with cervical SCIs (Fehlings et al. 2011). The promising results of the study can also expand the therapeutic armamentarium in veterinary practice. Additional clinical trials aimed to prove the efficacy of cethrin in patients with TM are currently in progress.

Minocycline

Minocycline, a second-generation semisynthetic tetracycline analogue, is a highly lipophilic drug with antibiotic properties. For about 30 years, it has been successfully used to treat bacterial infections (Garrido-Mesa et al. 2013). However, experimental models of ischaemia, traumatic brain injury, neuropathic pain, Parkinson's disease, Huntington's disease, ALS, Alzheimer's disease, multiple sclerosis and SCI also confirmed its neuroprotective effects (Garrido-Mesa et al. 2013). Minocycline crosses the brain-spinal cord barrier, inhibits microglial and immune cell activation and proliferation, improves the integrity and viability of membranes, attenuates inflammation, reduces neuronal and glial apoptosis through suppression of pro-nerve growth factor (proNGF) synthesis in microglia, and inhibition of caspase-1, caspase-3 (Garrido-Mesa et al. 2013). Minocycline can be administered orally (100 mg capsule every 12 h), intravenously (initial dose of 90 mg/kg followed by 45 mg/kg every 12 h for 5 d), or locally (Teng et al. 2004). Side effects (e. g. nausea and vomiting, diarrhoea, yellow tint of the skin, sclerae, dark urine, blurry vision, headache, ringing in ears), dissolve after termination of treatment (Garrido-Mesa et al. 2013).

Melatonin

Hormone melatonin (5-methoxy-N-acetyltryptamine) is primarily secreted by the pineal gland during the dark phase of the circadian cycle, preparing the body for sleep, regulating sleep-wake timing, blood pressure fluctuations, and seasonal reproduction in animals. Melatonin, an FDA approved remedy for insomnia, also has antioxidant, antiinflammatory, antiapoptotic, and neuroprotective effects, mediated by activation of the Wnt/β-catenin signalling pathway (Aydemir et al. 2016). Administration of 2–8 mg/kg/d improved the outcome in humans with cervical TM without the appearance of negative side effects, dependance or withdrawal symptoms after termination of the treatment (Zhang et al. 2018).

Statins

Atorvastatin, lovastatin, pravastatin, and simvastatin, drugs competitively inhibiting HMG-CoA (3-hydroxymethylglutaryl-coenzyme A) reductase, are widely used in the treatment of dyslipidaemias and prevention of atherosclerotic cardiovascular complications. They are also able to support neuronal survival and improve functional recovery after SCI (Bimbova et al. 2018). The positive influence of statins on neuronal survival and restriction of TM size is mediated by activation of the Wtn/β-catenin signalling pathway, reduction of levels of inflammatory factors (such as TNF-α, and IL-1β), infiltration of SC by destructive M_1 macrophages, restriction of endothelial nitric oxide, and by inhibition of caspase-3 and caspase-9 cleavage in SC neurons, astrocytes, and oligodendrocytes (Bimbova et al. 2018). Although a long-term statin therapy can cause myopathy which may progress to

rhabdomyolysis, new-onset type-2 diabetes mellitus and, probably, haemorragic stroke, the less serious adverse effects of statin therapy generally resolve rapidly when administration is terminated (Peto and Collins 2018).

Curcumin

Curcumin (diferuloylmethane) is the main bioactive component of turmeric (*Curcuma longa* L.), an evergreen plant cultivated extensively in India and China and widely used in gastronomy and traditional medicine. Oral administration of the drug to rats with TM inhibited the expression of proinflammatory cytokines, reduced production of the glial fibrillary acidic protein, suppressed the reactive gliosis, and improved the microenvironment for nerve growth without imposing any negative side-effects (Verma et al. 2018).

Anti-Nogo-A therapy

The neurite outgrowth inhibitor A (Nogo-A), one of the most potent myelin-associated outgrowth inhibitors, contributes to a non-permissive environment in the CNS (Cafferty et al. 2010). It is expressed on the surface of adult oligodendrocytes and is responsible for the inhibition of axonal sprouting. Positive results achieved in rat SCI studies following administration of a monoclonal Nogo-A antibody (ATI-355) inspired Kucher et al. (2018) to conduct a human clinical trial in 52 humans with paraplegia or tetraplegia. The intrathecal administration of ATI-355 at a dose of 5–32 mg/ml/day for 28 d in a continual 24-h infusion was well tolerated, and the therapy significantly improved the functional outcome in all members of the study group (Kucher et al. 2018).

Stem/precursor cell

Stem/precursor cell (SC/PCs) transplantation as a treatment modality for tissue damage was inspired by the fact that embryonic stem cells (ESCs) arising from a fertilized egg have the potential to produce any specialized cell type and develop into a whole organism. Stem cells which normally occur in adult tissues maintain their viability during the whole life span by replacement of dead cells (Schroff 2016). However, a destruction of the blastocyst is necessary to obtain ESCs. Since the utilisation of ESCs is controversial (even prohibited in several countries), and results of replacement therapy in patients with TM have not met the expectations, the interest of neuroscientists concentrated on the use of mesenchymal stromal cells (MSCs), present in the non-blood producing fraction of the bone marrow, in fat or skin. Multiple experiments have shown that bone marrow-derived mesenchymal stromal cells (BMSCs), have the capacity to expand, transdifferentiate to multipotent progenitors, replace damaged cells, produce growth factors and trophic mediators. The acquisition and expansion of BMSCs does not cause ethical or legal problems, and their transplantation had a positive effect on the locomotor recovery in rats following SCI (Oliveri et al. 2014). Laboratory studies also showed that implantation of biomaterial scaffolds supplied by stem cells was able to improve the ability of SC to bridge post-injury cavities, and protect transplanted cells from a hostile post-SCI environment (Liu et al. 2018). The positive results achieved in various models of SCI following the application of this method are encouraging, however, further scrutiny is necessary before its introduction into the health care practice.

In conclusion, it is important to stress that trauma triggers TM by different mechanisms. No one treatment strategy is able to provide protection against all harmful events accounting for the development of neurological deficit in SCI patients. Simultaneous and sequential use of several therapeutic measures can improve the situation.

Acknowledgements

The accumulation and study of literature dealing with different aspects of spinal cord injury treatment as well as preparation of the presented paper was supported by the grant of the Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic for the Structural Funds of EU, ITMS 26220220202 and VEGA grant No 1/0898/15.

References

Ahuja CS, Nori S, Tetreault L, Wilson J, Kwon B, Harrop J, Choi D, Fehlings MG 2017: Traumatic spinal cord injury - repair and regeneration. Neurosurgery **80**: S9-S22

Alkabie S, Boileau AJ 2016: The role of therapeutic hypothermia after traumatic spinal cord injury – a systematic review. World Neurosurg **85**: 432-449

Al Taweel W, Seyam R 2015: Neurogenic bladder in spinal cord injury patients. Res Rep Urol **7**: 85-99

Aydemir S, Dogan D, Kocak A, Dilsiz N 2016: The effect of melatonin on spinal cord after ischemia in rats. Spinal Cord **54**: 360-363

Bimbova K, Bacova M, Kisucka A, Pavel J, Galik J, Zavacky P, Marsala M, Stropkovska A, Fedorova J, Papcunova S, Jachova J, Lukacova N 2018: A single dose of atorvastatin applied acutely after spinal cord injury supresses inflammation, apoptosis, and promotes axon outgrowth, which might be essential for favorable functional outcome. Int J Molec Sci **19**: 1106

Bracken MB 2012: Steroids for acute spinal cord injury. Cochrane Database Syst Rev **18**: 1: CD001046

Brisson BA 2010: Intervertebral disc disease in dogs. Vet Clin North Am Small Anim Pract **40**: 829-858

Cafferty WB, Duffy P, Huebner F, Strittmatter SM 2010: MAG and Omgp synergize with Nogo-A to restrict axonal growth and neurological recovery after spinal cord trauma. J Neurosci **30**: 6825-6837

Chang MC, Cho YW 2017: Effects of pulsed radiofrequency on spasticity in patients with spinal cord injury: a report of two cases. Neural Reg Res **12**: 977-980

Chikuda H, Yasunaga H, Takeshita K, Horiguchi H, Kawaguchi H, Ohe K, Fushimi K, Tanaka S 2014: Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: a propensity-matched analysis using a nationwide administrative database. Emerg Med J **31**: 201-206

Duble A 1996: The pharmacology and mechanism of action of rizulole. Neurology **47**: S233-S241

Eldahan KC, Rabchevsky A 2018: Autonomic dysreflexia after spinal cord injury: systemic pathophysiology and methods of management. Auton Neurosci **209**: 59-70

Enslin JMN, Fieggen AG 2016: Surgical management of spasticity. S Afr Med J **106**: 753-756

Fehlings MG, Theodore N, Harrop J, Maurais G, Kuntz C, Shaffrey CI, Kwon BK, Chapman J, Yee A, Tighe A, McKerracher L 2011: A phase I/IIa clinical trial of recombinant Rho protein antagonist in acute spinal cord injury. J Neurotrauma **28**: 787-796

Fehlings MG, Tetreault LA, Wilson JR, Kwon BK, Burns AS, Martin AR 2017: A clinical practice guideline for the management of acute spinal cord injury: Introduction, rationale, and scope. Global Spine J **7**: 845-945

Garrido-Mesa N, Zarzuelo A, Gálvez J 2013: Minocycline: far beyond an antibiotic. Br J Pharmacol **169**: 337-352

Gedrova S, Galik J, Marsala M, Zavodska M, Pavel J, Sulla I, Gajdos M, Lukac I, Kafka J, Ledecky V, Sulla jr I, Karasova M, Reichel P, Trbolova A, Capik I, Lukacova V, Bimbova K, Bacova M, Stropkovska A, Lukacova N 2018: Neuroprotective effect of local hypothermia in a computer-controlled compression model in minipig: Correlation of tissue sparing along the rostro-caudal axis with neurological outcome. Exp Ther Med **15**: 254-270

Grossman RG, Fehlings MG, Frankowski RF, Burau KD, Chow DS, Tator C, Teng A, Toups EG, Harrop JS, Aarabi B, Shaffrey CI, Johnson MM, Harkema SJ, Boakye M, Guest JD, Wilson JR 2014: A prospective, multicenter, phase I matched-comparison group trial of safety, pharomacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. J Neurotrauma **31**: 239-255

Hachem LD, Ahuja CS, Fehlings MG 2017: Assessment and management of acute spinal cord injury: from point of injury to rehabilitation. J Spinal Cord Med **40**: 665-675

Hughes M 2014: Bowel management in spinal cord injury patients. Clin Colon Rectal Surg **27**: 113-115

Jeffery N, Boudreau CE, Konarik M, Mays T, Fajt V 2018: Pharmacokinetics and safety of oral glyburide in dogs with acute spinal cord injury. PeerJ **6**: e4387

Kim SJ, Lee JK, Kim DK, Shin JH, Hong KJ, Heo EY 2016: Effect of antibiotic prophylaxis on early-onset pneumonia in cardiac arrest patients treated with therapeutic hypothermia. Korean J Crit Care Med **31**: 17-24

Kruger EA, Pires M, Ngann Y, Sterling M, Rubay S 2013: Comprehensive management of pressure ulcers in spinal cord injury: current concepts and future trends. J Spin Cord Med **36**: 572-585

Kucher K, Johns D, Meier D.Abel R, Badke A, Baron H, Thietje R, Casha S, Meindl R, Gomez-Mancilla B, Phister C, Rupp R, Weidner N, Mir A, Schwab ME, Curt A 2018: First-in-man intrathecal application of neurite growth-promoting anti-Nogo-A antibodies in acute spinal cord injury. Neurorehabil Neural Repair **32**: 578-589

Kumar B, Jalodia K, Kumar P, Gautam HK 2017: Recent advances in nanoparticle mediated drug delivery. J Drug Delivery Sci Technol **41**: 260-268

Lewis MJ, Olby NJ 2017: Development of a clinical spasticity scale for evaluation of dogs with chronic thoracolumbar spinal cord injury. Am J Vet Res **78**: 854-861

Liu S, Schackel T, Weidner N, Puttagunta R 2018: Biomaterial-supported cell transplantation treatments for spinal cord injury: challenges and perspectives. Front Cell Neurosci **11**: 430

Lorenz MD, Coates JR, Kent M 2011: Handbook of Veterinary Neurology. WB Saunders, St. Louis, 545 p.
Lui J, Sarai M, Mills PB 2015: Chemodenervation for treatment of limb spasticity following spinal cord injury: a systematic review. Spinal Cord **53**: 252-264
Mahfouz W, Corcos J 2011: Management of detrusor external sphincter dyssynergia in neurogenic bladder. Eur J Phys Rehabil Med **47**: 639-650
Martyrosian NL, Patel AA, Carotenuto A, Kalani MY, Bohl MA, Preul MC, Theodore N 2017: The role of therapeutic hypothermia in the management of acute spinal cord injury. Clin Neurol Neurosurg **154**: 79-88
McIntyre A, Mays R, Mehta S, Jawcen S, Towson A, Hsieh J, Wolfe D, Teasell R 2014: Examinig the effectiveness of intrathecal baclofen on spasticity in individuals with chronic spinal cord injury: a systematic review. J Spinal Cord Med **37**: 11-18
McMurray G, Casey JH, Naylor AM 2006: Animal models in urological disease and sexual dysfunction. Br J Pharm **147**: S52-S79
Mehta RI, Totsun C, Ivanova S, Tsymbalyuk N, Famakin BM, Kwon MS, Castellani RJ, Gerzanich V, Simard JM 2015: Sur1-Trmp4 cation channel expression in human cerebral infarcts. J Neuropathol Exp Neurol **74**: 835-849
Meshkini A, Salehpour F, Aghazadeh J, Mirzali F, Alavi SAN 2018: Riluzole can improve sensory and motor function in patients with acute spinal cord injury. Asian J Neurosurgery **13**: 656-659
Mizokami F, Furuta K, Utani A, Isogai Z 2013: Definition of the physical properties of pressure ulcers and characterisation of their regional variance. Int Wound J **10**: 606-611
Musselman KE, Shah M, Zariffa J 2018: Rehabilitation techniques and interventions for individuals with spinal cord injury: transitional potential of current trends. J NeuroEng Rehab **15**: 40
Nardone R, Florea C, Höller Y, Brigo F, Versace V, Lochner P, Golaszewski S, Trinka E, 2017: Rodent, large animal and non-human primate models of spinal cord injury. Zoology (Jena) **123**: 101-114
Oliveri RS, Bello S, Biering-Sorensen F 2014: Mesenchymal stem cells improve locomotor recovery in traumatic spinal cord injury: systematic review with meta-analyses of rat models. Neurobiol Dis **62**: 338-353
Peto R, Collins R 2018: Trust the blinded randomized evidence that statin therapy rarely causes symptomatic side effects. Circulation **138**: 1499-1501
Qaseem A, Mir TP, Starkey M, Denberg TD 2015: Risk assessment and prevention of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med **162**: 359-369
Readdy WJ, Chan AK, Matijakovich DJ, Dhall SD 2015: A review and update on the guidelines for the acute non-operative management of cervical spinal cord injury. J Neurosurg Sci **59**: 119-128
Rouanet C, Reges D, Rocha E, Gagliardi V, Silva GS 2017: Traumatic spinal cord injury: current concepts and treatment update. Arq Neuropsiquiatr **75**: 387-393
Saghazadeh A, Rezaei N 2017: The role of timing in the treatment of spinal cord injury. Biomed Pharmacother **92**: 128-139
Salisbury DB, Parsons TD, Monden KR, Frost Z, Driven SJ 2018: Brain-computer interface for individuals after spinal cord injury. Rehab Psych **61**: 436-441
Schroff G 2016: Human embryonic stem cell therapy in chronic spinal cord injury: a retrospective study. Clin Transl Sci **9**: 168-175
Shah PK, Garcia-Alias G, Choe J, Gad P, Gerasimenko Y, Tillakarante N, Zhong H, Roy RR, Edgerton VR 2013: Use of quadruped step training to re-engage spinal interneuronal networks and improve locomotor function after spinal cord injury. Brain **136**: 3362-3377
Teng YD, Choi H, Onario RC, Zhu S, Desilets FC, Lan S, Woodard EJ, Snyder EY, Eichler ME, Friedlander RM 2004: Minocycline inhibits contusion-triggered mitochondrial cytochrome C release and mitigates functional deficits after spinal cord injury. Proc Natl Acad Sci USA **101**: 3071-3076
Verma RK, Kumari P, Maurya RK, Verma RB, Singh RK 2018: Medicinal properties of turmeric (Curcuma longa L.): a review. Int J Chem Studies **6**: 1354-1357
Wang J, Pearse DD 2015: Therapeutic hypothermia in spinal cord injury: the status of its use and open questions. Int J Mol Sci **16**: 16848-16879
Wu Y, Satkunendrajah K, Teng Y, Chow DS-L, Buttigieh J, Fehlings MG 2013: Delayed post-injury administration of Riluzole is neuroprotective in a preclinical rodent model of cervical spinal cord injury. J Neurotrauma **30**: 441-452
Yu W, He D 2015: Current trends in spinal cord injury repair. Eur Rev Med Pharmacol Sci **19**: 3340-3344
Yue JK, Winkler EA, Rick JW, Deng H, Partow CP, Upadhyayula PS, Birk HS, Chan AK, Dhall SS 2017: Update on critical care for acute spinal cord injury in the setting of polytrauma. Neurosurg Focus **43**: E19
Zhang Y, Zhang W-X, Zhang Y-J, Liu Y-D, Liu Z-J, Wu Q-C, Guan Y, Chen X-M 2018: Melatonin for the treatment of spinal cord injury. Neural Reg. Res. **13**: 1685-1692
Zielinska P, Soroko M, Zwyrzykova A, Kielbowicz Z 2017: The use of laser biostimulation in human and animal physiotherapy – a review. Acta Vet Brno **86**: 91-96