Hypothermia as a potential remedy for canine and feline acute spinal cord injury: a review

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Abstract

Severe spinal cord injury (SCI) resulting in permanent sensory-motor and autonomic dysfunction caudal to a damaged spinal cord (SC) segment is a catastrophic event in human as well as in veterinary medicine. The situation of paraplegic/tetraplegic people or animals is further impaired by serious complications and often displays an image of permanent suffering. Therapeutic hypothermia (TH) has shown neuroprotective capacity in numerous experimental and several clinical studies or case reports. Hence, the method draws increasing attention of neuroscientists as well as health care workers. While systemic TH is a too complex procedure for veterinary practice, local application of TH with a reduced risk of the whole body temperature fluctuations and minimal side effects can become one of the therapeutic tools considered in the treatment of acute traumatic SCIs in bigger animals, especially when surgical decompression of spinal medulla and vertebral column reconstruction is indicated. Still, additional large prospective randomized studies are essential for the standardization of therapeutic protocols and the introduction of the method into therapeutic armamentarium in canine and feline spinal traumatology. The research strategy involved a PubMed, MEDLINE (Ovid), EMBASE (Ovid), and ISI Web of Science search from January 2000 to July 2021 using the terms "canine and feline spinal cord injury", "hypothermia", and "targeted temperature management" in the English language literature; also references from selected studies were scanned and relevant articles included.

Dog, cat, spinal trauma, targeted temperature management

Spinal cord injuries (SCIs) occur in both humans and animals. Their incidence is not high, but the spinal cord (SC) lesion often results in permanent neurological deficit characterized by partial or complete loss of motor, sensory, and autonomic functions caudally from the site of the lesion (Bednarik et al. 2010; Lorenz et al. 2011; Spinal cord injury facts and figures 2012). The aetiology of SCI can be traumatic or ischaemic (Beattie et al. 2002). Within minutes, the initial impact is followed by a cascade of destructive processes that are similar regardless of the original cause. They persist for weeks and months and considerably increase the area of the original spinal cord (SC) damage (Olby 2010; Oyinbo 2011). The natural history of spontaneous recovery following SCI is discouraging. Currently available therapeutic interventions (limited to controversial administration of methylprednisolone, surgical decompression of neural structures, rehabilitation, and physical therapy) fail to significantly improve outcomes (Olby et al. 2003; Zielinska et al. 2017; Rouanet et al. 2017). The quality of life of tetraparetic/tetraplegic, paraparetic/paraplegic patients is further negatively affected by serious complications (Boakye et al. 2012). The SCI therefore represents a catastrophic event in human as well as in veterinary medicine (Ahuja et al. 2017; Gallucci et al. 2021). Due to the unsatisfactory prognosis and permanent suffering of paralyzed animals, the authorities, as well as the community consider euthanasia the best solution to the situation. However, an intense emotional relationship can develop between an owner and his/her pet animal. Even in a case of serious disability,

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pet owners look for various therapeutic options and often are ready to spend substantial sums of money to help their pets. Promising results of laboratory research (Hosier et al. 2015), favourable outcomes recorded in some patients with cervical traumatic SCIs following the application of therapeutic hypothermia (TH) (Hansebout and Hanseobout 2014; Cappuccino et al. 2017) and the contemporary effort to translate this remedy into a human as well as veterinary medicine (Kaneko et al. 2017; Kafka et al. 2020) inspired the authors to review the current literature dealing with therapeutic hypothermia/targeted temperature management (TH/TTM) following acute traumatic canine and feline SCIs.

Aetiology

In humans, the main cause of an acute SCI is compression, contusion, distension, laceration, and partial or complete transection of the spinal medulla (Hachem et al. 2017). The impact on the SC is usually inflicted by fractured or luxated vertebrae, foreign bodies, sequesters of extruded cervical or thoracic intervertebral discs, dorsal osteophytes and protruded spinal ligaments (Griffiths 1978; Rouanet et al. 2017). Spinal cord injury in humans usually originates in traffic accidents, falls, criminal activity, degenerative changes of the vertebral column. Less frequently, medullary lesion develops due to ischaemia-reperfusion injury during an aortic reconstruction (Salzano et al. 1994; Cheung et al. 2005; Hachem et al. 2017; Rouanet et al. 2017). The mechanisms of canine and feline medullary lesions are similar, but the most common cause of an acute SCI in dogs is spondylosis/intervertebral disc disease, followed by fibrocartilaginous embolism (FCE), and trauma; in cats, trauma dominates, followed by intervertebral disc disease, and FCE (Griffiths 1978; Olby et al. 2003; Mikszewski et al. 2006). Critical situations are traffic accidents, falls, animal-animal or human-animal interactions, marked degenerative changes of the vertebral column, intervertebral disc extrusion/herniation, and ischaemia-reperfusion caused by FCE (Olby 2010; Henke et al. 2013; DeRisio 2015; DeDecker et al. 2017).

Pathomechanism

Spinal cord injury is a complicated process divided into two phases (Olby 2010; Oyinbo 2011; Teh et al. 2017). Following a short period of ischaemia-reperfusion or mechanical trauma, spinal cord cells can become necrotic, fully or partially recover, or enter a path leading to programmed cell death (apoptosis) (Polderman 2009). The primary injury (phase) lasts for a maximum of 2 h and can result in relatively localized tissue destruction (Beattie et al. 2002; Park et al. 2004; Anwar et al. 2016; Visavadia et al. 2016; Rouanet et al. 2017; Hachem et al. 2017). Within minutes after the initial impact, a secondary injury (phase) starts, usually divided into acute (lasting 2–48 h), subacute (48–14 d), transitional (14 d–6 m), and chronic phase (> 6 m). The secondary injury processes mediated by a cascade of multiple pathologic events include haemorrhage, breakage of the microvascular bed, vasospasm, ischaemia, mitochondrial damage and dysfunction, cell membrane leakage, disruption of the blood spinal cord barrier, oedema formation, ion pump derangement, an intracellular shift of Ca^{2+} and Na^{+}, an extracellular drift of K^{+}, excessive release of neurotransmitters, free radical production (O_2, NO, H_2O_2, OH), the release of excitotoxic amino acids (especially glutamate), and prostaglandins, lipid peroxidation, influx of immune cells (neutrophils, T-lymphocytes, macrophages, monocytes), the release of cytokines, apoptosis, calpain-mediated proteolysis, and DNA damage. During the secondary injury phase, the size of the primary lesion will spread to the healthy surrounding area and cause extensive SC tissue destruction (Beattie et al. 2002; Park et al. 2004; Olby 2010; Oyinbo 2011; Anwar et al. 2016;

Teh et al. 2017). An important point is that all the above-mentioned processes are temperature dependent – they are stimulated by fever and mitigated by hypothermia (Rokkas et al. 1995; Nishi et al. 2007; Dietrich et al. 2009; Polderman 2009; Grulova et al. 2013; Karnatovskaia et al. 2014; Spetzler et al. 1988).

Therapeutic capacity of TH

Numerous experimental studies as well as clinical experiences have demonstrated the significant protective influence of TH (defined as a controlled induction of subnormal body temperature in a homeothermic organism) in cases of extensive soft tissue contusion or inflammation, hyperpyrexia, sudden cardiac arrest when the return of spontaneous circulation has been achieved but coma persists, complex cardiovascular or neurosurgical interventions, ischaemic stroke, neonatal ischaemic or hepatic encephalopathy, as well as acute traumatic brain injuries (Spetzler et al. 1988; Salzano et al. 1994; Cambria et al. 2000; Cheung et al. 2005; Casas et al. 2005; Kwon et al. 2008; Al Sibae et al. 2009; Dietrich et al. 2009; Lakhan and Pamplona 2012; Varon et al. 2012; Batchelor et al. 2013; Wei et al. 2013; Soleimanpour et al. 2014; Wassink et al. 2014; Kim et al. 2016; Brodeur et al. 2017; Martinello et al. 2017; Kafka et al. 2020). Remarkable attention of neurotraumatologists as well as the SCI community has been paid to reports describing significant improvement of complete tetraplegia or paraplegia caused by acute spinal trauma following application of TH or TH in combination with methylprednisolone administration, surgical decompression and vertebral column stabilization (Levi et al. 2010; Dididze et al. 2012; Hansebout and Hansebout 2014; Cappuccino et al. 2017). The beneficial effects of TH are executed by retardation of basic enzymatic activity, reduction of oxygen consumption and energy demands, increased adenosine triphosphate storage, maintenance of physiological transmembrane ion gradients, amelioration of the disruption of the blood spinal cord barrier, suppression of oedema formation, axonal swelling, and development of gliosis, reduction of oxidative stress, free radical generation, glutamate excitotoxicity, metalloproteinase-mediated extracellular matrix damage, inflammatory cell infiltration, delay, and suppression of the release of proinflammatory cytokines and noxious neurotransmitters, mitigation of the calpain-mediated proteolysis and mitochondrial membrane permeabilization – a point-of-no-return in apoptosis (Beattie et al. 2002; Morino et al. 2008; Alkabie and Boileau 2016; Ahuja et al. 2017; Gedrova et al. 2018; Zavodska et al. 2018; Kafka et al. 2020). Whether apoptosis will develop is determined by cellular processes such as mitochondrial dysfunction, disorders in cellular energy metabolism, and release of caspase enzymes. Importantly, TH can interrupt the apoptotic pathway leading to cell death at early stages of the process (Polderman 2009). Some authors imply that cold-induced proteins play one of the key roles in hypothermia neuroprotection, especially the cold-inducible RNA-binding protein (CIRBP) and cold-inducible RNA-binding protein motif 3 (RBM3). They are expressed in low doses by cells of the human pancreas, heart, thyroid gland, and also in the brain, lungs, stomach, and spinal cord of rats. They protect the central nervous system against various toxic insults and are able to interrupt the apoptotic pathway in hypothermic conditions, when their expression is enhanced (Zhu et al. 2016).

Application of TH

There are two basic techniques for induction and maintenance of TH/TTM – local (regional) and systemic (general) TH (Cambria et al. 2000; Dididze et al. 2012; Ok et al. 2012; Kaneko et al. 2017; Gedrova et al. 2018). Clinical use of TH/TTM in humans requires deep sedation or general anaesthesia, and permanent monitoring of physiological

functions (Varon et al. 2012; Karnatovskaia et al. 2014; Kafka et al. 2020). In animals, general anaesthesia accompanied by monitoring is a necessary prerequisite for the application of this method (Yoshitake et al. 2007; Brodeur et al. 2017; Zavodska et al. 2018).

Local (regional) TH

This technique permits much deeper cooling of the spinal medulla (targeted epidural temperature 4–6 °C) along with maintenance of physiological values of core body (rectal) temperature (Alkabie and Boileau 2016; Zavodska et al. 2018). To minimize variability in rectal temperature during TH and side effects of temperature management, the patients or experimental animals should be covered with an isothermal foil. If rectal temperature drops below 36 °C, the human or animal patient can be heated by warm air blown below the covering blanket (Gedrova et al. 2018; Zavodska et al. 2018). Several physical methods are used to achieve and maintain local TH. Transcutaneous cooling of the brain is usually executed by cold water circulating through a special helmet or tubing placed against the surface of the head (Kwon et al. 2008; Kafka et al. 2020). In emergency situations, the transcutaneous cooling of the spinal medulla is usually performed by ice-cold pads or heat exchangers placed on the skin above the paravertebral muscles in the region of spinal trauma (Morochovic et al. 2008; Howes et al. 2010; Hansebout and Hansebout 2014). However, the temperature exchange can be limited by a thick layer of subcutaneous fat in obese individuals. In such situations, the surface cooling technique is less reliable (Jung et al. 2015). Hence some authors reduce the temperature of damaged SC tissue by paravertebrally implanted silicone or copper tubing cooled by circulating cold water, epidurally (through laminectomy) implanted heat exchangers or special chambers perfused with cold saline, Ringer's solution, eventually cell culture media, such as Dulbecco's Modified Eagle's Medium (DMEM), or enriched DMEM (e-DMEM), i. e. Dulbecco's Modified Eagle's Medium supplemented by fibroblast growth factor, brain-derived neurotrophic factor, glial cell-derived neurotrophic factor, vascular endothelial growth factor and creatine (Yoshitake et al. 2007; Hansebout and Hansebout 2014; Kaneko et al. 2017; Teh et al. 2017; Kafka et al. 2020). Another alternative is a direct intrathecal lavation of the epicentre of the SC lesion by the above mentioned cooling solutions (Gedrova et al. 2018; Zavodska et al. 2018). The positive effect of TH is expressed by improvement of motor functions, preservation of SC white matter, grey matter, and neurofilaments. The locomotion in rodents is usually assessed by the BBB scale (Basso et al. 1995). The 21 point scale can be used for the same purpose in minipigs (Gedrova et al. 2018). The volume/percentage of preserved white matter and grey matter is evaluated in histological sections stained by Luxol fast blue and Cresyl violet, the rate of preserved neurofilaments in SC specimens processed by monoclonal anti-filament marker SMI 312 (Casas et al. 2005; Yoshitake et al. 2007; Morochovic et al. 2008; Grulova et al. 2013; Henke et al. 2013; Zavodska et al. 2018). Some basic facts related to local (regional) application of therapeutic TH are presented in Table 1.

General (systemic) TH

According to the reduction of core body temperature, TH is classified as profound (< 30 °C), moderate (30–32 °C), modest (32–34 °C) and mild (35–35.5 °C) (Polderman 2009). There are two basic approaches to reduce the whole body temperature and maintain TH: physical and pharmacological. Surface cooling with ice packs or heat-exchange devices applied to the axillae and groins, cold air or water circulating blankets, cold wrapping garments or vests, and internal cooling techniques using intravenous infusions of cold saline, gastric or rectal administration of cold non-irritant solutions provide for physical TH (Polderman et al. 2009; Karnatovskaia et al. 2014; Cappuccino et al. 2017;

Table 1. Selected studies reporting on local application of therapeutic hypothermia.

Study	Subjects/level of SCI	Time to TH/interventions	Outcome
Hansebout and Hansebout 2014	20 humans, 14 C, 6 T mean age 26.5 y 14 C, 6 T	3.3–12 h, d. temp. 6 °C, c. t. 3.7 h, steroids, decompression	ASIA A 7 pts ASIA B 6 pts ASIA C 5 pts ASIA D 2 pts
Gedrova et al. 2018	F M-G-L m-pigs, SCI at L3 level, i. f. 8N	SCI to TH 30 m, epidural TH with saline 4 °C, c. t. 5 h	recovery of m.f. signif. exceeded non-treated anim., signif. lesser damage of WM, GM, and NFs
	F M-G-L m-pigs, SCI at L3 level, i. f. 8N	SCI to TH 30 m, epidural TH with DMEM 4 °C, c. t. 5 h	recovery of m. f. ≈ equal score as non-treated anim., n. s. diff, in damage of WM, GM, NFs
	F M-G-L m-pigs, SCI at L3 level, i. f. 15N	SCI to TH 30 m epidural TH with saline 4 °C, c. t. 5 h	recovery of m. f. exceeded non-treated anim. by 1 point, sign. diff. in GM, n. s. diff. in WM and NFs
Zavodska et al. 2018	F M-G-L m-pigs, SCI at L3 level, i. f. 18N	SCI to TH 30 m intrath. adm. saline 4 °C, c. t. 5 h	recovery of m. f. ≈ equal score as non-treated anim., sign. diff. in WM, diff. in GM and NFs n. s.
	F M-G-L m-pigs, SCI at L3 level, i. f. 18N	SCI to TH 30 min. intrath. adm. DMEM 4 °C,	recovery of m. f. ≈ equal score as non-treated anim., diff. in WM, GM, NFs n. s.
	F M-G-L m-pigs, SCI at L3 level, i. f. 18N	SCI to TH 30 min intrath. adm. e-DMEM 4 °C, c. t. 5 h	recovery of m. f. exceeded non-treated anim. by 3 p., sign. diff. in WM, GM, NFs
	F M-G-L m-pigs, SCI at L3 level, i. f. 18N	SCI to TH 30 min. epid. adm. saline 24 °C, c. t. 5 h	recovery of m. f. ≈ equal score as non-treated anim., sign. diff. in WM, GM, NFs

ASIA - American Spinal Injury Association impairment scale (ASIA 2015); C - cervical; c. t. - cooling time; diff. - difference; d. temp. - dural temperature; DMEM - Dulbecco's Modified Eagle's Medium; e-DMEM - enriched DMEM; epid. adm. - epidural administration F - female; GM - grey matter; h - hour; TH - therapeutic hypothermia; i. f. - impact force; intrath. adm. - intrathecal administration; M - male; m - minute; M-G-L m-pigs - Minnesotta-Göttingen-Liběchov minipigs; N - Newton; NFs - neurofilaments; n. s. - non-significant; p. - point; SCI - spinal cord injury; sign. - significant; T - thoracic; y - year; WM - white matter

Kafka et al. 2020). Pharmacological TH is related to the administration of drugs influencing the brain's thermoregulatory centre, e.g. cannabinoids, opioid receptor activators, neurotensins, thyroxine derivates, dopamine receptor activators, TH-inducing gases, adenosine and adenine nucleotides (Polderman et al. 2009; Kafka et al. 2020). However, pharmacological interventions also have their limitations, as each organism may reveal different drug tolerance and the application of any medicament may disturb the metabolic and/or circulatory balance of the body. To reduce potential side effects of medicaments and shorten the time window until the targeted core body temperature is achieved allows a combination of physical cooling methods with hypothermic drugs administration (Jung et al. 2015). Table 2 presents some basic facts related to the application of systemic (general) TH.

Table 2. Selected studies reporting on systemic application of therapeutic hypothermia.

Study	Subjects/level of SCI initial ASIA	Time to TH/interventions	Outcome
Levi et al. 2010	14 humans / 14 C, sex unlisted m. a. 39.4 y (16–62) ASIA A	9.17 ± 2.24 h, 33 °C, c. t. 47.6 ± 3.1 h, duration TH 93.6 ± 4 h, decompression, no steroids	ASIA A 8 ASIA B 3 ASIA C 2 ASIA D 1
Dididze et al. 2013	35 humans (27M, 8F), m. a. 36.1 y (18–65) 35 C region, ASIA A	SCI to TH 5.76 ± 0.45 h, 33 °C, c. t. 46.8 ± 1.7 h, duration TH 113.6 h, decompression, no steroids	ISNCSCI A 20 ISNCSCI B 6 ISNCSCI C 4 ISNCSCI D 4 ISNCSCI E 1
Cappuccino et al. 2017	1 man, 25 y, C, ASIA A	ext. c. 15 m post SCI, intravasc. TH 34.5–35.2 °C during surg ≈4 h, steroids, decompression; 20 h post op. TH 33.5 °C ≈36 h, then rwm	ASIA D 4 mths post SCI

ASIA - American Spinal Injury Association impairment scale (ASIA 2015); C - cervical; c. t. - cooling time; ext. c. - external cooling; F - female; h - hour; TH - therapeutic hypothermia; ISNCSCI - International Standards of Neurological Classification of Spinal Cord Injury (ASIA 2019); M - male; m. a. - mean age; m - minute; mth - month; op - operation; rwm - rewarming; surg - surgery; y - year.

Studies dealing with the clinical use of general TH call attention to three important phases of its application, which significantly influence the outcome. They include the induction of TH, duration of the cooling and maintenance period, and the rewarming period (Dietrich et al. 2009; Lakhan and Pamplona 2012; Varon et al. 2012; Gong et al. 2013; Kafka et al. 2020).

The induction phase (cooling) should be initiated as soon as possible after SCI and the reduction of core temperature should be rapid (Howes et al. 2010).

The maintenance phase (duration of TH application) usually depends on the severity of the initial injury, the time interval between the SCI and the moment the target temperature is achieved, and the preference of the authors. The main aim is to thoroughly control core temperature, with fluctuations restricted to a maximum of 0.2–0.5 °C (Kwon et al. 2008; Polderman et al. 2009; Dididze et al. 2012).

The rewarming phase (reestablishment of normal core temperature) should be slow, about 0.1–0.2 °C/h). In SCI patients this phase usually lasts 24–36 h. Rewarming should not exceed 37 °C (Kwon et al. 2008; Jung et al. 2015).

Side effects of TH

Therapeutic hypothermia inhibits cellular metabolism by 5–8% per 1 °C and induces several important changes throughout the body of homoiothermic organisms (Polderman 2009; Batchelor et al. 2013; Kafka et al. 2020). Reduction of the core body temperature causes shivering, piloerection, and cutaneous vasoconstriction, insulin resistance, reduction of metabolic rate, a decrease of oxygen consumption, and carbon dioxide production, disturbance of electrolyte stability, impairment of immune, cardiovascular, haemodynamic and renal functions, as well as coagulation and wound healing (Mercer 1991; Polderman 2009; Soleimanpour et al. 2014).

Shivering, piloerection, and cutaneous vasoconstriction

Stimulation of cold receptors leads to rapid physiological reactions aiming to maintain thermal balance in endothermic vertebrates. These reactions are defensive and offensive. The defensive response (mediated by the sympathetic nervous system) is characterized by piloerection, vasoconstriction of cutaneous and subcutaneous vessels, increase of vascular resistance, shift of blood flow from the skin and extremities to intrathoracic and intraabdominal organs (Brodeur et al. 2017). The offensive response to the stimulation of cold receptors is shivering, i.e. a muscle activity that generates heat in humans as well as in birds and mammals (Mercer 1991; Howes et al. 2010). In awake patients, shivering induces unfavourable effects that are mainly linked to enhanced haemodynamic and respiratory demands of skeletal muscles. Shivering complicates TH induction, leads to a significant increase in the metabolic rate, accompanied by tachycardia, tachypnoea, as well as increased oxygen consumption (about 40–100%), and is very uncomfortable for the patient (Mercer 1991; Polderman 2009; Karnatovskaia et al. 2014). So, it is important to prevent and aggressively treat this phenomenon. The shivering is usually effectively controlled by sedatives, low doses of narcotics, and muscle relaxants (Polderman 2009). Most human patients undergoing therapeutic TH require deep sedation, but general anaesthesia, intubation, muscle relaxation, and mechanical ventilation are more convenient (Martirosyan et al. 2017). In animals treated by TH, general anaesthesia, intubation, and mechanical ventilation are fully indicated (Mercer 1991; Varon et al. 2012; Brodeur et al. 2017; Kaneko et al. 2017; Gedrova et al. 2018; Zavodska et al. 2018).

Cardiovascular effects

Even mild induced TH (< 35.5 °C) can elevate the release of catecholamines, increase cardiac output, myocardial oxygen demand, cause haemodynamic imbalance and changes in ECG. They are characterised by sinus bradycardia associated with prolongation of PR and QT intervals, and QRS complex, ST segment elevation, T wave depression, occurrence of Osborn waves, sometimes AV blocks of the 1st–2nd grade (Soleimanpour et al. 2014). Moderate TH (32–34 °C) leads to diastolic as well as systolic dysfunction, a decrease of cardiac output (by about 25%), and sinus bradycardia (45–40/min). The shift of blood volume from the peripheral circulation to the central vessels and increased arterial resistance cause a slight elevation of central venous pressure as well as blood pressure. The reduction in cardiac output due to TH is approximately equal to the lowered metabolic demand of the organism (Polderman 2009; Karnatovskaia et al. 2014). TH-induced circulatory changes usually do not require treatment. If bradycardia becomes a problem, atropine is not effective, but the slight increase of a core temperature can help. In serious cases, a pacemaker should be applied (Polderman 2009).

Metabolic effects

Therapeutic hypothermia decreases the metabolic rate, decreasing O_2 consumption and CO_2 production by the same percentage (Aslami et al. 2010). Accordingly, blood gas levels should be monitored and the ventilator rate adjusted to prevent the development of hypocapnia (causing alkalosis leading to cerebral vasoconstriction and brain ischaemia). The increase of arterial partial pressure of oxygen (PaO_2) may enhance the risk of spinal cord reperfusion injury (Polderman 2009; Karnatovskaia et al. 2014). Therapeutic hypothermia also causes an increase in fat metabolism, leading to increased glycerol, free fatty acids, ketones, and lactate concentrations. This, in turn, can cause mild metabolic acidosis, however, the phenomenon does not require therapeutic intervention (Aslami et al. 2010; Karnatovskaia et al. 2014). Another consequence of TTM is decreased insulin secretion accompanied by moderate (sometimes severe) insulin resistance in the majority of patients. To maintain glucose concentrations within an acceptable range, a significant increase in doses of insulin is necessary (Polderman 2009). The temperature dependence of insulin requirements is particularly important in the rewarming period of the procedure, when insulin sensitivity may return rapidly to normal and induce severe hypoglycaemia/hypoglycaemic shock (Polderman 2009; Karnatovskaia et al. 2014).

Wound healing and infection

Systemic TH is associated with an increased risk of development of wound, respiratory, and urinary tract infections, decubital sepsis as well as impaired wound healing (Brodeur et al. 2017). These complications are attributed to the peripheral vasoconstriction, decreased pool of circulating leukocytes, diminished release of white blood cells from bone marrow, upregulation of immunosuppressive cytokines secretion, compromised migration of leukocytes and phagocytes into tissues as well as TH-induced insulin resistance and hyperglycaemia (Kwon et al. 2008; Geurts et al. 2014; Karnatovskaia et al. 2014; Brodeur et al. 2017). That is why a prophylactic antibiotic administration is recommended, and prevention of bedsores (decubital necroses) in paralytic humans/animals is particularly important (Kim et al. 2016). Special care should be directed to wounds, surgical incisions, endotracheal and intravenous cannulas and urinary catheters (Geurts et al. 2014; Soleimanpour et al. 2014).

Haemocoagulation

Reduction of body temperature increases susceptibility to bleeding and extends the bleeding time. The effects of TH on coagulation are direct (inhibition of enzymatic clotting processes), and indirect (transient thrombocytopaenia, restricted platelet aggregation). Thrombocytopaenia and impaired platelet clustering are mainly caused by the sequestration of thrombocytes in the spleen and liver. The problem is solved when platelets re-enter the circulation after rewarming (Karnatovskaia et al. 2014). Since blood is warmed for standard prothrombin/activated partial thromboplastin time (PT/aPTT) testing, these analyses will not reflect the real situation. Rewarming will facilitate the restoration of normal haemocoagulation activity, so the administration of plasma products is not indicated (Polderman 2009; Brodeur et al. 2017).

Renal system

Cold-induced increase of the urine output in hypothermic patients occurs due to suppression of ADH production, shunting of peripheral blood to central vessels, and decreased reabsorption of solutes in the ascending loop of Henle (Polderman 2009). Cold diuresis also supports renal excretion of electrolytes and medicaments such as vasopressors, myorelaxants, phenytoin, sedatives and opiates. Potential electrolyte abnormalities are hypophosphataemia, magnesium deficiency, and hypokalaemia (Karnatovskaia

et al. 2014). An untreated cold diuresis leads to hypovolaemia, haemoconcentration, and an increase of blood viscosity (2% per 1 °C of core temperature drop). The negative effects of induced TH on renal functions should be anticipated, serum electrolytes regularly monitored, and every disorder promptly compensated for (Karnatovskaia et al. 2014; Brodeur et al. 2017).

Conclusion

Considering that the optimal target temperature after an acute SCI, time interval between SC trauma and induction of TH, duration of the cooling period, application of TH in combination with other therapeutic and/or neuroprotective procedures have not been defined so far, these variables should be thoroughly scrutinized. The currently available information on the therapeutic capacity of TH/TTM justifies a realization of further preclinical and clinical trials to evaluate all uncertain issues.

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