PRE-HOSPITAL GUIDELINES I SPINAL CORD INJURY

Optimizing the pre-hospital phase for patients with 'suspected'-spinal cord injury (SCI) - the first element of the SCI-care chain

Prof. Dr med. Dr rer. nat. Jan Schwab & Prof. Dr med. Claudius Thomé
on behalf of Wings for Life (Nov 25, 2018)

CONTENT

RATIONALE & CONSIDERATIONS & DISCLAIMER

Considerations for a medical need: This guideline is inspired by the imperative to better use the first "golden hour(s)" after spinal cord injury in order to protect spinal cord tissue in a high-risk sport scenario offering formidable options for preemptive care. Feasibility is particularly high in case the medical team is already on-site, with immediate access to the patient.

The proposed guideline takes a consequent (neuro-) protective approach. This short-guideline can be understood as an additional option of SCI care focusing on the pre-hospital phase. Every patient has the freedom to reject this additional option.

Rationale: The guideline summarizes pragmatic options, which are supported by undisputed pathophysiological evidence derived from published peer-reviewed research including replicated results from experimental SCI models, observational human SCI studies and studies investigating different but related paradigms of human CNS injury, such as ischemic brain injury. Of note, available and integrated human data is of correlative but not causative nature. In addition, the guideline respects treatment principles, which have reached guideline status for hospital care already and extend them to the preclinical phase (e.g. prevention of hypotensive episodes). The guideline has been compiled considering for active sport athletes.

Disclaimer: This pre-hospital care guideline will not represent a standard of care and cannot therefore be enforced. This pre-hospital guideline can be understood as an additional comprehensive and intensified treatment option. The presented options will not induce any costs charged to the patient and may include off-label use of well known FDA-approved drugs in an approved dose range characterized by a well-defined profile of side-effects. Consequently, *a benefit-risk ratio evaluation can be done safely by the treating pre-hospital physician on site or medical team on-site.* At present there is no evidence of Phase III studies (randomized controlled trial, RCT) available proofing superiority of the entire suggested treatment package over "standard of care". Of note, there is not even an established pre-hospital standard of SCI care present to compare the proposed guideline package with.

SPECIFIC TASKS ALONG THE PRE-HOSPITAL ELEMENT OF THE SCI CARE CHAIN AS OUTLINED IN 1-4:

1. DURING THE ENTIRE PRE-HOSPITAL PHASE (UNTIL REACHING THE HOSPITAL):

Keep systolic blood pressure above 120 mmHg or mean arterial blood pressure between 85-90mmHg. Lowering below those limits will reduce blood perfusion-pressure at the spinal cord lesion site – and is associated with impaired neurological recovery.

Consider rapid escalation of i.v. fluid/volume (doing sport the patient is likely dehydrated as being very active/sweating for a certain episode - therefore a bolus of 1-2 liter within 30 min is safe). Prioritize physiological NaCl. No plasma expander, no glucose addition. Tight blood pressure-control every 10 min – to monitor success of ramping up/maintaining blood pressure.

See guideline of the American Association of Neurosurgery (level III recommendation; Ryken et al., 2013).

2. INJURY SITE

Placing patient on vacuum mattress first - then transfer to board in order to immobilize patient and preventing pressure ulcers. Goal: Not lying on metal board = causing pre-ulcer. Ulcer development is associated with inferior recovery and prolonged hospital stay.

Early infection-prevention (aspiration...) incl. pro-active use of suction devices to reduce risk of pneumonia. Also instruct the patient to take intermittently deep breaths (prevention of atelectasis). Aspiration and/or atelectasis leads to pneumonia/infections, which impede recovery (Failli et al., 2012; Kopp et al., 2017; Gallagher et al., 2018).

3. PRAGMATIC TREATMENT BY MEDICAL TEAM:

Being on site when the injury happens offers a unique accessibility to the so-called "golden hour" (the first hour after CNS injury – characterized by the best chance to modify outcome).

A. **Continue i.v. body core cooling** to maintain aggressive normothermia (no increase of body temperature, stabilizing in between 36.5° - 37°C) (Induced Normothermia). Besides i.v. application of fluids also cold sheets can be

placed. Lowering body temperature has been shown to demonstrate improved outcomes (Batchelor et al., 2013A) and can be considered a method to reduce spinal cord swelling (Batchelor et al., 2011) and thereby extend the therapeutical time-frame for decompressions surgery ("buy time for acute care treatment", Batchelor et al., 2010, 2011). Whereas data for hypothermia (below 35°C) have been questioned (given a higher rate of complications), induced normothermia to stabilize the core temperature has been helpful for fever prophylaxis. Thus, normothermia should be maintained as long as possible.

B. **Maintain blood pressure above limits:** 120mmHg systolic or in the range of 85-90mmHg mean arterial blood pressure (MAP): How? Using i.v. infusion (safe: patient is dehydrated).

C. **Apply glyburide (Glybenclamide) in case of glucose levels above 126 mg/dl** (Kobayakama et al., 2014). This requires control of blood sugar levels. In case of elevated blood sugar levels (blood glucose > 126 mg/dl) start of off-label treatment of Glyburide. The stress response of the body drives a hypergylcaemic response (high blood sugar) – which is bad for outcome (e.g. propagates larger bleeding (hematoma) into the lesioned spinal cord ("sugar rush bleeds the spinal cord", Nieswandt and Stoll, 2011; Liu et al., 2011) and boosts progressive edema formation. This hematoma extension into the spinal cord lesion and edema is reduced by Glyburide (Simard et al., 2013; Popovich et al., 2012; Hosier et al., 2015). Glyburide is a FDA approved oral medication with established dosing scheme (Pallan and Ahmed, 2014).

4. WHERE TO REFER THE PATIENT TO? EARLY AND DIRECTED REFERRALS!

Quality over distance (access to specialized SCI care)

A. Prioritize Level I Trauma Center with specialized SCI care over Level I Trauma center w/o specialized SCI care
B. Prioritize Level I Trauma Center over Level II and Level III or lower

Level I Trauma Hospital required to allow for 24/7 coverage in order

to guarantee:

- Early decompression ("time is spine")
- Early immediate intervention in case of complications requiring surgical therapy/or immediate intensified therapy
- Less SCI typical complications (Level I Centers with more cases of spinal cord injury)

Referral to level I trauma centers is associated with a lowered mortality (Demetriades et al., 2005).

The effect of early spinal cord decompression surgery is supported by multicenter studies (Fehlings et al., 2012) and preclinical meta-analysis with an effect size up to 30% (Batchelor et al., 2013B).

Early referral to a specialized hospital is associated with a lower number of complications (Bourassa-Moreau et al., 2013).

Centers of specialized rehabilitative SCI care should be identified before the race as a natural part of preparation. Medical arguments strongly support the need to be transferred to specialized SCI care centers.

CONTACTS (PLEASE KEEP IN CONFIDENCE)

Prof. Dr med. Dr. rer. nat. Jan Schwab
USA-based; available during daytime hours Eastern Standard Time
E-mail: Jan.Schwab@osumc.edu
Mobile: +1 (614) 400 1081

Prof. Dr med. Claudius Thomé
Europe-based; available during daytime hours Central European Time
E-mail: claudius.thome@tirol-kliniken.at
Mobile: +43 (0)676 835627454

REFERENCES

Batchelor PE, Skeers P, Antonic A, Wills TE, Howells DW, Macleod MR, Sena ES. Systematic review and meta-analysis of therapeutic hypothermia in animal models of spinal cord injury. PLoS One. 2013A Aug 9;8(8):e71317.

Batchelor PE, Wills TE, Skeers P, Battistuzzo CR, Macleod MR, Howells DW, Sena ES. Meta-analysis of pre-clinical studies of early decompression in acute spinal cord injury: a battle of time and pressure. PLoS One. 2013B Aug 23;8(8):e72659.

Batchelor PE, Kerr NF, Gatt AM, Cox SF, Ghasem-Zadeh A, Wills TE, Sidon TK, Howells DW. Intracanal pressure in compressive spinal cord injury: reduction with hypothermia. J Neurotrauma. 2011 May;28(5):809-20.

Batchelor PE, Kerr NF, Gatt AM, Aleksoska E, Cox SF, Ghasem-Zadeh A, Wills TE, Howells DW. Hypothermia prior to decompression: buying time for treatment of acute spinal cord injury. J Neurotrauma. 2010 Aug;27(8):1357-68.

Bourassa-Moreau É, Mac-Thiong JM, Ehrmann Feldman D, Thompson C, Parent S. Complications in acute phase hospitalization of traumatic spinal cord injury: does surgical timing matter? J Trauma Acute Care Surg. 2013 Mar;74(3):849-54.

Demetriades D, Martin M, Salim A, Rhee P, Brown C, Chan L. The effect of trauma center designation and trauma volume on outcome in specific severe injuries. Ann Surg. 2005 Oct;242(4):512-7; discussion 517-9.

Failli V, Kopp MA, Gericke C, Martus P, Klingbeil S, Brommer B, Laginha I, Chen Y, DeVivo MJ, Dirnagl U, Schwab JM. Functional neurological recovery after spinal cord injury is impaired in patients with infections. Brain. 2012 Nov;135(Pt 11):3238-50.

Fehlings MG, Vaccaro A, Wilson JR, Singh A, W Cadotte D, Harrop JS, Aarabi B, Shaffrey C, Dvorak M, Fisher C, Arnold P, Massicotte EM, Lewis S, Rampersaud R. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One. 2012;7(2):e32037.

Gallagher MJ, Zoumprouli A, Phang I, Schwab JM, Kopp MA, Liebscher T, Papadopoulos MC, Saadoun S. Markedly Deranged Injury Site Metabolism and Impaired Functional Recovery in Acute Spinal Cord Injury Patients With Fever. Crit Care Med. 2018 Jul;46(7):1150-1157.

Hosier H, Peterson D, Tsymbalyuk O, Keledjian K, Smith BR, Ivanova S, Gerzanich V, Popovich PG, Simard JM. A Direct Comparison of Three Clinically Relevant Treatments in a Rat Model of Cervical Spinal Cord Injury. J Neurotrauma. 2015 Nov 1;32(21):1633-44.

Kobayakawa K, Kumamaru H, Saiwai H, Kubota K, Ohkawa Y, Kishimoto J, Yokota K, Ideta R, Shiba K, Tozaki-Saitoh H, Inoue K, Iwamoto Y, Okada S. Acute hyperglycemia impairs functional improvement after spinal cord injury in mice and humans. Sci Transl Med. 2014 Oct 1;6(256):256ra137.

Kopp MA, Watzlawick R, Martus P, Failli V, Finkenstaedt FW, Chen Y, DeVivo MJ, Dirnagl U, Schwab JM. Long-term functional outcome in patients with acquired infections after acute spinal cord injury. Neurology. 2017 Feb 28;88(9):892-900.

Liu J, Gao BB, Clermont AC, Blair P, Chilcote TJ, Sinha S, Flaumenhaft R, Feener EP. Hyperglycemia-induced cerebral hematoma expansion is mediated by plasma kallikrein. Nat Med. 2011 Feb;17(2):206-10.

Nieswandt B, Stoll G. Sugar rush bleeds the brain. Nat Med. 2011 Feb;17(2):161-2.

Pallan TV, Ahmed I. Glyburide in Treating Malignant Cerebral Edema. Blocking Sulfonyl Urea One (SUR1) Receptors. J Vasc Interv Neurol. 2014 Nov;7(4):23-5

Popovich PG, Lemeshow S, Gensel JC, Tovar CA. Independent evaluation of the effects of glibenclamide on reducing progressive hemorrhagic necrosis after cervical spinal cord injury. Exp Neurol. 2012 Feb;233(2):615-22.

Ryken TC, Hurlbert RJ, Hadley MN, Aarabi B, Dhall SS, Gelb DE, Rozzelle CJ, Theodore N, Walters BC. The acute cardiopulmonary management of patients with cervical spinal cord injuries. Neurosurgery. 2013 Mar;72 Suppl 2:84-92.

Simard JM, Popovich PG, Tsymbalyuk O, Caridi J, Gullapalli RP, Kilbourne MJ, Gerzanich V. MRI evidence that glibenclamide reduces acute lesion expansion in a rat model of spinal cord injury. Spinal Cord. 2013 Nov;51(11):823-7.