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ORIGINAL ARTICLE

Design and rationale of a Prospective, Observational European Multicenter study on the efficacy of acute surgical decompression after traumatic Spinal Cord Injury: the SCI-POEM study

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Objectives: Despite many years of research, there is currently no treatment available that results in major neurological or functional recovery after traumatic spinal cord injury (tSCI). In particular, no conclusive data related to the role of the timing of decompressive surgery, and the impact of injury severity on its benefit, have been published to date. This paper presents a protocol that was designed to examine the hypothesized association between the timing of surgical decompression and the extent of neurological recovery in tSCI patients.

Study design: The SCI-POEM study is a Prospective, Observational European Multicenter comparative cohort study. This study compares acute (<12 h) versus non-acute (>12 h, <2 weeks) decompressive surgery in patients with a traumatic spinal column injury and concomitant spinal cord injury. The sample size calculation was based on a representative European patient cohort of 492 tSCI patients. During a 4-year period, 300 patients will need to be enrolled from 10 trauma centers across Europe. The primary endpoint is lower-extremity motor score as assessed according to the 'International standards for neurological classification of SCI' at 12 months after injury. Secondary endpoints include motor, sensory, imaging and functional outcomes at 3, 6 and 12 months after injury.

Conclusion: In order to minimize bias and reduce the impact of confounders, special attention is paid to key methodological principles in this study protocol. A significant difference in safety and/or efficacy endpoints will provide meaningful information to clinicians, as this would confirm the hypothesis that rapid referral to and treatment in specialized centers result in important improvements in tSCI patients.

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Keywords: spinal cord injury; decompression; timing of surgery; observational study; comparative cohort study; study protocol

INTRODUCTION

In his seminal paper on the treatment of spinal injuries published in 1905, Dr Burrell postulated two important assumptions related to the role of surgical decompression in traumatic spinal cord injury (tSCI).[1] Related to the 'window of opportunity' for surgical decompression, his first assumption was '*that if pressure on the cord is allowed to remain for many hours, irreparable damage to the cord may take place*'. In his second assumption Burrell refers to the 'window of severity' for surgical decompression: '*that unless it is perfectly clear that the cord is irremediably damaged an open operation to establish the condition of the cord and to relieve pressure is imperative as soon as surgical shock has been recovered from*'. Nowadays, more than 100 years after Burrell's findings, the role of surgical treatment in tSCI is well recognized.[2,3] However, no conclusive data related to the role of the timing of decompressive surgery, and the impact of injury severity on its benefit, have been published to date.

The contemporary debate on the optimal timing of decompression in tSCI is based on a more recent concept that distinguishes primary from secondary mechanisms of injury.[4] The primary mechanism refers to the initial cord lesion resulted from the physical trauma to the tissue caused by a displacement of the surrounding spinal column. The primary mechanism in turn initiates a cascade of secondary injury mechanisms including ischemia, edema, increased excitatory amino acids and lipid peroxidation.[4] Pre-clinical data support the theory that persistent compression of spinal cord represents a cause of secondary injury and thus may be potentially reversible.[5,6] The National Acute Spinal Cord Injury Studies were the first large clinical studies supporting the concept of secondary mechanism of injury.[7–9] The accumulation of both experimental and clinical study results increasingly supported the potential therapeutic role of acute surgical decompression in tSCI.[10]

Dr Furlan *et al.*[3] recently published a review of clinical studies on the efficacy of surgical decompression in tSCI patients. Although the included studies showed some conflicting findings, a modified Delphi process led the authors to the conclusion and recommendation that surgical decompression of the injured spinal cord should be performed within 24 h after injury when medically feasible.[3] It was noted that this recommendation was based on 20 'level-4 evidence'

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studies and 2 'level-2b evidence' studies.[11] But what could be the explanation for the lack of robust evidence on such a burning issue in the management of spinal trauma patients?

With a reported incidence rate ranging from 10.4 to 83 cases per million population worldwide,[12] tSCI is not only relatively uncommon, but is also markedly heterogeneous in terms of anatomic level and severity.[13] Another aspect limiting the feasibility of conducting a surgical randomized controlled trial on the acute management of tSCI is the difficulty to recruit potentially eligible subjects in the early hours after the injury. The foremost explanation for this is the required transfer time to specialized trauma centers.[14] Given these and other practical and ethical limitations,[15,16] a well-powered prospective, comparative cohort study would be the second best study design of choice.

The aim of this article is to describe a protocol that was designed to examine the hypothesized association between the timing of surgical decompression and the extent of neurological recovery in tSCI patients. The purpose of this observational study is to determine the safety, effectiveness and feasibility of early surgical treatment for tSCI among patients with a traumatic spinal column injury. The primary aim of this study is to determine whether acute (<12 h) surgical treatment results in better neurological recovery 12 months after injury when compared with non-acute (>12 h, <2 weeks) surgical treatment in tSCI patients.

MATERIALS AND METHODS

Study design

A Prospective, Observational European Multicenter comparative cohort study, which has the acronym 'SCI-POEM', will be undertaken.

Setting and patient recruitment

Setting and investigational sites. Patients will be identified and recruited in European level I and II trauma centers. To diminish the putative confounding effect of differences in perioperative care and acute rehabilitation, the number of tSCI patients treated at participating investigational sites needs to be at least 10 per year during the past 3 years. Furthermore, to aim for high-quality outcome research, participating investigational sites have to ensure that physicians obtain a complete neurological examination before surgical intervention and that designated personnel are willing to attend outcome measurement instructional courses. As there is (1) conflicting evidence on the therapeutic efficacy of methylprednisolone administration in tSCI patients and (2) increasing evidence on complications associated with its administration,[17–19] it was decided to exclude those trauma centers that administer methylprednisolone to acute tSCI patients per protocol.

Patient recruitment, eligibility criteria and informed consent. All adult patients admitted with a traumatic spinal column injury to one of the participating hospitals will be assessed for eligibility. Upon admission to hospital, all trauma patients undergo clearance protocols of the cervical[20] and thoracolumbar[21] spine. In line with common practice, a mandatory computed tomography (CT) scan is performed in all patients where the spinal column cannot be cleared. Additional magnetic resonance imaging (MRI) of the spine is not mandatory and left to the preference of the treating physician. Patients with a detected, significant spinal column injury undergo a detailed neurological examination. All patients with a significant traumatic spinal column injury and concomitant spinal cord injury are considered eligible for inclusion in the SCI-POEM study. A detailed list of eligibility criteria is presented in Table 1.

The treating spinal surgeon assesses the eligibility for inclusion in this study. Eligible patients are approached by a local study coordinator who is not involved in the treatment-decision making and inquires about their interest of participating in this study. Because of the observational nature of this study, written consent—or verbal assent—may also be obtained days after the, often hectic, early phase after the injury. On the basis of previous experience, the recruitment, or allocation, ratio for acutely and non-acutely decompressed patients is estimated to be 1:2.

Treatment protocol and follow-up

General treatment regimen. During both the acute phase and early rehabilitation, all tSCI patients will be treated at each institution per standard of care.[22] All patients are managed according to advanced trauma life support principles. During the first 2 weeks after injury, hemodynamic and respiratory functions are monitored and supported to reach appropriate levels of cord perfusion and oxygenation.[23] Special attention is given to the prevention of respiratory adverse events, thromboembolic events, urogenital adverse events, bowel obstruction, pressure sores, muscle contractures and periarticular ossifications.[24,25] Dependent on the level and severity of injury, individually tailored rehabilitation programmes will vary in focus and intensity.

Treatment protocol: Surgical treatment regimen. Depending on the preference of the spinal surgeon, the following surgical approaches are performed consistent with the standard of care provided by each of the participating hospitals:

- Closed: Closed reduction and external fixation
- Open: Posterior approach
- Open: Anterior approach
- Open: Circumferential approach (one or two stage)

Table 1 Eligibility criteria

Inclusion criteria	*Exclusion criteria*
Diagnosis of blunt spinal column injury and spinal cord injury, including conus medullaris and/or cauda equina injuries	Diagnosis of traumatic brain injury (Glasgow Coma Scale score $\leqslant 13$)[54]
Age $\geqslant 18$ years	Diagnosis of subclinical or clinical polyneuropathy[a] using information from the patients' medical files
Injury treated surgically $\leqslant 2$ weeks after the injury	Spinal cord injury caused by a penetrating injury
Able and willing to give consent to participate in the study	Non-traumatic or pathologic fractures or cord compression (for example, tumor, infection)
	No complete neurological examination obtained before surgical intervention
	Cognitive impairment prohibiting to give consent to participate in the study
	Unable to cooperate with physical examination (preoperative, $\leqslant 2$ weeks after injury) because of cognitive impairment, as assessed by the examiner
	Previous spinal column or spinal cord injury
	Morbid obesity (BMI >35)
	ASA classification: score 4 or 5[55]
	Diagnosis of spondyloarthropathy (inflammatory or non-inflammatory)

Abbreviations: ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index.
[a]Presence of bilateral impairment of strength, sensation, and/or deep tendon reflexes with symmetrical and distal distribution and/or neurophysiological abnormalities.[56]

If an open approach follows a closed approach, details of both approaches are recorded. If applicable, additional details of closed and open surgeries (for example, duration of traction, performance of a laminectomy) are also collected. The type and duration of postoperative spinal immobilization and perioperative pharmaceutical interventions are also recorded.

The following information related to the principle exposure under study, the timing of surgical decompression, will be documented:

- Date, time and location of injury
- Date and time of arrival of patient in participating hospital
- Date, time and method of surgical decompression

The timing of decompression is defined as the date and time of the applied intervention leading to a successful decompression as confirmed with MRI. A successful decompression is defined as either when the transverse spinal area (TSA)[26] of the injured level is at least 90% of the average TSA of the rostral and caudal levels, or as presence/restoration of hyperintense cerebrospinal fluid signal around the spinal cord on transverse T2 MR images. To gain additional information on the feasibility of acute surgical decompression for tSCI, details on delays in patient transfer, diagnostic work-up and treatment will be documented.

Follow-up and data collection. Follow-up assessments will take place at routine visits 3, 6 and 12 months after injury. Source data collection will be performed by a local research coordinator at each participating hospital using paper case-record forms. After the initial data collection, the source data will be transferred from case-record forms onto the electronic data capturesystem in a de-identified manner and latest within 14 calendar days of study enrollment and follow-up measurements. De-identified DICOM images will be transferred to the clinical research organization (CRO) and stored on secure operating servers.

Study endpoints and adverse events (AEs)

Primary endpoint. The primary outcome is the:

- Lower-extremity motor score (LEMS) as assessed according to the 'International standards' for neurological and functional classification of SCI at 12 months after injury

All neurological outcomes will be assessed according to the 'International standards' for neurological and functional classification of SCI developed by the American Spinal Injury Association (ASIA) committee.[27] The International standards provide a standardized quantitative description of the neurological level of injury and sensorimotor function above and below this level.

Motor function testing according to International standards encompasses 10 bilateral myotomes, more specifically C5–T1 and L2–S1, corresponding to the five key muscle groups in each of the four limbs. The total motor score can be divided into two subscales, an upper-extremity motor score (UEMS) and a LEMS, each consisting of a total of 10 key muscles.[28] Motor score testing of the key muscles is graded on a five-point scale adapted from the Medical Research Council scale. In a recent review, Furlan *et al.*[29] demonstrated a high reproducibility and a good responsiveness to change of the International standards as a whole.

Secondary endpoints. The secondary outcomes are the:

- LEMS as assessed according to the 'International standards' at 3 and 6 months after injury
- UEMS in tetraplegic patients as assessed according to the 'International standards' at 3, 6 and 12 months after injury

The LEMS and UEMS will be assessed and scored as described above.

- Aggregated sensory score as assessed according to the 'International standards' at 3, 6 and 12 months after injury

Sensory examination comprises testing of what are known as key points in each of the 28 dermatomes on both the left and right sides of the body. The key points correspond with a defined area of skin in each dermatome where overlapping innervation to adjacent dermatomes is at a minimum, thereby making these areas most suitable for testing the function of each specific dermatome. The dermatomes extend from level C2 to S5, where S4 and S5 are considered as one dermatome. Each key point, including the perianal region, is tested for light touch (with a cotton tip applicator or similar object) and pain (using a pin or similar object). Sensory function is graded as follows: normal = 2; impaired/distorted = 1; absent = 0; not testable = NT. The latter may be due to a local injury, amputation or a cast covering the area.[27]

- The ASIA/International Spinal Cord Society neurological standard scale (ASIA Impairment Scale, AIS) at 3, 6 and 12 months after injury

On the basis of the sensorimotor scores as assessed according to the 'International standards', the level and the severity of the SCI can be determined. The scale most commonly used to classify the severity of the injury is the ASIA/ISCoS neurological standard scale AIS. Using the AIS the severity of the injury can be categorized into five grades (A–E, see Table 2).[27] As previous studies indicated that the AIS may not be responsive enough to detect small neurological improvements,[30] this commonly applied outcome measure was not applied as a primary outcome measure in the current study.

- The Spinal Cord Independency Measure III (SCIM-III) at 3, 6 and 12 months after injury

The SCIM is a disability scale that specifically addresses patients with spinal cord lesions describing their ability to accomplish activities of daily living. It has undergone two revisions,[31,32] the most recent one resulting in the SCIM-III.[32] The SCIM-III consists of 19 subitems and cover the following three main categories (1) self-care, (2) respiration and sphincter management, and (3) mobility. Main areas and subitems are weighted according to their assumed clinical relevance in relation to the overall activity of the SCI population. The maximal total score of the SCIM-III amounts to 100 points. Previous studies demonstrated excellent reliability and construct validity of the SCIM-III.[32–34]

- Fracture consolidation at 6 months after injury

To improve the understanding of the effect of post-traumatic spinal column characteristics on neurological and functional outcomes, several routine spinal column outcome measures will be recorded. A fracture is defined as healed if there is complete or almost complete resolution of the fracture line or if there are visible bony trabeculations crossing the fracture line.[35] Non-union, or pseudoarthrosis, is defined as failure of fracture consolidation 6 or more months after injury. As no definitive method that defines fracture healing has been published to date, there is currently no consensus as to which is the best imaging study to use to affirm the presence of union or pseudarthrosis. Despite absence of a gold standard, presence of bony trabeculations as discerned on conventional or CT imaging is considered the next best approach.

- Sagital alignment at 3, 6 and 12 months after injury

The sagital alignment of the spinal column will be assessed according to the Cobb angle method. The Cobb angle is the angle between the superior endplate of the vertebral body one level above the injured vertebral body to the inferior endplate of the vertebral body one level below.[36] Kuklo *et al.*[36] demonstrated a good reproducibility and responsiveness to change of the Cobb angle method.

- Vertebral height at 3, 6 and 12 months after injury

The anterior vertebral height is the distance between the anterosuperior and anteroinferior corner of the vertebral body as described by Isomi *et al.*[37] The vertebral height ratio can be calculated by dividing the anterior vertebral height

Table 2 ASIA/International Spinal Cord Society (ISCoS) neurological standard scale, better known as the 'ASIA Impairment Scale'[27]

	ASIA Impairment scale	*Lesion*
A	No motor or sensory function is preserved in the sacral segments S4–S5.	Complete
B	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4–S5.	Incomplete
C	Motor function is preserved below the neurological level, and more than half of the key muscles below the neurological level have a muscle grade <3.	Incomplete
D	Motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle grade of $\geqslant 3$.	Incomplete
E	Motor and sensory function are normal.	Normal

Abbreviation: ASIA, American Spinal Injury Association.

by the posterior vertebral height, which is defined as the distance between the posterosuperior and posteroinferior corners of the vertebral body. No data regarding the validity, reproducibility or responsiveness of these measures have been published to date.

- Spinal canal compromise at 3, 6 and 12 months after injury

The extent of spinal canal encroachment will be determined by measuring the TSA as described by Rasmussen *et al*.[26] The TSA, or total canal cross-sectional area, is defined as the total area of the canal bordered anteriorly by the posterior border of the vertebral body, posteriorly by the convergence of the superior border of the laminae at the midline of the spinous process, and laterally by the medial border of the pedicles.[38] The maximum encroachment at the affected level can be expressed as a percentage by dividing the TSA by the average TSA of the unaffected levels rostral and caudal to the level of injury (% Canal encroachment $= 100$—$(2\mathrm{TSA}_{\mathrm{Injured}}/(\mathrm{TSA}_{\mathrm{Rostral}} + \mathrm{TSA}_{\mathrm{Caudal}}) \times 100))$. Although construct validity has been proven,[26] no data regarding the reproducibility or responsiveness of the TSA measure have been published to date.

Outcome assessors. Although blinding to important prognostic factors and treatment modalities is theoretically possible, blinding of neurological and functional outcome assessors is not regarded as a feasible option in this study. The number of trained and qualified assessors per investigational site is expected to be low and the bias-prone effect of knowledge of prognostic factors on outcomes is considered to be minimal. Radiologists, however, will be blinded to specific clinical information (severity and level of neurological deficit and timing of surgery) and will examine de-identified medical images independently of treating surgeons.

AEs and safety. AEs are defined as any unfavorable and unintended sign, symptom, disease or clinical event occurring to a subject during the study, whether or not considered related to the intervention under study. The research coordinator of each participating hospital records all AEs on a study worksheet. The worksheet will capture the date of onset, severity, duration, outcome and relationship to the treatment or protocol.

Serious AEs (SAEs) are defined as events that led to a death or led to a serious deterioration in the health of a subject. In case an SAE occurs, the research coordinator is required to notify the principal investigator and to contact the CRO as soon as possible. The research coordinator will report any and all SAE to the institutional review board (IRB) as required.

Anticipated AEs are those that might reasonably be expected, or have previously been reported, to occur in the spinal column injury and spinal cord injury population. These can include, but are not necessarily limited to those outlined and defined in Table 3.

Statistical analyses

Sample size. For the sample size calculation we used a representative European patient cohort of 492 tSCI patients (see Table 4), for whom clinical characteristics have been documented in detail in a recent study.[39] Given the heterogeneity of recovery patterns in the tSCI population,[40] it was decided to stratify the study population into the four AIS categories and to conduct a separate sample size calculation for each AIS grade. Furthermore, given that the primary outcome recovery profile for tetra- and paraplegic patients was remarkably similar in all of the AIS grade groups (data not presented; available upon request), it was decided not to stratify by the 'level of injury'. The following equation was used to calculate the sample size for each AIS grade group:[41]

$$m = \left(\frac{1+\lambda}{\lambda}\right)\frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2_{\mathrm{Plan}}}$$

All sample size calculations are based on at least 80% power and 95% certainty. The anticipated therapeutic effects of acute decompression are 7 LEMS points for AIS grade A, 10 LEMS points for AIS grade C and D and 3 LEMS points for AIS grade D. The estimated allocation and drop-out ratios are 1:2 (acute:non-acute) and 1:10, respectively. On the basis of these conditions and estimations the sample sizes were set at 114 AIS grade A patients, 63 AIS grade B patients, 60 AIS grade C patients and 63 AIS grade D patients. This means that the total required study sample is 300 patients.

Analysis. Frequencies and percentages or means and SD will be calculated where appropriate, to describe patient characteristics for the entire cohort and for the two study groups. Patient characteristics will be compared between the two study groups using two-sample *t* tests for continuous variables and χ^2-tests for categorical variables. Within-group changes from baseline to the 3-, 6- and 12-month follow-up assessments will be examined by a paired samples *t*-test.

Confounding by indication is an inherent limitation of non-randomized comparative studies. Covariate, or patient characteristic, imbalances between the two study groups resulting from selection bias may lead to incorrect estimations of the attributable effect of the timing of surgical decompression on neurological recovery. Analysis of covariance, with adjustment for the propensity score, will be used to adjust for covariates including age, gender, (concomitant) injury characteristics (for example, ISS, fracture classification) and co-morbidities.[42–45] A propensity score is the likelihood of exposure to a treatment, given a subject's observed covariates, and is estimated by using a logistic regression model of observed covariates with treatment exposure as the outcome variable. The propensity score can be used to balance the covariates in the two groups, and thus reduce the magnitude of selection bias.[46] Multiple imputation techniques will be used to replace missing data rather than discarding incomplete records.[47]

Interim analysis. As both acute and non-acute decompression are current spinal injury management practices, it is expected that the IRBs will advise that repeated interim analyses for safety outcomes are not required. However, a superiority interim analysis will be performed once 50% of participants have reached the primary endpoint.

Study organization

Protocol implementation. The study protocol will be instructed by the CRO study monitor to all designated physicians and paramedical staff through site visits, telephone/audio–video conferences and study progress meetings. Each investigational site will need to nominate at least two physicians and medic staff members for an 'outcome assessment' course. Only those assessors who successfully completed the instructional course will be allowed to examine

Table 3 Definitions, categorizations and/or classifications anticipated adverse events

Adverse events	*Diagnostic assessments*	*Definitions, categorizations and/or classifications*	*Ref.*
Spinal injury-related events			
Intraoperative vascular injury	Clinical observation	(1) Minor vascular injury: the need for a simple suture repair to a major-named vein that continues to bleed after applying pressure. (2) Major vascular injury: any arterial injury or a venous injury that requires more than a simple suture repair.	57
Postoperative bleeding	Clinical observation	(1) A bleeding requiring the transfusion of >2 units blood derivatives, or (2) A bleeding requiring a reoperation.	58
Dural tear	Clinical observation	(1) Intraoperative occurrence, or (2) Indirect observation upon detection of cerebrospinal fluid leakage.	59,60
Cerebrospinal fluid leakage	Physical examination, imaging, laboratory test (if indicated)	A subfascial or subcutaneous fluid collection, or wound drainage, with or without postural headache. If uncertainty still exists, detection of β-2-transferrin confirms the diagnosis/adverse event.	59,60
Neurological deterioration	Physical examination	Any worsening of neurological functions after the initial (preoperative) neurological examination as assessed by the 'International Standards for Neurological Classification of Spinal Cord Injury (2002)'.	27
Screw misplacement	CT	Breaching of the cortex of the pedicle, lateral mass or vertebral body in any direction. Grade (1) Screw threads just into the cortex (no perforation). Grade (2) Screw perforates the cortex by $\leqslant 2$ mm. Grade (3) Screw perforates the cortex by >2 mm.	61–63
Loosening of instrumentation[a]	Imaging	(1) New radiolucency of 1 mm or wider at the bone–instrumentation interface, and/or (2) Any change in the position of instrumentation between two consecutive (follow-up) imaging time points.	64
Breakage of instrumentation[a]	Imaging	Breakage of instrumentation as discerned on imaging.	
Surgical site infection (SSI)[b]	Physical examination, bacterial culture	Any postoperative surgical wound with signs of pain, erythema, swelling, warmth, tenderness to palpation, fever ($>38\,^{\circ}C$) or (purulent) wound drainage that requires treatment with (1) oral or intravenous antibiotics, or (2) surgical debridement, unless an aseptically obtained culture of fluid or tissue from the wound is negative.	65,66
Pin track infection (external fixator)	Inspection	Aseptic: Loosening of pin without clinical evidence of infection, responds to minor tightening of pin (no infection). Class I: Focal infection and no pin loosening, responsive to local measures, responds to local pin tract care, antibiotics per os. Class II: Pin loosening and productive purulent drainage, requires pin removal and local debridement. Class III: Intracranial abscess or craniofacial abscess, surgical debridement/reconstruction, intravenous antibiotics.	67
Halo pin penetration	Physical examination, CT (if indicated)	(1) Penetration through outer table of the skull. (2) Penetration through inner table of the skull.	68,69
Dysphonia	Observation (physician- or patient-reported)	A disturbance in vocal quality, pitch or intensity with or without pain with talking.	70
Dysphagia	Observation (patient-reported)	Any impairment or abnormality of the oral, pharyngeal or upper esophageal stage of deglutition.	71
Pressure ulcers	Physical examination (EPUAP pressure ulcer classification)	Grade (1) Non-blanchable erythema of intact skin.[c] Grade (2) Partial thickness skin loss involving epidermis, dermis or both. The ulcer is superficial and presents clinically as an abrasion or blister. Grade (3) Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. Grade (4) Extensive destruction, tissue necrosis or damage to muscle, bone, or supporting structures with or without full thickness skin loss.	72
Other events			
Death	—	All cause mortality.	—
Cardiac events	Clinical examination, electrocardiography, biochemical analysis, imaging	Occurrence of (1) prolonged myocardial ischemia, (2) myocardial infarction, (3) congestive heart failure, or (4) supraventricular or ventricular tachyarrhythmias. Ad (1) Prolonged myocardial ischemia was defined as a new ST-T abnormality (ST depression $\geqslant 1$ mm at 60 ms after the J point) on at least two successive daily electrocardiograms. Persistent T-wave inversion was also considered prolonged myocardial ischemia. Ad (2) The diagnosis of postoperative myocardial infarction required new Q waves on the electrocardiogram that were at least 0.04 s in duration and 1 mm in depth, persistent ST-segment depression associated with an elevation in the serum creatine kinase-MB isoenzyme (to $\geqslant 20\,ng\,ml^{-1}$), or autopsy evidence. Ad (3) Congestive heart failure was defined as the need for sympathomimetic support (dopamine, dobutamine) during the postoperative period, associated with hemodynamic and pulmonary findings consistent with the diagnosis: pulmonary rales and orthopnea, classic chest film changes, or pulmonary–capillary wedge pressure persistently >18 mm Hg in patients undergoing hemodynamic monitoring. Ad (4) Atrial and ventricular tachyarrhythmias were defined as documented atrial or ventricular tachycardia or fibrillation.	73

Table 3 (Continued)

Adverse events	*Diagnostic assessments*	*Definitions, categorizations and/or classifications*	*Ref.*
Respiratory tract infection	Physical examination, imaging	Fever with (1) pulmonary infiltration as demonstrated with imaging techniques, or (2) dyspnea or cough or purulent sputum, or (3) isolation of bacteria in tracheal secretion (only intubated patients).	74
Acute respiratory distress syndrome	Arterial blood gas, imaging	Presence of bilateral pulmonary infiltrates with a $PaO_2/FiO_2 \leqslant 200$ mm Hg^{-1} and pulmonary capillary wedge pressure $\leqslant 18$ mm Hg or no clinical evidence of congestive heart failure.	75
Atelectasis	Imaging	Displacement of a fissure along with opacification of a lobe or lobar segment as demonstrated with imaging techniques.	76,77
Pulmonary embolism	Physical examination, Spiral CT, ventilation-perfusion scan	A segmental or larger pulmonary artery filling defect on a spiral CT scan or ventilation-perfusion scan interpreted as high probability, with associated typical symptoms, such as pleuritic chest pain, dyspnea or hemoptysis.	78
Deep vein thrombosis	Ultrasound imaging, venography	A non-compressible segment on compression leg vein ultrasound imaging or an intraluminal filling defect on venography.	79
UTI	Urine test dip strips: nitrite, RBCs and WBCs, urine sediment, bacterial culture.[d]	(1) A positive test dip strip for WBCs or nitrite with clinical symptoms including dysuria, stranguria, urinary frequency or urgency, leading to antibiotic treatment, and/or (2) Growth of at least 100 000 colonies of a single organism in the culture.	74,80
Dehydration	Clinical examination, biochemical analysis	Clinical signs of dehydration supported by renal failure oliguria (<1 L/24 h) or hypernatraemia (>148 mmols l^{-1}) or raised creatinine concentration (>125 mmols l^{-1} or $>20\%$ if previously high).	81
Renal failure	Biochemical analysis	Calculated creatinine clearance <30 ml min^{-1} (not pre-existent).	81
Ileus	Physical examination, imaging (if indicated)	At least three of the following five symptoms: (1) nausea, (2) abdominal pain, (3) vomiting, (4) abdominal distention, (5) absence of flatus and/or stool in the last 24 h (with or without radiographic evidence of small bowel dilatation and/or obstruction) requiring insertion of a nasogastric tube.	82,83

Abbreviations: CT, computed tomography; EPUAP, European Pressure Ulcer Advisory Panel.
[a]Instrumentation includes: screws, rods, plates, wires, cages and/or grafts,
[b]Distinction between a superficial (skin and/or subcutaneous tissue) or deep (fascial/muscle layer) SSI has to be made by the treating physician. A combination of the two will be classified as a deep SSI only,
[c]Discolouration of the skin, warmth, edema, induration or hardness may also be used as indicators, particularly in individuals with darker skin. Whether the erythema can be blanched or not (by means of a finger or a transparent disk) is the most important distinction between a normal physiological reaction of the tissue to pressure and shearing forces, and grade 1 pressure ulcer.[70]
[d]Urine samples collected out of catheters or midstream urine.

Table 4 LEMS recovery patterns stratified by the AIS grading system in a European cohort of 492 tSCI patients[39]

	N	*Range*	*Mean and Δ Mean*	*SE*	*SD*
All patients					
LEMS (<2 weeks)	492	0–50	11.7	0.76	16.8
LEMS (1 year)	487	0–50	20.8	0.96	21.1
			Δ9.1		
AIS grade A					
LEMS (<2 weeks)	240	0–44	1.6	0.38	5.9
LEMS (1 year)	238	0–50	5.0	0.77	11.9
			Δ3.4		
AIS grade B					
LEMS (<2 weeks)	66	0–50	4.0	1.13	9.2
LEMS (1 year)	65	0–50	19.4	1.93	15.5
			Δ15.4		
AIS grade C					
LEMS (<2 weeks)	76	0–27	10.7	0.91	7.9
LEMS (1 year)	75	0–50	33.6	1.76	15.2
			Δ22.9		
AIS grade D					
LEMS (<2 weeks)	110	7–50	39.0	0.92	9.7
LEMS (1 year)	109	32–50	47.3	0.40	4.2
			Δ8.3		

Abbreviations: AIS, ASIA Impairment Scale; LEMS, lower-extremity motor score; tSCI, traumatic spinal cord injury.

included patients for the current study. All outcome assessors will be provided explanatory documentation and standardized recording forms.

Follow-up compliance. Patients will be followed from the day of inclusion to the study endpoint 12 months after the injury. This will include time while hospitalized, routine standard of care visits (or consultations while in rehabilitation center), unplanned visits and planned routine visits at 3, 6 and 12 months after injury. Patients will receive reminders by (electronic) mail for upcoming study visits. In case a patient does not show up for a follow-up visit, designated local staff will contact the subject to schedule a new visit and to update any changes in residence and contact details.

Monitoring. The CRO will regularly check the study database to identify missing data or unrealistic values. Inconsistencies will be resolved by contacting the participating hospital and asking for clarification or by asking the local research coordinator to contact the subject, subject's physicians, or querying the subject's source documents or medical record. In addition, the CRO study monitor will visit each participating hospital to examine recruitment procedures, ensure data quality and monitor compliance with the study protocol.

Data integrity and management. All case-record forms are kept in locked file cabinets in secure areas. De-identified data transfer to the electronic data capture system will be encrypted. The electronic data capture system is located at a secure premise, has restricted access and maintains a continuous advanced mirroring back-up system on secure operating servers.

Ethical aspects and informed consent. Consent will be specifically sought for follow-up participation and the use and storage of de-identified data for the current research project. A local study coordinator will approach eligible subjects and will explain (1) the purpose of the study, (2) the procedures, (3) the risk/benefits, (4) alternatives to participation, (5) and their confidentiality. The study monitor will emphasize that the current non-experimental study does not influence the type or quality of treatment or provided

healthcare by any means. Each subject choosing to participate will sign (or will approve a relative to sign) and date an informed consent form. Either in writing or verbally and at all times enrolled patients will have the right to withdraw their consent. A register will be kept of all spinal column injury patients with spinal cord injury who are ineligible, not consenting to participate or withdraw from the study. The reason for ineligibility, not consenting and consent withdrawal will be documented along with the following core patient characteristics: age, gender and level and severity of spinal cord injury.

Given the lack of standard operating procedures for the assessment of non-experimental clinical studies by ethics committees across European countries,[48] the need for approval of the current study protocol and consent forms will be checked for each participating investigational site separately.[49]

DISCUSSION

The conduct of a surgical randomized controlled trial on the acute management of tSCI is a very challenging, if not infeasible, undertaking. For this reason we designed a prospective, comparative cohort study protocol. One of the major limitations of non-randomized comparative studies is the susceptibility to confounding by indication. With use of advanced statistical approaches, including the use of a propensity score, we try to correct and even reduce the magnitude of selection bias.

The diagnostic and prognostic role of MRI in the management of tSCI patients remains a heavily debated topic. Although some specialists perform MRI in all alert patients presenting with signs of spinal cord injury,[50] others rely on neurological examination and CT only and order MRI in those cases where neurological findings do not correspond with the injury pattern as discerned on CT images.[14] Given this variety in diagnostic work-up, and also the fact that MRI does not provide information relevant for the primary study endpoint under study, pre-decompression MRI is not considered as a mandatory investigation in the current study. This approach will also enable us to compare the time between hospital admission and treatment between institutions with a 'routine MRI protocol' and institutions without such a protocol.

To our knowledge, we are the first authors defining the successfulness of a decompression of the traumatic spinal cord in such detail. As opposed to the pre-surgical work-up, MRI is mandatory after the intervention to confirm the successfulness of the decompression. As not all tSCI patients with spinal column injury present with a (continued) compression of the neurological structures, this may be interpreted as an inconsistency in the diagnostic work-up and a limitation of the study design. However, the intention of this study is not to demonstrate to what extent a certain compression of the cord has been decompressed by comparing two MRI series, but rather to demonstrate the effect of the timing of a confirmed decompressed, or non-compressed, spinal cord after the intervention and relate this to neurological outcomes. Nonetheless, an ancillary analysis will be performed in those patients with available pre-surgical MRI to assess the relation between the extent of pre-surgical spinal cord compression and neurological outcomes. Finally, the impact of metal-induced susceptibility artifacts on the accuracy of TSA measurements—due to encoding difficulties in MRI and to beam hardening in CT—warrants careful consideration and optimization of imaging processing.[51,52]

It is planned to commence patient recruitment at the first investigational sites autumn 2012. Aiming for a total of 10 participating investigational sites and considering the tSCI incidence rate for each AIS grade specifically, it is expected that the study will take approximately 5 years to complete. At the time of submission of this paper not all participating centers have yet been identified, and funding is still being sought from local and international sources. As reported throughout this study protocol, this prospective, comparative cohort study will adhere to key methodological principles for minimizing bias and reducing the impact of confounders. The findings of this study will be reported according to the STROBE statement.[53] A significant difference in safety and/or efficacy endpoints will provide meaningful information to clinicians, as this would confirm the hypothesis that rapid referral and treatment in specialized centers result in important improvements in tSCI patients.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Author contributions. JJvM drafted the study protocol and manuscript. AH contributed to the design of the study protocol. GB and MS provided feedback during the development of the study protocol. AH, GB and MS co-authored the writing of the manuscript. All the authors read and approved the final manuscript. For the primary report of the clinical results, the authorship will be determined according to the recommendations of the International Committee of Medical Journal Editors where special attention will be paid to collaborators' intellectual and operational contribution (including the number of patients with complete follow-up in each center). GB is the current chairman of AOSpine Europe Research Commission.

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