

The Effect of Extracorporeal Shock Wave Therapy (ESWT) In Acute Traumatic Complete (AIS A) And Incomplete (AIS B-D) Cross-Sectional Lesions On Motor And Sensory Function Within Six Months After Injury: A Two-Arm Three-Stage Adaptive, Prospective, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Background: The pathological mechanism in acute spinal cord injury (SCI) is dual sequential: the primary mechanical lesion and the secondary injury due to a cascade of biochemical and pathological changes initiated by the primary lesion. Therapeutic approaches have focused on modulating the mechanisms of secondary injury. Despite extensive efforts in the treatment of SCI, there is yet no causal, curative treatment approach available.

Extracorporeal shock wave therapy (ESWT) has been successfully implemented in clinical use. Biological responses to therapeutic shock waves include altered metabolic activity of various cell types due to direct and indirect mechanotransduction leading to improved migration, proliferation, chemotaxis, modulation of the inflammatory response, angiogenesis and neovascularization thus inducing rather a regeneration than repair.

Objective: The aim of this clinical study is to investigate the effect of ESWT in humans within the first 48 hours after an acute traumatic SCI, with the objective to intervene in the secondary injury phase in order to reduce the extent of neuronal loss.

Study design: Two-arm three-stage adaptive, prospective, multi-center, randomized, double-blind, placebo-controlled study.

Methods: The study has been initiated in July 2020 and a total of 82 patients with acute traumatic SCI will be recruited for the first stage in 15 participating hospitals as part of a two-armed three-stage adaptive trial design. The focused ESWT (energy flux density: 0.1 - 0.19 mJ/mm², Frequency: 2-5 Hz) is applied once at the level of the lesion, five segments above / below and on the plantar surface of both feet within the first 48 hours after trauma.

The degree of improvement between the follow-up examinations over six months in motor and sensory function is the primary endpoint of the study. Secondary endpoints include routine blood chemistry parameters, the degree of spasticity, the ability to walk, urological function, quality of life, and the independence in everyday life.

Hypothesis: The application of ESWT activates the nervous tissue regeneration involving a multitude of various biochemical and cellular events and leads to a decreased neuronal loss. ESWT might contribute to an improvement in the treatment of acute traumatic SCI in future clinical use.

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Background

Spinal cord injury (SCI) results in devastating, lifelong effects on the health and quality of life of affected patients and high financial burdens on affected individuals, their families and the health care system in

general. Beyond the primary trauma of the spinal cord, secondary health complications lead to considerable reduction in quality of life.[11]

For traumatic spinal cord injury (tSCI), an estimated global annual incidence rate of 23 per million is reported.[11], [12] In Western Europe there are around 16 people per year and one million people who suffer from a tSCI. Globally, the incidence as well as the prevalence of tSCI is low.[12]

In developed and developing countries, men between the age of 18 and 32 are most affected by tSCI. In developed countries, due to an aging population, males and females above the age of 65 are affected by falls from low altitudes (one meter or less).[12] Age at injury has increased from 28.7 years in the 1970s to 42.2 years during 2010 to 2014 in the US.[13] Worldwide, the mean age of patients sustaining a tSCI is reported as 33 years.[14]

The leading causes of tSCI are road traffic accidents, falls and violence. Overall, road traffic collisions are the most common cause of tSCI.[13], [15] While transport is a significant cause of SCI in all age groups, falls are the most common cause over the age of 60.[15] Although, sports-related injuries account for only 8.7% of all SCI, they represent the second most frequent cause of tSCI in those under the age of 30 years. [16], [17] Literature reports that sports with high risk of sustaining SCI are diving, skiing, rugby, horseback riding, hockey, American football and snowboarding.[11], [17] Cervical injury is by far the most predominant level of injury for hockey (81.5% cervical), skiing (81.1%), diving (98.2%), and American football (96.3%). Over half of injuries due to horseback riding and snowboarding accidents affect the thoracic or lumbosacral neurological level.[11]

One-third of patients with SCI are reported to be tetraplegic and more than 50% presenting as AIS A grade (= a complete lesion).[14], [17] The worldwide overall sex distribution (men/women) is reported to be 3.8/1 independent of injury cause and age.[14] The proportion of cervical injuries has increased over the last decades.[18]

Improvements in diagnostics, pre-hospital management, fast transfer to specialized units, good shock management, the potential for early surgical decompression, and advanced medical rehabilitation methods result in higher life expectancy and lower mortality rates in high-income countries.[7], [15] Though, life expectancy after SCI is reduced compared to the general population. The mortality depends on the level and severity of the lesion and the availability of clinical care. Mortality is particularly high in the first year after injury.[15]

Despite worldwide intensive efforts, SCI remains a devastating condition for which there is yet no causal treatment available.[2]

1.1 Pathophysiology

Based on imaging and histology of injured human spinal cord, tSCI is classified as a “contusion with cavity formation”, “massive compression”, or “laceration”. [2] The primary injury mechanism involves the

initial mechanical damage due to local deformation and energy transformation that occurs within the spinal cord at the moment of injury, which is irreversible.[5] This primary mechanical injury leads to a cascade of biological events, described as “secondary injury”, which occurs within minutes to weeks after the injury and further compromises neurological function.[2]

Injuries to nervous tissue are followed by a rapid process of degenerative events called Wallerian degeneration in anterograde direction from the initial injury site.[19], [20] Wallerian degeneration as one of the initial pathological results of axotomy is considered an unavoidable consequence of SCI.[21] In the central and peripheral nervous system, the early phase of Wallerian degeneration includes the granular disintegration of the cytoskeleton, in which the cytoskeletal proteins of the axon are rapidly degraded to granular residues. This occurs between 18 and 48 hours after injury and progresses away from the lesion site.[20] The proximal nerve stump retrograde from the initial lesion is also affected and chromatolysis reaches up to the first Ranvier node.[19] Numerous biochemical mechanisms that might explain the progressive post-traumatic damage of spinal cord tissue have been postulated: Vascular changes including hemorrhage, vasospasm, thrombosis, loss of autoregulation, breakdown of blood brain barrier and infiltration of inflammatory cells leading to edema, necrosis and ischemia; free radical formation and lipid peroxidation that cause oxidative death in spinal cord neurons; disruption of ionic balance; glutamate excitotoxicity; apoptosis; and an inflammatory response following the trauma. Subsuming, the secondary injury leads to neurological impairments in both anterograde and retrograde directions owing to white matter demyelination, gray matter dissolution, connective tissue deposition and glial scar formation. The glial scar acts like a physical barrier, preventing axons to grow through it.[2]

In addition to loss of sensory and motor function, central neuropathic pain in many cases is a consequence of SCI due to maladaptive synaptic circuits in the spinal dorsal horn that result in neuronal hyperexcitability. Pain transmission in the spinal dorsal horn is persistently increased due to neuronal hyperexcitability. These neurochemical and neuroanatomical changes often elicit chronic pain syndromes after SCI.[22], [23]

It has been postulated, that mechanisms of secondary injury are preventable, and potentially reversible. [2], [5], [7]

1.2 Classification

The American Spinal Injury Association (ASIA) International Standards for Neurological Classification of SCI (ISNCSCI) is the standard for assessing and classifying the neurological level and extent of SCI. The classification system contains three elements: ASIA Impairment Scale (AIS A-E); motor score (based on the neurological examination of muscle function); and sensory score (based on the neurological examination of sensory function).[15], [24]–[27]

1.3 Extracorporeal shock wave therapy (ESWT)

Shock waves are short-term acoustic pressure pulses that travel through tissue in a wave like manner. Shock waves can be produced by electrohydraulic, electromagnetic and piezo-electric sources.

Extracorporeal shock wave therapy is subdivided into the categories "high-energy" (for bone tissue) and "low-energy" (for soft tissue) according to the energy flux density measured in mJ/mm². Another classification is "focused" or "de-focused" depending on the reflector shape. Defocused shock wave applicators provide a larger diameter of the shock wave field and therefore enable the treatment of a larger tissue area. Focused shock waves allow for concentration of energy at one small therapeutic area of interest and are typically used for lithotripsy and to foster bone healing.[19], [28]

The physical impact of shock waves including pressure, tensile and shearing forces are translated to complex biochemical signals. This signaling process is called mechanotransduction. The underlying mechanism of mechanotransduction is that organ formation and tissue regeneration is the dynamic interaction between a cell and its microenvironment, including forces applied to them. [19], [29]

Several biological responses to therapeutic shock waves have been postulated, including angiogenesis and neovascularization, anti-inflammatory and antimicrobial effects, the release of growth factors, the activation of mesenchymal stem cells, stimulated cell proliferation and differentiation, and suppression of nociception.[19], [29], [30]

ESWT has been clinically implemented in the treatment of chronic wounds, venous or diabetic ulcers, ischemic heart disease and to stimulate and reactivate bone healing in non-healing fractures and the integration of skin grafts.[19], [28], [30], [31]

In December 2018, STORZ MEDICAL has received the CE approval for transcranial pulse stimulation for the treatment of patients with Alzheimer's disease. This technology allows a focused stimulation of the brain at a depth of up to 5 centimeters.[32]

1.4 Pre-clinical and clinal data on the effect of ESWT on nerve regeneration

Hausner et al. found significantly greater numbers of myelinated fibers in peripheral nerves after a single ESWT application in an experimental model on rats after a homotopic nerve autograft into the sciatic nerve.[8]

Lobenwein et al. performed a spinal cord ischemia model in mice in their study. ESWT was applied immediately after surgery and the treated animals showed a significantly better motor function and decreased neuronal degeneration compared to the control group within the first 7 days after surgery. In the same study, ESWT was applied to human spinal cord slices ex vivo two hours post-mortem. They found significantly higher numbers of cells in the treatment group at 24 and 48 hours after treatment compared to the control slices.[9]

Yamaya et al. investigated the effect of low-energy ESWT for the duration of three weeks on a thoracic spinal cord contusion injury model in rats. Animals in the ESWT group demonstrated significantly better locomotor improvement and reduced neuronal loss compared to the control animals at 7, 35, and 42 days after contusion.[10]

Lohse-Busch et al. conducted a study on the effect of focused transcranial ESWT in patients with unresponsive wakefulness syndrome (apallic syndrome). At study inclusion patients had suffered from apallic syndrome for more than five years. The ESWT was applied to the neurocranium three times a week for four weeks with an energy flow density between 0.2 and 0.3 mJ/mm². An improvement of 135.9% in the German Coma Remission Scale (KRS) and 43.6% in the Glasgow Coma Scale (GCS) was observed after four to eight (average of 4.5) treatment series. No adverse effects and no triggering of epileptic seizures have been reported.[33]

Davis et al. found significantly reduced inflammatory cell infiltrate of both neutrophils and macrophages in ESWT-treated burn wounds in a murine burn wound model 24 hours following burn injury. The ESWT was applied once one hour after the burn injury. This study found, that a one-time ESWT significantly downregulated the expression of several acute-phase pro-inflammatory cytokines in mice.[34]

Holfeld et al. reported, that expression of the anti-inflammatory cytokine IL-10 was significantly enhanced at two, four and six hours after shock wave therapy which was applied to human umbilical vein endothelial cells.[35]

Sukubo et al. investigated shock wave application to monocyte-derived macrophages in vitro and found, that shock waves did not induce activation of resting macrophages at any energy level used. Shock wave application also affected cytokine and chemokine production, inducing in particular a significant increase in IL-10 and reduction in IL-1b production. The authors concluded that macrophage exposure to low energy ESWT reduces the expression of pro-inflammatory cytokines and promotes the acquisition of anti-inflammatory cytokines.[36]

Summarizing these results, it can be hypothesized, that a one-time ESWT modulates the inflammatory response in several tissues when applied within the acute phase of injury.[34], [35], [37] Also, no neural tissue damage, such as hemorrhage or vacuole formation was observed in histological analysis after the application of low-energy ESWT to the spinal cord in a spinal cord contusion model in rats.[10]

1.4.1 Clinical data

Extracorporeal shockwave therapy (ESWT) in patients with chronic complete paraplegia (AIS A) at the thoracic level

In 2015 recruitment for a multi-center prospective randomized double-blind clinical study was started including patients suffering from chronic paraplegia (lesion between THII and THX, AIS A = complete central lesion) at least for 1 year after the initial trauma without spontaneous recovery within the last six months. In general, a spontaneous recovery of the senso-motoric function is decreasing with the time from injury and is therefore not expected in the study population. In these cases, treatment options are mainly limited to improvement of the quality of life.

Currently 34 patients from intended 50 have been included in the study and recruitment is ongoing until the end of 2020. Therefore, results are not available yet. Until now, no severe side effect or adverse effect occurred to the study participants. Besides the multi-parametric evaluation (neurological, neurophysiological, clinical as well as functional), blood samples have been collected to multiplex protein assessment miRNA analysis.

1.4.2 Unpublished preliminary results in experimental studies

ESWT in sub-acute and chronic traumatic spinal cord injury in rodents

At the same time to the previously mentioned clinical study experimental studies in rodents have been started in order to analyze biological pathways induced by the application of ESWT. Therefore, a standardized contusion model was established in rodents at the thoracic level. In a first safety study, it was proved, that low-energy ESWT did not cause any damage to neither neural, nor adjacent tissue (i.e. lung).

In the following studies, ESWT was applied three times within three weeks either two weeks after spinal cord contusion (= sub-acute model) or after five weeks (= chronic model). Animals were monitored in their functional abilities (BBB-score and Catwalk®) and blood samples were drawn for bio-molecular analysis. The experiment was determined 12 weeks after the first ESWT and tissue samples were collected for further analysis.

In the functional BBB-score a significant difference could be detected between the control group and the two ESWT groups (sub-acute and chronic). Within both ESWT groups a significant improvement of the functional abilities could be clearly demonstrated after treatment onset (Fig. 1).

A variety of different imaging methods, which were partly developed and further established, were applied in order to determine (ultra-)structural tissue damage induced by the initial contusion impact concomitant with potential influence of ESWT (Fig. 2). A decrease of the cysts and syrinx volumes could be detected in the ESWT groups compared to the control group lacking a therapeutic regime.

A combination of this imaging technology with histological (MSB, HE) as well as immunohistochemical stainings (neurofilament, GFAP, acetylcholinesterase) additionally allows to draw conclusions about the regenerative ability of ESWT. First analysis shows promising results implicating the regenerative potential of ESWT.

To evaluate the therapeutic effect of ESWT on a biomolecular level, screening for miRNA candidates showing different expression patterns in serum samples was performed. In total, almost 190 targets were gathered. Several significant altered expression patterns could be detected in particular before and after ESWT. Especially miRNAs coding for neuroprotection and anti-inflammatory responses (and as a response anti-scarring) show significant changes in the samples analyzed so far, all suggesting and indicating for the regenerative potential of ESWT in the indication of spinal cord injury. (Fig. 3)

1.4.3 Safety and efficacy study: Shock wave therapy in patients with ischemic spinal cord injury

Holfeld and colleagues are working on an ongoing controlled, multicenter, open trial assessing the safety and efficacy of extracorporeal shock wave therapy in patients with ischemic spinal cord injury after aortic surgery or endovascular aortic repair. The study started in July 2017. Until now, five patients have been included in the study and no severe side effect or adverse effect occurred to the study participants.

1.4.4 Pilot study: The effect of ESWT on peripheral nerve regeneration

Hausner et al. are currently working on a prospective randomized double-blind pilot study in which the authors investigate the effect of ESWT on nerve regeneration after acute traumatic complete dissection of either the median or ulnar nerve and subsequent microsurgical nerve coadaption. Until now, nine patients have been included in the clinical trial and no severe side effect or adverse effect due to the ESWT occurred to the study participants.

1.5 Need for the study

Despite extensive efforts in the treatment of SCI, there is yet no causal, curative treatment approach available.[2] The current standard therapy in Austria is the early surgical decompression and stabilization [5]–[7] and in some cases the additional administration of steroids (methylprednisolone) in the acute phase of the injury (in the first 24–48 hours, the latter being controversial)[2], [38]–[41].

ESWT is already being used in clinical practice such as chronic wounds, non-healing fractures, tendinopathies, myocardial ischemia and lithotripsy. The application after acute spinal cord injury would thus be an expansion of indication for this therapy method, which has already been used in Austria for several years.[19], [28], [30], [42]–[44]

ESWT could provide an easy-to-use, risk-free therapeutic method in the treatment of acute SCI in addition to surgical decompression with the aim of optimizing the clinical outcome.

The underlying study aims to investigate the effect of ESWT after acute traumatic spinal cord injury in humans within 48 hours of trauma in order to intervene in the secondary injury phase with the objective to reduce the extent of neuronal damage.

1.6 Risks and benefit

Previous literature reports, that in the planned energy flux density and pulse range, no therapy-associated tissue damage has been observed neither in neural tissue nor in muscle / tendon tissue - even with repetitive application.[28], [33], [42], [44]

We consider the application of low-energy ESWT after acute traumatic SCI ethically justifiable because previous studies have shown no adverse events and a positive impact on the central and the peripheral

nervous system.[8], [10], [19], [28], [42] The risk to potential benefit ratio is considered in favor of the patients benefit.

Study Objectives

2.1 Primary objective

The primary aim of this study is to investigate whether a greater improvement in motor and sensory function (the AIS grade) can be achieved in patients after spinal trauma (AIS A-D) by applying a single extracorporeal shockwave therapy compared to the control group.

The primary endpoint is the degree of motor and sensory impairment in the American Spinal Injury Association (ASIA) Impairment Scale (AIS) and the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) Score.

The results are compared over the course of time in both groups between the treatment group (one-time low-energy focused ESWT) and the control group (placebo-ESWT).

2.2 Secondary objective

The secondary objectives include the assessment of changes in spasticity, the ability to walk, urological function, quality of life and independence in everyday life over time and in comparison between the groups.

Design Of The Clinical Trial

3.1 Description of the clinical trial

This is a two-arm three-stage adaptive, prospective, multi-center, randomized, double-blind, placebo-controlled clinical trial according to the MPG (Medizinproduktegesetz [Medical Devices Act])" which is designed as a two-arm three-stage adaptive trial.

Fourteen treating hospitals and three rehabilitation centers in Austria and Germany will participate. The allocation of the study groups will occur by means of a block randomization, in order to guarantee the best possible balance between the treatment group, the control group and the treating hospitals. The study groups are comprised of a treatment group (extracorporeal shock wave therapy by means of electrohydraulic shock wave generation) and a control group (placebo ESWT).

To gain as homogenous groups as possible, a stratified block randomization with a block size of four will be done. The assignment to treatment and placebo group will be made in a ratio of 1:1. For stratification, three different neurological levels of injury will be used:

1. Cervical injuries: C1-C8

2. Thoracic and lumbar injuries (T1-L1)
3. Peripheral nervous system injuries (Cauda equina and conus medullaris syndromes[45]; L2-S5)

Recruitment of patients takes place continually at admission to acute care in one of the 14 participating hospitals (13 in Austria, 1 in Germany). Patients and assessors of study relevant data are blinded to group allocation. The operating room staff and persons involved in the application of the study intervention are not blinded to group allocation and are required to keep it as a secret.

3.2 Study endpoints

3.2.1 Primary endpoint

It is assumed that patients who suffer acute SCI regain more of their motor and sensory functions because of treatment with EWST than patients in the control group. To measure this, the degree of motor and sensory improvement within six months, compared to the baseline is determined. Thus, the primary composite endpoint is calculated as the difference between the upper and lower extremities motor score (ULMS + LLMS), light touch (LT), and pin prick (PP) at two points in time.

$$\text{delta.TMSC} = \text{TMSC}_{\text{after 6 month}} - \text{TMSC}_{\text{at baseline}}$$

TMSC = Total motor and sensory score

3.2.2 Secondary (exploratory) endpoints and control variables

- AIS classification
- Degree of spasticity according to Penn Spasm Frequency Scale
- Walking ability
 - WISCI II (Walking Index for Spinal Cord Injury II)
 - TUG (Timed Up and Go Test)
 - 10-meter timed walk
 - 6-minute walk test
 - Urological function
 - Hand motor function
 - Plantar reflex
 - Independence in everyday life of patients is assessed with the Spinal Cord Independence Measure (SCIM II)
 - The number of study related adverse events (AEs) are measured according to NCI CTCAE, version 5.0.

3.3 Schedule

Recruitment of the study participants will begin after receiving a positive vote by the ethics committee. The planned start is fall 2019. Thereafter, recruitment will take place on an ongoing basis by admission of patients with acute spinal cord injuries. Recruitment duration is three years in total.

For patients who are included in the study, the follow-up phase after the baseline assessment will take approximately six months.

A planned interim analysis will be carried out after 41 patients have been included in each of the both groups and all follow-up examinations have been completed. A further interim analyses will be planned after 82 patients. With unexpected major effects, the study will be prematurely terminated or, with low chances of success, will be cancelled. An unplanned interim analysis will take place, should adverse events or side-effects occur.

3.4 Requirements for participating centers and examiners

Participating hospitals and rehabilitation centers are highly specialized in the treatment of patients with SCI. All necessary equipment for the implementation of the study are equally present in all participating hospitals. Additionally, as part of the study, the hospitals will be equipped with an electro-hydraulic shock wave device.

The investigators involved in the study (specialists in neurology and trauma surgery and physiotherapists) are sufficiently familiar with the diagnostic methods. In addition, training is provided at all participating centers before the start of the study:

- For medical doctors: application of the ESWT
- For medical doctors and physiotherapists: neurological assessment of sensory and motor function according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) of the American Spinal Cord Injury Association (ASIA)

3.5 Premature termination of the clinical trial

The clinical trial is terminated prematurely if:

- the patient recruitment rate is inadequate to reach the aims of the study
- serious, unexplained problems with the quality of the collected data occur
- unpredictable circumstances have occurred in the respective test center which do not allow continuation of the clinical trial
- the early detection of superiority or inferiority of the treatment group (as defined by interim analysis) is provided

- unacceptable risks and toxicities have occurred (decision after new risk analysis and evaluation of the test product)
- new scientific information comes up during implementation of the clinical trial which does not allow the continuation of the clinical trial for ethical or scientific reasons

Study Population

Included are female and male patients with an acute spinal cord lesion regardless of the neurological level of the lesion. Patients with either complete (AIS A) or incomplete (AIS B - D) lesion are included. A minimum age of 18 years must be reached at enrollment. No other age limit was defined. A gender distribution in favor of male patients is expected due to the higher incidence (men / women = 3.8 / 1) of traumatic SCI.[14]

4.1 Sample size

As already mentioned, a two-arm three-stage adaptive trial design is planned. This adaptive design consists of two interim phases (stage 1 + 2) and a confirmatory phase (stage 3). The objective of the first two stages is to obtain information regarding the effect of the treatment in the treatment group and to provide the investigator with the opportunity of stopping the trial early due to futility or efficacy based on accrued data. As a result, the possibility or necessity of shortening the study could arise.

In addition, this design allows for adjustments in the Statistical Analysis Plan (SAP). In particular, level 1 could result in a more precise definition of the exclusion criteria, and a re-evaluation of the sample size might be required. If so, an application for amendment will be done.

The basis for calculating an appropriate sample size is an expected treatment effect. Due to a lack of knowledge about the impact of ESWT on sensory function (SF) and motor function (MF), the following approach proposed by Jaki et al.[46] is used: The probability that a randomly selected person in the treatment group observes a better result than a random person in the control group is $p = 0.6$ (60 percent). The uninteresting effect is chosen with $p_0 = 0.5$ (= 50%), which means that both the treatment and the control work equally well. The selected assignment ratio for treatment and control is 1:3. With a one-sided error rate of 5% and a planned power of 80%, the following design parameters could be calculated. For the upper and lower limits, the triangle test is selected.[47]

A more detailed explanation can be found in Chap. 8.

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	Stage 1	Stage 2	Stage 3
Cumulative sample size (control):	41	82	123
Cumulative sample size (treatment):	41	82	123
Maximum total sample size:	246		
Upper bound	2.13	1.89	1.85
Lower bound	0.00	1.13	1.85
p-value for H1 ((stopping for) success)	0.018	0.031	0.033
p-value for H0 (stopping for a lack of efficacy)	0.500	0.130	
Continue as planned at stage 1: $0.500 > p > 0.018$			
Continue as planned at stage 2: $0.130 > p > 0.031$			
The calculation was done with R package MAMS.			

4.2 Inclusion criteria

- Patients with acute traumatic spinal injuries who are awake, responsive, and oriented at admission
- Patients from the age of 18 years
- Admission to hospital within 24 hours after injury
- Written consent to participate in the study
- Participation in the Austrian Spinal Cord Injury Study (ASCIS)-Registry (only for the Austrian hospitals)

4.3 Exclusion criteria

- Patients who cannot cooperate or are not capable to give consent to participate
- Serious traumatic brain injuries that prevent accurate participation in study procedures and/or adequacy of informed consent
- Participation in other interventional clinical trials
- Serious concomitant injuries that prevent the neurological initial assessment
- Preexisting neurological conditions that affect the primary endpoint of the study and potentially mask or reduce the therapeutic effect of the ESWT application
- High dose administration of corticosteroids such as methylprednisolone, dexamethasone, etc.
- Complete spinal cord transection
- Patients with pacemakers or implantable defibrillators
- Patients who are using devices which are sensitive to electromagnetic radiation

- (potential) Pregnancy
- Patients with tumours
- Patients with severe coagulation disorders

4.4 Reasons for patient exclusion after enrollment (drop-out)

Patients have the option to leave the clinical trial at any time without giving reasons.

Additional neurological diseases or diseases that can cause damage to the nervous system and that are diagnosed or communicated after enrollment and the respective patient was therefore included in the study by error, lead to exclusion from the study.

4.4.1 Pre-existing deficits leading to the subsequent exclusion of study:

- Pre-existing functionally severe psychiatric disorders
- Neurological pre-existing diseases that affect motor and sensory function and therefore might reduce or mask the effect of the study intervention or impede the study related examinations:
 - Non-traumatic paresis or plegia
 - Peripheral nerve lesions above the level of the lesion
 - Radicular lesions
 - Pre-existing myelopathy with neurological symptoms which were already present prior to the acute spinal cord injury
 - Demyelinating diseases

Study Procedures

5.1 Consent to participate

If a patient presents in one of the participating hospitals, and meets inclusion and exclusion criteria, he or she is invited to participate in the study given that the study-specific procedures do not disturb the acute care of the patient. Every patient has to give his or her written informed consent to participate in the trial. The investigator, his / her representative, must inform the patient that there is no obligation to participate in the clinical trial and the option to leave the clinical trial at any time without giving reasons. If the patient has received and understood all information, there is sufficient time for questions and the patient agrees to participate, the patient should date and sign the declaration of consent.

No activities relevant to the clinical trial will be undertaken before the consent of the patient has been obtained. A copy of the signed consent form will be given to each patient. The original signed version will

be kept in the test center, as well as another copy in the medical files.

If new safety analyzes lead to a significant change in the risk analysis and risk assessment of the test product, the declaration of consent must be reviewed and, if necessary, revised.

5.1.1 Consent for adult patients who are physically incapable of sign the consent

For patients who are physically incapable to sign the consent to participate by their selves, but are awake, oriented and willing to participate, the investigator and one additional witness confirm the verbal consent with their signature.

5.2 Pre-Screening

- Check fulfillment of inclusion and exclusion criteria
- Written informed consent

5.3 Screening

- Pregnancy test for women with child bearing potential

5.4 Baseline examination pre-operative

- Short medical history
- AIS/ISNCSCI
- Diagnosis SCI according to radiological imaging via CT and/or X-Ray and/or MRI:
 - Level of fracture
 - AOSpine fracture classification
 - Cause of injury to the spinal cord (if no fracture is present): free text or “not specified”
 - Posterior vertebral wall affected? yes/no
 - Mechanism of injury (penetrating, not penetrating, not specified)
- Priapism (for male patients only): yes/no
- Plantar Reflex
- Primary closed manual reduction prior to surgical intervention: yes/no
- Documentation of parameters from routine blood chemistry
- OPTIONAL: Baseline blood sample at admission and prior to the surgical intervention and the application of the ESWT: one serum tube (8ml)

- Block randomization (Group allocation)

5.5 Operative treatment

5.6 Study intervention

- Opening of randomization envelope
- ESWT: Begin, number of impulses, energy flux density, frequency, end, local reactions

5.7 Post-operative documentation

5.7.1 Surgical interventions and intra-operative diagnosis

- Surgical approach: dorsal/ventral/combined
- Laminectomy: yes/no
- Direct surgical reduction of retropulsed fragments of the posterior vertebral wall: yes/no
- Corporectomy: yes/no
- Surgical decompression: Level of spinal segments (f.e. T2 – T5)
- Intra-operative findings: Opening of the dura: yes/no
- Intra-operative complications
- Implant-related revision surgery necessary: yes/no

5.7.2 Post-operative imaging

- Post-op CT and/or X-Ray and/or MRI (as part of standard clinical care)
- Restoration of alignment: yes/no
- Fracture morphology and instability criteria according the AO Spine classification

5.7.3 Time sequence of acute care chain

- Accident / injury time (date, time)
- Patient transport directly from the injury site to a study-center: yes/no
- Admission to the emergency room (date, time)
- Beginning of surgical intervention (skin incision) (date, time)
- Duration of surgery (minutes)
- Complete drug anamnesis: NSAID's, antidepressants, anticonvulsants, opioids, spasmolytics, sedative-hypnotics, neuroleptics, anticoagulants (drug name and dosage for all)
- Documentation of AEs and SAEs

5.8 1. Follow-up exam, 24–72 hours post-operative

- Comprehensive medical history: etiology
- Assessment of pre-existing neurological deficits
- Revision and completion of time sequence of acute care chain (if not properly documented at baseline)
- AIS/ISNCSCI
- Plantar Reflex
- Gait analysis
- SCIM (Spinal Cord Independence Measure)
- WISCI II (Walking Index for Spinal Cord Injury II)
- CCI (Charlson Comorbidity Index)
- ISS (Injury Severity Score)
- Urological function
- Drug anamnesis: NSAID's, antidepressants, anticonvulsants, opioids, spasmolytics, sedative-hypnotics, neuroleptics, anticoagulants
- Handing out patient diary (spasticity rating according to Penn Spasm Frequency Scale, subjective and objective other changes and special events)
- Documentation of parameters from routine blood chemistry
- Blood sample (only if baseline blood sample was collected): one serum tube (8ml)
- Documentation of AEs and SAEs

5.9 2. Follow-up exam, Day 14–21

- AIS/ISNCSCI
- Plantar Reflex
- Gait analysis
- SCIM (Spinal Cord Independence Measure)
- WISCI II (Walking Index for Spinal Cord Injury II)
- Urological function
- Retrospective assessment of physical activity prior to the injury
- Drug anamnesis: NSAID's, antidepressants, anticonvulsants, opioids, spasmolytics, sedative-hypnotics, neuroleptics, anticoagulants
- Assessment of hand motor function in those patients who have lesions above T5
- Differentiation: nerve root lesion vs. spinal cord lesion
- Check patient diary
- Documentation of parameters from routine blood chemistry
- Blood sample (only if baseline blood sample was collected): one serum tube (8ml)

- Planned inpatient rehabilitation: Where? When?
- Documentation: date of discharge from the hospital
- Documentation of AEs and SAEs

5.10 3. Follow-up exam, after 3 months +/-2 weeks

Patients who undergo rehabilitation in one of the three participating rehabilitation facilities in Austria have their follow-up exams there. All other patients are invited to the primary care center in which they received their initial treatment.

- AIS/ISNCSCI
- Plantar Reflex
- Gait analysis
- SCIM (Spinal Cord Independence Measure)
- WISCI II (Walking Index for Spinal Cord Injury II)
- Urological function
- Drug anamnesis: NSAID's, antidepressants, anticonvulsants, opioids, spasmolytics, sedative-hypnotics, neuroleptics, anticoagulants
- Assessment of hand motor function in those patients who have lesions above T5
- Differentiation: nerve root lesion vs. spinal cord lesion
- Check patient diary
- Documentation of parameters from routine blood chemistry
- Blood sample (only if baseline blood sample was collected): one serum tube (8ml)

5.11 4. Follow-up exam, after 6 months +/-2 weeks

- AIS/ISNCSCI
- Gait analysis
- SCIM (Spinal Cord Independence Measure)
- WISCI II (Walking Index for Spinal Cord Injury II)
- Urological function
- Stability of osteosynthesis according to X-Ray/CT
 - Loosening of osteosynthetic implants? yes/no
 - Revision surgery necessary? yes/no
- Drug anamnesis: NSAID's, antidepressants, anticonvulsants, opioids, spasmolytics, sedative-hypnotics, neuroleptics, anticoagulants
- Assessment of hand motor function in those patients who have lesions above T5

- Differentiation: nerve root lesion vs. spinal cord lesion
- Handing in patient diary
- Blood sample (only if baseline blood sample was collected): one serum tube (8ml)

Study Assessments

6.1 Concomitant medication

Any medication is documented as part of standard clinical care including dose, duration and mode of administration. Patients are encouraged to continue their medication after discharge in the prescribed form. If there is a change during the six months observation period, this has to be noted in the patient diary, stating the name of the drug, the dosage and the duration of the intake.

In the study visits 5–8 (Follow-up exams 1–4) the following categories of drugs are assessed: NSAID's, antidepressants, anticonvulsants, opioids, spasmolytics, sedative-hypnotics, neuroleptics, and anticoagulants including drug name and dosage.

The administration of corticosteroids in acute spinal cord trauma is controversial and the indication is discussed in the literature.[2], [38]–[41] If physicians decide to administer corticosteroids in high dosage, a participation in this study is no longer possible for those patients.

No additional medication is administered within the study.

6.2 Patient diary

The patient diary is checked by the examiner during each study visit and reviewed and discussed with the patients. The patient diary is handed out to every patient during the first post-operative days at the first study visit. Patients are required to record the following variables: spasms by spasticity rating according to Penn Spasm Frequency Scale, medication (drug name and dosage) and any important subjective or objective changes in the neurological symptoms. The item spasms shall be documented on a weekly basis immediately after receiving the patient diary. Changes in medication or important events shall be documented depending on their occurrence after discharge from the hospital. All entries shall be dated.

6.3 Blood samples

Blood sample collection is optional at the baseline examination. If a blood sample has been taken at baseline, it is mandatory at every other follow-up visit until the 2nd follow-up between day 14 and 21. If no blood sample has been collected at baseline, no further blood samples are intended.

The blood tube (one 8 ml serum tube) is cooled after removal at 4°C. and then centrifuged at 3500g for about 15 minutes and then frozen to -80°C. Parameters to be analyzed are pro-inflammatory and anti-inflammatory cytokines and proteins (some examples are: S100b, IL-6, GFAP, NSE, tau, pNF-H) and serological biomarkers which are discovered and published during the time course of the study.

Blood sample collection will only take place in those hospitals where technical feasibility is given (-80° freezer and a centrifuge).

Additionally, parameters from routine blood chemistry shall be documented in the eCRF at baseline, the 1st, 2nd, and 3rd follow-up exam. The following markers will be included in the eCRF: WBC, lymphocytes, eosinophils, PLT, MCHC, MCH, MCV, albumin, ALP, creatinine, bilirubin, uric acid, calcium, chloride, co2 content, and sodium.

6.4 AIS/ISNCSCI

The spinal cord segment will be determined where the motor and sensory function still fully exists. Underneath this segment, the categorization is made into complete or incomplete.

The distinction between incomplete and complete paraplegia symptoms is only possible by the examination of the sacral segments (S4-S5, presence of an arbitrary anal sphincter contraction). Complete paraplegia (AIS A) can be diagnosed only when these segments completely fail in motor and sensory function.[15], [24]–[27]

6.5 Spasticity assessment

The degree of spasticity will be assessed with the self-rated Penn Spasm Frequency Scale (PSFS) [48]–[50] on a weekly basis in the patient diary.

We refrained from a clinically rated assessment of spasticity because the level of spasticity is known to vary over time, thus a single clinical assessment will not necessarily reflect accurately an individual's overall level of spasticity. The principal clinical outcome measure for spasticity has been the long-established Modified Ashworth Scale (MAS).[51], [52] Previous literature investigating the MAS reported poor inter-rater reliability [53]–[56] and a poor correlation with self-rated assessments of spasticity.[57] Joint contractions further decrease the reliability of the MAS.[56] Furthermore, the MAS does not account for the dependence of the resistance to the velocity of the movement and therefore does not comply with the concept of spasticity.[58]

6.6 Gait analysis

The following scores / gait tests are assessed in patients who regain walking ability with or without auxiliaries:

- WISCI II (Walking Index for Spinal Cord Injury II)
- TUG (Timed Up and Go Test)
- 10-Meter Timed Walk
- 6-Minute Walk Test

6.7 Urological function

- Permanent catheter: yes/no
- Sensation of urinary bladder filling: yes/no
- Documentation of the first attempt of bladder emptying: pos/neg, date
- Self-catheterization: yes/no
- Do you feel sensory innervation of the external genitalia (penis / labia)?
- Do you feel the change of the catheter or manipulations on the catheter?
- Do you feel the urge to defecate?
- Do you feel stool evacuation?
- Male patients: Have you had an erection since your injury?
- Female patients: Have you felt sexually aroused since your injury?

6.8 Hand motor function

An evaluation of hand motor function is assessed in those patients who have their lesions above the level T5.

- Nine-Hole Peg Test (NHPT) (if feasible)[59]
- Grasp and Release Test (GRT)[60]
- Additionally, the following grasp tasks are recorded:
 - Pinch grip: yes/no
 - Clenched grip: yes/no
 - Pencil grip: yes/no
 - Lumbrical grip: yes/no

6.9 Differentiation: nerve root lesion vs. spinal cord lesion

In order to differentiate between isolated nerve root lesions and spinal cord lesions, the following query shall be completed by a neurologist:

- Nerve root lesion very unlikely
- Combined lesion: spinal cord lesion and nerve root lesion
- Isolated nerve root lesion
- Not specified, because _____

6.10 Charlson Comorbidity Index (CCI)

Comorbidities are quantified with the CCI once during the inpatient stay within the first days. The CCI serves as possible explanatory variable in statistical analysis.

6.11 Injury Severity Score (ISS)

The Injury Severity Score (ISS) is recorded once during the inpatient stay (ideally pre-operatively; if this is not possible for reasons of timing, within the first 3 days) and serves as an explanatory variable.

6.12 Subjective physical activity prior to injury

Physical activity prior to the injury is assessed retrospectively at the second follow-up examination (day 14–21) using a subjective self-administered questionnaire. The level of physical activity is considered to be an important confounder on rehabilitation. The questionnaire has been compiled exclusively for this use case and this patient population. Different types of sport are listed, and the patients should give an estimation on how often, how long and at what intensity they used to participate in sports.

6.13 Imaging

The radiological examination by X-ray and/or CT and/or MRI is carried out as part of standard clinical care and data are used for study-related purposes as well.

Spinal fractures are graded according to AO-classification of the spine (AO 50–53).[61]–[63]

If fracture classification is not possible with data from the CT scan, an MRI is recommended and the following items should be assessed: i) spinal lesion, ii) bone marrow edema, and iii) ligamentous lesion (Fig. 4). For the evaluation of spinal lesions, the MR classification system based on axial images for cervical compressive myelopathy will be used.[64]

Ligamentous lesions will be quantified by assessment of the integrity of the posterior ligament complex. [65]–[67] Data from the MRI scan should be stored on a CD and sent to the Austrian Spinal Cord Injury Study (ASCIS) office in Salzburg, where a trained neuroradiologist will evaluate the images. This should provide a deeper insight in the prognostic value of fracture morphology.

The distance between skin surface and spinal cord should be measured at the level of the lesion according to CT to determine the pressure during ESWT treatment in order to reach the spinal cord sufficiently.

An MRI is mandatory as early as possible in cases suspicious for complete transactional medulla lesions according to neurological examination. In addition to the standard spinal imaging, a diffusion tensor imaging (DTI) medium resolution sequence with 3 b values is recommended.

Investigational Medical Device (Imd)

7.1 Name and Description of Investigational Medical Device

The Medical Device used in this trial is a shockwave generator produced by MTS Medical UG, 78467 Konstanz, Germany. The orthogold100® uses patented MTS Spark Wave® technology.

The shockwave generator orthogold 100® generates high-energy acoustic waves that behave much like other sound waves except that they have much greater pressure and energy. As with sound waves, Spark Waves® can easily travel great distance as long as the acoustic impedance stays the same. However, when the acoustic impedance changes, energy is released; the greater the change in impedance the greater the release of energy. There is a much higher release of energy at the soft tissue/bone interface than at a muscle/fascia interface. The release of energy from the Spark Wave® within the region of the affected tissues and the resultant compression and tension of cells creates a positive physiological effect. Mechano-transduction is the physiological effect thought to be responsible for stimulating normal and injured cells to produce healing factors.

7.2 Applicators

The orthogold100® is available with various applicator therapy heads, providing a range of penetration depth, energy and focal size. Probe selection can be determined with the aid of ultrasound to measure depth of the intended target. For this trial applicator OE050 will be used.

7.3 Known Side effects

No serious side effects have been reported by clinicians even when using highest energy settings, however the following minor side effects have been observed in isolated cases:

- Minor petechial bleedings may occur if the coupling between the probe cushion and skin is not air exclusive
- Occasional soft tissue swellings over treated tendons
- Pulmonary tissue tearing and extra-systoles
- Some patients experience a three to four day period of incomplete and transient pain reduction after ESWT
- Numbness over the treated area

No correlation to outcome or future responses to therapy has been established in cases where soft tissues swelling occurs. Aiming at pulmonary tissues or the trachea should be avoided.

The result of ESWT is not analgesia, but rather pain reduction. During this period it is important that patients rest in order to avoid over-working an injury thus risking re-injury. This should be taken onto consideration prior to performing ESWT on an athlete.

7.4 Contraindications

Below you will find the listed contraindications according to the manufacturer of the Investigational Medical Device.

- Do not use the orthogold100® in patients with pacemakers or implantable defibrillators.
- Do not use the orthogold100® in patients who are using devices which are sensitive to electromagnetic radiation.
- Do not use the orthogold100® in confirmed or suspected pregnancy.
- Do not adjust the therapy focus on internal organs (especially lungs).
- Do not use the orthogold100® for the treatment of patients with tumours.
- Do not use the orthogold100® for the treatment of patients with severe coagulation disorders.
- Do not use the orthogold100® for extracorporeal shock wave lithotripsy.
- Do not use the orthogold100® for the treatment of patients younger than 18 years or of patients with open epiphyseal plates.
- Do not direct the shock waves on large vessels.
- Do not direct the shock waves on internal airfilled organs (especially lungs).
- All other Contraindications mentioned in scientific literature

Due to our new scientific approach to use shockwaves in spinal cord injuries, some of the contraindications are not applicable for this study:

- Do not use the orthogold100® for the treatment of vertebrae, skull bones and ribs.
- Do not direct the shock waves on large nerves.

7.5 Mode of administration

The extracorporeal shockwave therapy is applied once at the level of lesion and 5 segments above and below or below the occiput (in lesions higher than C6) and above the sacrum (in lesions lower than T12). The transducer is held in an approximated angle of 45° paravertebral from both sides. In addition, the ESWT is applied to the soles of both feet on the medial side of the plantar surface. In patients who require surgical treatment, the ESWT is applied peri-operatively under extension (about 15 to 20 minutes) of the general anesthesia (ideally post-operative immediately after skin closure) or within the first 48 hours after trauma.

If no surgery is required, the ESWT or placebo application is applied as soon as possible within 48 hours from the first recognition of neurological symptoms both in the intensive care unit after surgery or in the normal ward.

For the application a sterile film is placed in the treatment area and ultra sound gel is used. The study intervention takes approximately 20 minutes. In the control group, the same procedure is performed, but

without the device emitting extracorporeal shock waves using a dummy head.

Attention: The foot-operated switch of the ESWT device must not be used in the operating theatre for reasons of safety. Also, it has to be ensured that the air condition is working properly in the operating room before the application of ESWT.

The application of the ESWT, as well as placebo ESWT takes place in prone position if surgical treatment takes place in prone position. If surgery takes places in supine position, patients are placed in lateral or prone position post-operatively to apply ESWT.

The treating physician together with the team of medical staff will decide whether an additional 20 minutes of anesthesia is justifiable for the individual patient. For those who cannot give consent to participate prior to the surgical intervention and are still eligible post-operatively (still within the time frame of 48 hours) the medical team has to weigh up if a change of position to prone or lateral position is possible without compromising the individual medical condition.

The follow-up examinations shall be blinded.[68] In order to ensure blinding of the examiner, the entire operating room staff and all persons involved in the application of the study intervention are required to keep the group allocation as a secret.

7.6 Parameters of the ESWT

- ESWT head: focused (OE50)
- Level of filling of the therapy head: 1 (1–5)
- Frequency: 5 (3–5) Hz
- Energy flux density: 0,19 (0,15–0,23) mJ/mm²
- Measurement of the distance between skin surface and spinal cord at the level of the lesion according to CT to determine the pressure during treatment in order to reach the spinal cord sufficiently
- Number of impulses: 5000 at the level of the lesion (2500 pulses bilaterally paravertebral) and 1000 on the medial side of the plantar surface on both feet (500 pulses per foot)
- Area of treatment: 2500 pulses bilaterally paravertebral and 4 segments above and below (3–5 segments: 3 segments for focal lesions and 5 segments for extensive lesions)

7.7 Placebo, Comparator

For patients randomized into the control group a dummy applicator will be connected to the shockwave generator.

7.8 Access and Documentation

Access to the investigational device shall be controlled. Medical device must only be used in the clinical trial in accordance with the clinical trial protocol.

The sponsor has to keep records, to which document the current location of all delivered investigational medical devices including their return or disposal.

The investigator or an authorized representative has to keep records, to document the receipt, use, return and disposal of the care IMD. These records should include the following points:

- a) Date of receipt
- b) Identification of the IMD (batch number, serial number or an unique code)
- c) Expiry date (if applicable)
- d) Date of application
- e) Identification of test subject
- f) date of return/explanation from test subject (if applicable)
- g) Date of return of unused, expired or non-functional IMDs (if applicable)
- h) Training of the user

7.9 Blinding and Unblinding

7.9.1 Blinding

The study will be blinded for treatment so that the patient and the assessor of the gait analyses are unaware of the treatment group assigned. The randomization list will be opened after the study database has been locked. The patients randomized to the non-treatment group, who will receive placebo treatment after surgery, will receive a shockwave application with a dummy sonic head, the connected device is the same as in treatment group.

7.9.2 Emergency Envelopes

As the shockwave treatment has no influence on the emergency treatment, we waive the use of emergency envelopes. If the information is needed, the monitor can be asked. The reason, time and date of un-blinding has to be documented.

7.9.3 Unblinding

Unblinding ahead of schedule

If DSMB decides, that unblinding ahead of schedule should be performed.

Scheduled Unblinding

The regular unblinding will be done after the completion of data entry (after closure of data base).

Statistics

8.1 Study sample size

The basis for calculating an appropriate sample size is an expected treatment effect. Due to a lack of knowledge about the impact of ESWT on sensory (SF) and motor functions (MF), the following approach proposed by Jaki et al.[46] is used:

With MAMS no effect or variability needs to be specified for the calculation of the sample size. To get an appropriate sample size, the package refers to the "worst-case configuration" (LFC, Dunnett 1984). Hereby the power is defined as the probability with which the H₀ should be rejected. Here the following applies:

$$\mu_1 - \mu_0 = \delta \text{ and } \mu_k - \mu_0 = \delta_0$$

for 1,...,K = treatments

δ = interested effect, that – if present – should be identified.

δ_0 = effect, that - if present - is of no interest (here: no improvement compared to the control group)

The effect sizes δ and δ_0 are parameterized in the MAMS package as those probabilities p and p0 with which the interesting or the non-interesting effect is to be identified. The p-value of 0.6 chosen for the study means that a randomly chosen person in the treatment group has a 60% probability of achieving a better result than a randomly chosen person in the placebo group. The effect of no interest was assumed with p0 = 0.5. This means that both the experimental treatment and the placebo treatment performed equally well. As already mentioned, this form of parameterization does not require any knowledge of the variance (Jaki et al., 2019).

With this p-value, the following formula can now be used to calculate the usual effect size δ

$$p = \Phi(z) = \Phi(\delta / (\text{SQRT}(2) * \sigma))$$

For our study, this would result in an effect size of approx. $0.35 * \sigma$.

With a one-sided error rate of 5% and a planned power of 80%, the following design parameters could be calculated. For the upper and lower limits, the triangle test is selected.[47]

	Stage 1	Stage 2	Stage 3
Cumulative sample size (control):	41	82	123
Cumulative sample size (treatment):	41	82	123
Maximum total sample size: 246			
Upper bound	2.13	1.89	1.85
Lower bound	0.00	1.13	1.85
p-value for H1 ((stopping for) success)	0.018	0.031	0.033
p-value for H0 (stopping for a lack of efficacy)	0.500	0.130	
Continue as planned at stage 1: $0.500 > p > 0.018$			
Continue as planned at stage 2: $0.130 > p > 0.031$			
The calculation was done with R package MAMS.			

8.2 Randomization

The randomization will be done with <https://www.randomizer.at/>, a tool that is provided by the MED UNI Graz. The following parameters will be used:

- Blinding: double-blind
- Blinding Table Size: 246
- Blinding Table Layout: Single blocks
- Code block Size: 4

The number begins with an abbreviation of the respective hospital (e.g. LI-04 means patient number 5 in the Linz Trauma Center).

8.3 Data Analysis:

According to the intention-to-treat approach (ITT), all randomized patients are included in the assessment. For metric variables, the mean values, the standard deviations (SD), the median values and the minimum / maximum values are specified. For ordinal variables, only the medians and the minimum / maximum values are determined. The characteristics of nominal variables are described by numbers and percentages. In addition, the frequency and proportion of people who regain motor and sensory levels are listed and shown in diagrams. Missing values are not taken into account when calculating the percentages.

Primary composite endpoint: Delta in total motor and sensory score (delta.TMSC)
For this study, the "International Standards for the Neurological Classification of Spinal Cord Injuries" (ISNCSCI) were

chosen as basis for the primary endpoint. This score contains the following subscores.

Motor Scores (MS)	
“Upper Extremity Motor Score” (UEMS) = UEL + UER	“Lower Extremity Motor Score” (LEMS) = LEL + LER
„Upper Extremity Left“ (UEL)	„Lower Extremity Left“ (LEL)
„Upper Extremity Right“ (UER)	“Lower Extremity Right“ (LER)

Sensory Scores (SS)	
“Light Touch Total”(LTT) = LTL + LTR	“Pin Prick Total”(PPT) = PPL + PPR
„Light Touch Left“ (LTL)	“Pin Prick Left“ (PPL)
„Light Touch Right“ (LTR)	“Pin Prick Right“ (PPR)

$$\text{ISNCSCI-Score} = \text{UEMS} + \text{LEMS} + \text{LTT} + \text{PPT} = \text{TMSC}$$

Composite Endpoint: $\Delta \text{TMSC} = \text{TMSC}_{\text{after 6 month}} - \text{TMSC}_{\text{at baseline}}$

The primary endpoint comprises these listed subscores and is calculated from the difference in the total points achieved between the baseline and follow-up measurements.

One problem with spinal trauma is that it usually occurs as a result of external violence (e.g. from a car or motorcycle accident, falling from great heights) and is also associated with injuries to the extremities. Due to the selected treatment strategy for the affected extremities (e.g. plaster cast, orthosis, surgical bandage), these are not accessible for the purposes of validly assess the specified subscores. In order to minimize falsification of the study results as well as possible, these subscores are not taken into account when calculating the composite endpoint, even if the score will be recorded during the follow-up measurement.

Regarding the composite endpoint: It is expected that treatment with ESWT will have a positive effect on all subscores. For this reason, the total score is viewed as a “composite endpoint”, an alpha error correction is renounced and power is gained. Although the subscores are evaluated and reported, these subscores are **not used to test any hypotheses**. However, the Holm method is used to avoid the accumulation of alpha errors.

With this procedure we follow the recommendations of the “U.S. Department of Health and Human Services Food and Drug Administratio ” (source: <https://www.fda.gov/regulatory-information/search-fda>

[guidance-documents/multiple-endpoints-clinical-trials-guidance-industry](#)). As already mentioned, there is no problem of multiplicity in this case.

In short: The aim of longitudinal assessments is to look for improvements over time. The treatment group is expected to achieve better results than the control group. Therefore, the individual differences of the TMSC are calculated as follows:

$$\text{delta.TMSC} = \text{TMSC}_{\text{after 6 month}} - \text{TMSC}_{\text{at baseline}}$$

Based on this Score, the following hypotheses will be tested:

H1: delta.TMSC treatment group > delta.TMSC control group

H0: delta.TMSC treatment group \leq delta.TMSC control group

Assuming that the data are normally distributed and that an ANOVA is robust against violations of the normal distribution, a randomized complete block design ANOVA is performed to compare the mean delta differences between the two groups. The three different neurological levels for stratification will be the block variable (as a random factor).

Furthermore, the mean values of all subscores with their 95% confidence intervals are displayed per group. In addition, charts are created based on descriptive analysis to capture results at a glance.

Although this selected type of endpoints incorporates different components of SCI, there will be no concerns about multiplicity because they should be concordant. However, when the treatment effects do not affect the different components of the endpoint congruently, then an adjustment for multiplicity will be done (Holm Procedure).

In addition, we want to get insights whether the results change when something about the way we approach the data analysis changes. Therefore, a sensitivity analyses (SA) to assess the robustness of the statistical analyses will be conducted. Especially the impact of outliers, baseline imbalance, and missing data will be in focus of this SA.

Secondary (exploratory) endpoints and control variables

Depending on the scales, the secondary endpoints will be reported descriptively as means with standard deviations, medians and frequencies. If tests will be conducted, then an alpha less than 0.05 is considered as significant. All these tests are exploratory in order to get additional ideas on the impact of the treatment. The following enumeration gives an overview over the intended scores:

- AIS grade
- Degree of spasticity according to Penn Spasm Frequency Scale
- Walking ability

- WISCI II (Walking Index for Spinal Cord Injury II)
- TUG (Timed Up and Go Test)
- 10-meter timed walk
- 6-minute walk test
- Urological function
- Hand motor function
- Plantar reflex
- Independence in everyday life of patients is assessed with the Spinal Cord Independence Measure (SCIM II)
- The number of study related adverse events (AEs) are measured according to NCI CTCAE, version 5.0.
- Spinal cord segment (s) of mechanical damage (according to imaging and confirmed intraoperatively)
- Level of physical activity prior to the SCI
- Injury Severity Score (ISS)
- Charlson Comorbidity Index (CCI)
- Pre-operative / Baseline AIS

8.4 Definition of collective analysis

All patients who fulfill the determined inclusion criteria will be used for the data analysis, independent of whether the intended shock wave therapy is performed as planned (intention-to-treat analysis).

8.5 Handling of missing, unused or faulty data, drop-outs and terminations

In order to counteract missing values as best as possible, the study will be carried out according to the GCP principle (Good Clinical Practice). Additionally, a regular evaluation of the collected data will take place. If missing values are detected, an attempt will be made to subsequently determine them and/or to document the reasons.

Missing values concerning the primary endpoint are estimated according to the Last Observation Carry Forward principle (LOCF). If possible, the same procedure is used for the secondary endpoints. In all other cases, an analysis of the observed data will be carried out.

The systematically documented reasons for drop-outs will be evaluated to see if they can be used as a predictor for the endpoints and thereby additional insights into the therapy can be gained.

A sensitivity analysis will be performed in order to estimate the effect of missing data and outliers on the study endpoints.

Adverse Events

9.1 Summary of known and potential Risks of the Medical Device

Provide a summary of all known adverse events and risks of the medical device and other interventions (preferably in a table). Define device deficiencies, use the instructions for use (IFU)

In addition to adverse event reporting, non-medical complaints such as malfunction, misuse, use error not leading to an adverse event, shall be documented throughout the clinical investigation and shall be reported as specified by local (or national?) law.

All complaints of a non-medical nature shall be handled under the sponsor's quality management system.

9.2 Adverse Event (AE)

A clinical trial adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a patient or clinical trial subject C or not related to the investigational medical device. This includes events related or not to a comparator and procedures involved.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

9.3 Serious Adverse Event (SAE)

If a Serious adverse event (SAE) occurs, the Investigator must alert the sponsor without unjustified delay to any AE (whether causally or not) from this study that results in one of the following outcomes, or is significant for any other reason:

- death (excluding death from progressive disease)
- a life-threatening experience – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- initial hospitalization, or prolongation of existing inpatients hospitalization
- persistent or significant disability or incapacity
- congenital anomaly or birth defect
- occur a malignant tumor

Medical judgment should be exercised in deciding whether an AE/ADE is serious in other situations. Important AE/ADEs that are not immediately life-threatening or do not result in death or hospitalization

but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Patients should be closely followed for adverse events while receiving treatment with the investigational device and for 3 weeks after discontinuation from study therapy in order to detect delayed toxicity.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Disease progression will not be reported as AE or SAE unless the progression is unexpected in severity or early occurrence. Progressive disease will be appropriately documented on the case report form as part of the efficacy parameters.

9.4 Adverse Device Effect (ADE)

An Adverse device effect (ADE) is an adverse event, which is related to the use of an investigational medical device. All untoward and unintended responses to an IMD related to any dose administered. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction, use error or intentional misuse of the investigational medical device.

9.5 Serious Adverse Device Effect (SADE), Anticipated Serious Adverse Device Effect (ASADE) and Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse events that are considered to be related to the medical device are serious adverse device effects (SADE). SADE's comprise unanticipated serious adverse device effects (USADE) and anticipated serious adverse device effects (ASADE).

USADE means any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

ASADE means any serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report.

9.6 Definition of Device Deficiency

Please find the definition of device deficiencies in the attached document: MTS_RA_OW100_Device-Deficiency_E_A.pdf

9.7 Pregnancy

Any pregnancy that occurs during study participation must be reported to the investigator/sponsor immediately.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications (including spontaneous abortions) and elective terminations must be reported as an AE or SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the IMD, must be promptly reported to the sponsor.

As the consent for the study does not cover the consent for the follow-up of the pregnancy, a separate consent has to be obtained.

9.8 Severity of Adverse Events (AE)

The severity of clinical AEs/ADEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the CRF.

If the severity of an AE/ADE worsens during medical device administration, only the worst intensity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

Mild

Event may be noticeable to subject; does not influence daily activities; the AE/ADE resolves spontaneously or may require minimal therapeutic intervention.

Moderate

Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed; the AE/ADE produces no sequelae.

Severe

Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; the AE/ADE produces sequelae, which require prolonged therapeutic intervention.

A mild, moderate or severe AE/ADE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically

serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

9.9 Causality

For all, the investigator will assess the causal relationship between the medical device and the AE using his/her clinical expertise and judgment according to the following algorithm that best fits the circumstances of the AE:

Unrelated

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow known response pattern to the suspect medical device (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Unlikely

- There is a reasonable temporal relation between the AE and the medical device, but there is a plausible other explanation for the occurrence of the AE.

Possibly

Follow a reasonable temporal sequence from administration of the medical device.

- The AE may equally be explained by the study subject's clinically state, environmental or toxic factors, or concomitant therapy administered to the study subject.
- The relationship between the medical device and AE may also be clinically plausible.

Probably

- Follows a reasonable temporal sequence from administration of the medical device, and plausible reasons point to a causal relation with the medical device.

Related

- Follows a reasonable temporal sequence form administration of the medical device.
- Follows a known response pattern to the medical device (if response pattern is previously known).
- No other reasonable cause is present.

Not assessable

- The causal relationship between the medical device and the AE cannot be judged.

9.10 Reporting Procedures

9.10.1 Reporting Procedures for Adverse Events (AEs)

A special section is designated to adverse events in the case report form. The following details must thereby be entered:

- Type of adverse event
- Start (date and time)
- End (date and time)
- Severity (mild, moderate, severe)
- Serious (no / yes)
- Unexpected (no / yes)
- Outcome (resolved, resolving, not resolved, resolved with sequelae, unknown, fatal)
- Relation to medical device (Related/ Probably/ Possibly/ Unlikely/ Not related/ Not assessable)

Adverse events are to be documented in the case report form in accordance with the above mentioned criteria.

9.10.2 Reporting Procedures for Serious Adverse Events (SAEs)

In the event of serious, the investigator has to use all supportive measures for best patient treatment. A written report is also to be prepared and made available to the clinical investigator immediately. The following details should be at least available:

- Patient number
- Patient: initials, age in years, sex
- The suspected medical device
- The adverse event assessed as serious
- Short description of the event and outcome
- Device related or non-device related

The written report is divided into two parts:

- Initial report: Informs about what has happened (AE/ADE assessed as serious), if there is a relationship to the medical device, and which action was set.
- Follow up-Report: informs about the outcome

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall:

- review the investigators assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device
- review all devices deficiencies and determine and document in writing whether they could have led to a serious adverse device effect
- report or ensure the reporting of all SAEs, whether or not related to the medical device, to the EC and regulatory authorities (BASG)

Documentation

The accomplishments of the study in agreement with the EN ISO 14155 guidelines, the MD and the clinical investigational plan as well as the trueness of all data documented in the CRF are the responsibility of the Investigator. All collected data of this study have to be recorded in the CRF by appropriate authorized persons. This is also valid for data of patients, who dropped-out of the study.

The Investigator records the participation in a special identification list of patients. This list gives the possibility to a later identification of the patients and contains the patient number, full name, date of birth and the date of the enrollment in the study. The identification list of patients remains in the study center after the closure of the study. Additionally, the participation of the patient in this clinical study has to be recorded in the patient chart (investigational device, number of patient or randomization, start and end of the study).

Further it has to be assured, that this person, who is responsible for the documentation in the eCRF, can be identified. A list with signatures and identification code of the persons, who are allowed to make entries in the eCRF, will be archived in the Investigator Site File and the Trial Master File.

10.1 Data Recording (eCRF)

It is the responsibility of the investigator to document all data of the clinical study correctly and completely into the database. Corrections in the eCRF (electronic Case Report Form) can only be made by people authorized by the principal investigator and have to be justified. Corrections are filed in a way that previous data can be recalled. All data and corrections are traced with date, time and person.

10.2 Trial Folders

The trial folders should contain the complete documentation of the trial. Individually or together, they should allow the evaluation of the trial conduct and its data quality.

10.2.1 Trial Master File (TMF)

The paper-based TMF, established at the beginning of the trial and secured in a safe place, contains all essential documents that demonstrate that the trial is conducted in accordance with regulatory requirements and ICH GCP. All documents will be maintained and updated as appropriate throughout the

trial. Previous versions of the documents must be retained in the TMF and will be clearly labelled as outdated or will be relocated in a section for outdated documents. The TMF is archived at the end of the study for 15 years.

10.2.2 Investigator Site File (ISF)

The paper-based ISF, established at the beginning of the trial will be secured in a safe place (the file is provided to the site at the site initiation visit). It contains all essential documents maintained by the PI(s). All documents will be maintained and updated as appropriate throughout the trial. Previous versions of the documents must be retained in the ISF and will be clearly labelled as outdated or will be relocated in a section for outdated documents. Within the Monitoring, the ISF will be checked up on actuality and completeness in accordance with the formalities. After completion or discontinuation of the study this ISF has to be kept for 15 years.

10.3 Data Storage

10.3.1 Storage duties of the Sponsor

The Sponsor has to keep all essential documents of the clinical investigation after completion or discontinuation of the study for a minimum of 15 years. The Sponsor has to archive all study-relevant documents in accordance with the legal regulation.

10.3.2 Storage duties of the Investigator

The Investigators have to keep all records and documents, which are related with the study or the allocation of investigational device (e.g. data entry form, informed consent form, list of the allocations of investigational devices and further relevant documents), for a minimum of xx years.

Medical records and other original data have to be kept for the longest possible duration, which the hospital, the institution or the private praxis permits.

Data Management

Data are managed and collected by the Askimed () software. Askimed is a cloud-based web platform that provides an all-in-one solution for medical studies of any size. Askimed main features are (1) data collection based on electronic case report forms (eCRF), (2) data management including a permission system for study collaborators and (3) data preparation for data analysis. Each study collaborator uses Askimed as the central information source and is guided by the platform in all three study phases. Askimed integrates user friendly tools for error elimination, data reproducibility and data security. All study data is stored in a MySQL database, and the software uses state-of-the-art technologies to secure all server communication and user actions. Its internal architecture is designed to manage and analyze millions of data items from eCRFs. For eCRF creation itself, Askimed provides a graphical tool (Askimed Editor) to generate the questionnaire dynamically. Several different questionnaire types (e.g. textboxes, comboboxes, radio buttons, pictures, numbers) are available and plausibilities as well as jumps can be coded by using Askimeds eCRF engine. To support different languages, the eCRF logic is defined once

and can be used for all available study languages. Changes are tracked by the Askimed system and allows to update the CRF at any time. Data collection can be done via a web browser or by using a Desktop client, in which data is synchronized with the Askimed database. Askimed also includes an audit trail, study monitoring (e.g. query workflow, interview signing), management of collaborators and probands as well as the creation of data dictionaries of all available variables.

The Askimed system has been developed at the Medical University of Innsbruck and is used in several major epidemiological studies and patient registers. Overall, Askimed provides an efficient way to store all study specific data in one central repository and improves the overall quality compared to paper-based CRFs.

Validation of data is made by programmed checks of range, validity and consistency. If necessary, queries are made by the study software or an authorized person. Based on the queries the investigator can check and clarify discrepancies.

For completion of the study after the record of all entries and clarification of all queries, the data base will be closed. This process has to be documented.

Protocol Deviations

a) Statement specifying that the investigator is not allowed to deviate from the CIP, except as specified in EN ISO 14155 4.5.4 b:

- Requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation;
- Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

b) Procedures for recording, reporting and analyzing of the CIP deviations.

c) Notification requirements and time frames.

d) Corrective and preventive measures and criteria for the exclusion of the principal investigator.

Quality Management

Training, monitoring and audits are performed for quality assurance within this clinical study. Monitoring and auditing procedures developed or endorsed by the Sponsor will be conducted, in order to comply with ICH-GCP guidelines (EN ISO 14135) and local legal requirements to ensure acceptability of the study data.

13.1 Qualifications

The Sponsor is responsible for selecting the Investigator(s)/Institution(s). Each Investigator should be qualified by training and experience and should have adequate resources. Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s) (see ICH GCP E6).

13.2 Monitoring

The Investigator must grant direct access to on-site study documentation, including the patient's notes, to allow audits or inspections to be performed. No action will be taken that might infringe the patients' confidentiality.

Monitoring visits by representatives of the Sponsor will be carried out to review study plan compliance, to compare CRFs and individual patient's medical records, to perform accounting of study material, and to ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The frequency and duration of Monitoring visits will be determined according to clinical site accrual, site performance, adherence to the protocol, and data quality.

Further the Monitor confirms that:

- the clinical investigational plan is fulfilled and deviations have to be discussed with the investigator, documented and reported to the sponsor
- the product is used complied to the clinical investigational plan and changes of the product, its application or with the clinical investigational plan have to be reported to the sponsor
- for the investigator a sufficient amount of test subjects and products are provided
- a signed and dated consent form exists for each test subject at the time of admission and before initiation
- Inspection of the Investigator Site File (ISF)
- Documentation of the patient status
- CRF-data verification with the source data
- Evaluation of the SAEs reports according to the regulations
- a proceed regarding balancing and traceability of the products exists
- service and calibration of the devices are carried out and documented
- resignation of a test subject and/or non-compliance of the rules must be documented, discussed with the investigator and reported to the sponsor

The monitor has to treat all information confidential and protect the privacy of the patients.

Audits and Inspections

Regulatory authorities, the ethics committees, and Sponsor's delegates may perform on-site inspections or audits, for which the Investigator must provide support at all times.

During an audit following issues among other things will be inspected:

- Performance of the clinical trial according to the investigation plan
- Data validity
- Quality of the clinical trial according to the EN ISO 14155 guidelines

After each external audit an audit-certificate by the auditor has to be sent to the Investigator. This certificate has to be kept in the Investigator Site File (ISF) to evidence the audit to the regulatory authorities in the case of an inspection by them. The audit-report is sent to the Sponsor of the study. An audit-certificate will be attached to the final report at the end of the study. Additionally, according to the Austrian Medical Device Law (MPG) audits and inspections by regulatory authorities may be performed.

Reporting

For the documentation of the progress and development of the study, protocols about the meetings of the various group committees are necessary.

14.1 Final Study Report

All information regarding this clinical study has to be kept confidential. The statistical analysis and the integrated final study report will be prepared according EN ISO 14155 and finalized within 12 months after last patient last visit (LPLV) took place. The final study report will be reviewed and signed by the Sponsor, the Coordinating Investigator and all further responsible persons. All information in that report is strictly confidential.

Please choose:

- The coordinating investigator will sign the final study report of the clinical trial. This confirms that the report describes implementation and results of the clinical trial by the best of his knowledge.
- The investigator with most patients becomes the coordinating investigator of the final study report. If the coordinating investigator is unable to meet his obligation, the sponsor will determine a new coordinating investigator of the final study report.
- The coordinating investigator, employed by the sponsor, signs the final study report of this clinical trial. This confirms that the report describes implementation and results of the clinical trial by the best of his knowledge.

14.2 Publications

Data of the study will be published according to the publication guidelines. Publication of the study results is aspired in an adequately high ranked journal as soon as data analysis is finished.

The five best recruiting sites are entitled to co-authorship. The remaining persons will be entitled as "Group authorship" NeuroWAVE study group. This means that each person will be entered as collaborator names in Medline citation.

The sequence of authors will arise from the number of included subjects.

Amendments

After the protocol has been submitted to an ethics committee (EC), any substantial change will require a formal amendment. The amendment must be signed by all of the signatories to the original protocol. Once the study has started, amendments should be made only in exceptional cases. The ethics committees must be informed of all amendments. If necessary, approval must be sought for ethical aspects and must also be obtained from the competent authorities.

Ethical And Regulatory Aspects

16.1 Responsibilities of Sponsor and Investigator

The sponsor of this clinical trial will assume responsibility for inducement, organization and financing of the implementing trial according to the EN ISO 14155. The procedures set out in this study protocol are designed to ensure that the Sponsor and the Investigator comply with the principles of ICH-GCP the Declaration of Helsinki and the EN ISO 14155 guideline concerning the conduct, evaluation and documentation of the study. The study will also be performed adhering the local legal conditions and requirements. Each Investigator has to confirm this by signing the study protocol.

Responsibilities of the sponsor:

- Verification of the understanding of the instructions for use (IFU)
- Verification of the understanding of treatment schedule
- Ensuring for enough time and capacity for the implementation of this study
- Correct collection and documentation of data, reporting
- Provision of all data to the sponsor, monitor or relevant authorities for audits or inspections
- Assurance for the confidential handling of patients data and information

The Principal Investigator accepts the responsibility for the conduct of this clinical trial at this study site according to the EN ISO 14155.

16.2 Approval of Ethics Committee and Notification to the Authority

Prior to study start, the study protocol and/or other appropriate documents will be approved by the appropriate ethics committees and competent authorities.

16.3 Patient Information and Consent Form

Every patient has to give his/her written consent before the participation in the clinical trial. Before the patient gives his/her written consent the patient has to be informed completely in oral and written form in an understandable manner about character, importance, relevance and consequences of the clinical trial.

The content of the consent information is documented on the Patient information and Informed Consent form. The patient will be notified, if essential findings about the MD appear during the study.

The Informed Consent of the patient about the participation in the clinical trial has to be dated and signed by the patient and the Investigator. The patient receives a copy of the signed and dated Patient Information and Informed Consent Form. The Investigator stores the original signed and dated exemplar in the Investigator Site File.

It has to be explicitly pointed out, that before patient sign the Informed Consent form it is not allowed to perform any study specific actions with the patient.

16.4 Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with local legal requirements. The civil liability of the Investigator, all persons instructed and the hospital, practice or institute in which they are employed and the liability of the Sponsor in respect of financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable local law.

As a precautionary measure, the Investigator, the persons instructed and the hospital, practice or institute are included in such cover in terms of their work done in carrying out the study to the extent that the claims are not covered by their own professional indemnity insurance.

The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the study medication being tested or by medical steps taken in the course of the study. Such insurance is taken out by the Sponsor in accordance with or by way of analogy to both the Austrian and the other participating countries drug law.

16.5 Data Protection and Confidentiality

All local legal requirements regarding data protection will be adhered to. All study findings and documents will be regarded as confidential. The Investigator and members of the research team must not disclose any information without prior written approval from the Sponsor.

The pseudonymity of patients participating must be maintained. Throughout documentation and evaluation, the patients will be identified on CRFs and other documents by xxx. Documents that identify the patient personally (e.g., the signed informed consent, patient identification list) must be maintained in confidence by the Investigator. The patients will be informed in the ICF that all study findings will be stored on computer and handled in strictest confidence.

16.6 Financing

The present clinical trial is funded by AUVA (Austrian Worker's Compensation Board).

16.7 Regulatory Aspects

The processes set out in this study protocol are designed to ensure that the Sponsor and the Investigator abide the principles of the EN ISO 14155 and the Declaration of Helsinki concerning the conduct, evaluation and documentation of the study. The study will also be performed in compliance with the local legal conditions and requirements. Each Investigator has to confirm this by signing the study protocol.

Data Safety And Monitoring Board

The Data Safety and Monitoring Board is charged with overseeing the safety of the patients and reviewing the results according to the DSMB charta. The members are:

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For further information, please see the Guideline on Data Monitoring Committees (Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr).

Approval Of Ethics Committee And Notification To The Authority

Prior to study start, the study protocol and/or other appropriate documents will be approved by the appropriate ethics committees and competent authorities.

Site	Zentrumsname	Zuständige EK	Zuständige Behörde
A01	Landeskrankenhaus Feldkirch Abteilung für Unfallchirurgie	EK des Landes Vorarlberg	Bundesamt für Sicherheit im Gesundheitswesen
A02	Universitätsklinik Innsbruck Universitätsklinik für Unfallchirurgie	EK der Medizinischen Universität Innsbruck	BASG
A03	Unfallkrankenhaus Salzburg	EK des Landes Salzburg	
A04	Universitätsklinik für Orthopädie und Traumatologie Salzburg	EK des Landes Salzburg	
A05	Unfallkrankenhaus Linz	EK der AUVA	
A06	Universitätsklinik Linz Neurochirurgie	EK des Landes Oberösterreich	
A07	Universitätsklinikum St. Pölten	EK des Landes Niederösterreich	
A08	Unfallkrankenhaus Meidling	EK der AUVA	
A09	Unfallkrankenhaus Lorenz Böhler	EK der AUVA	
A10	SMZ Ost Wien, Donauspital Abteilung für Unfallchirurgie	EK der Stadt Wien	
A11	Universitätsklinik Wien, AKH	EK der Medizinischen Universität Wien	
A12	Unfallkrankenhaus Graz	EK der AUVA	
A13	Unfallkrankenhaus Klagenfurt	EK des Landes Kärnten	
G15	Unfallkrankenhaus Berlin BZ für Rückenmarksverletzte	EK des Landes Berlin + Landesamt für Gesundheit und Soziales	Bundesinstitut für AM und MP BfArM
Reha BH	Rehazentrum Bad Häring	EK der Med. Universität Innsbruck	BASG
Reha WH	Rehazentrum Weißer Hof	EK des Landes Niederösterreich	
Reha TB	Rehazentrum Tobelbad	EK der AUVA	

Abbreviations

ADE	Adverse Device Effect (Unerwünscht Wirkung des Produkts)
AE	Adverse Event (Unerwünschtes Ereignis)
AIS	American Spinal Injury Association (ASIA) Impairment Scale
AR	Adverse Reaction (Nebenwirkung)
AUVA	Allgemeine Unfallversicherungsanstalt
BASG	Bundesamt für Sicherheit im Gesundheitswesen
CCI	Charlson Comorbidity Index
CI	Coordinated Investigator
CIP	Clinical Investigation Plan (Klinischer Prüfplan)
CONSORT	Consolidated Standards of Reporting Trials
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board (Datensicherheitskomitee)
eCRF	electronic Case Report Form
ESWT	Extracorporeal shockwave therapy (extrakorporale Stoßwellentherapie)
EK	Ethics committee
EWR	European economic area (Europäischer Wirtschaftsraum)
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GRT	Grasp and Release Test
ICH	International Conference on Harmonization
ISF	Investigator Site File
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
ISO	International Organization for Standardization
ISS	Injury Severity Score
KG	Control Group (Kontrollgruppe)

KKS	Clinical Trial Center (Kompetenzzentrum für Klinische Studien)
LEMS	Lower Extremity Motor Score
LEL	Lower Extremity Left
LER	Lower Extremity Right
LTL	Light Touch Left
LTR	Light Touch Right
LOCF	Last Observation Carry Forward principle
LPLV	Last Patient Last Visit
MAS	Modified Ashworth Scale
MF	Motor Function
MP	Medical Device (Medizinprodukt)
MPG	Medical device law (Medizinproduktegesetz)
MeDRA	Medical Dictionary for Regulatory Activities
na	Not Applicable (nicht verfügbar)
NCI	National Cancer Institute
nd	Not Done (nicht durchgeführt)
NHPT	Nine-Hole Peg Test
NRS	Numeric Rating Scale
OEX	Upper Extremity (Obere Extremität)
PSFS	Penn Spasm Frequency Scale
PI	Principal Investigator
PPL	Pin Prick Left
PPR	Pin Prick Right
SADE	Serious Adverse Device Effects (Schwerwiegende Unerwünschte Wirkungen des Produkts)
SAE	Serious Adverse Event (Schwerwiegendes Unerwünschtes Ereignis)
SAP	Statistical Analysis Plan
SCI	Spinal cord injury (Rückenmarksverletzung)
SCIM	Spinal cord independence measure
SDV	Source Data Verification

SF	Sensory Function
SOP	Standard Operating Procedure
SPSS	Statistical Package for Social Sciences
TMF	Trial Master File
TMSC	Total Motor and Sensory Score
TSCI	Traumatic spinal cord injury (traumatische Rückenmarksverletzung)
TUG	Timed Up and Go Test
UEMS	Upper Extremity Motor Score
UEL	Upper Extremity Left
UER	Upper Extremity Right
UKH	Trauma Center (Unfallkrankenhaus)
USADE	Unanticipated Serious Adverse Device Effects (Unvorhersehbare Schwerwiegende Unerwünschte Wirkungen des Produkts)
WISCI II	Walking Index for Spinal Cord Injury II

Declarations

Ethics approval and consent to participate

Please refer to the WHO Trial Registration Data Set at the beginning of this document.

Consent for publication

Data of the study will be published according to the publication guidelines. Publication of the study results is aspired in an adequately high ranked journal as soon as data analysis is finished.

Availability of data and material

Data can be made available upon reasonable request to the senior author after study closure.

Competing interests

None to declare.

Funding

The present clinical trial is funded by AUVA (Austrian Worker's Compensation Board).

Authors' contributions

IL, RM, GM, LA, TH, HK, and WS were responsible for writing of the study protocol. LM was responsible for the radiological part of the study protocol (classification and the decision tree for imaging). HK was responsible for statistical planning. AGH was responsible for selection of neurological assessments. JH was responsible for critical review of the study protocol. All authors have read and approved the final study protocol.

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Figures

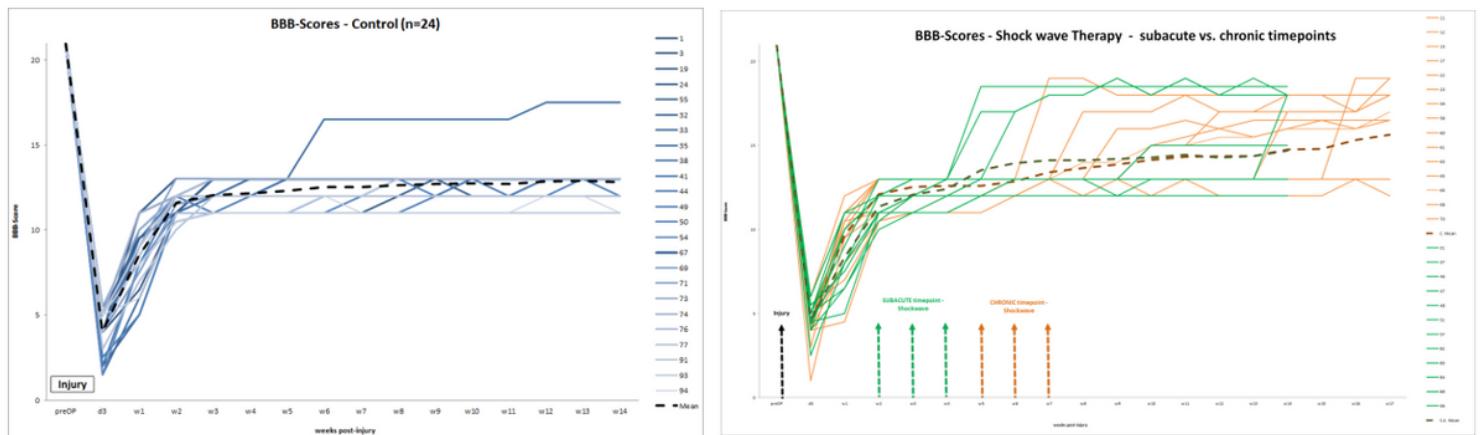


Figure 1

Open field test (BBB) evaluating functional behavior after infliction of spinal cord contusion in the control group (left) without further improvement after initial recovery in comparison to the ESWT groups (right). After ESWT, sub-acute and chronic groups showed a significant increase in the BBB score.

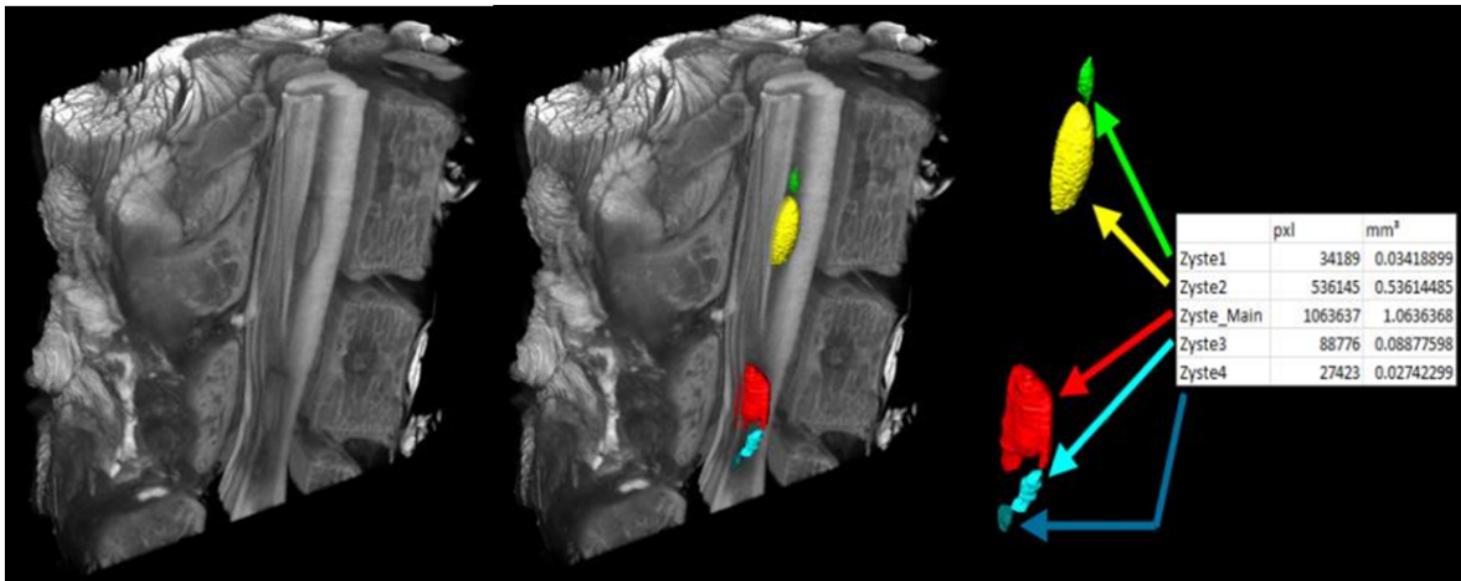


Figure 2

Staining with Lugol and high resolution µCT imaging allows 3-D illustration of the spinal cord. Cysts (red and blue) and syrinx (yellow), regularly developing after contusion trauma, could be depicted and further quantified with respect to their volume.

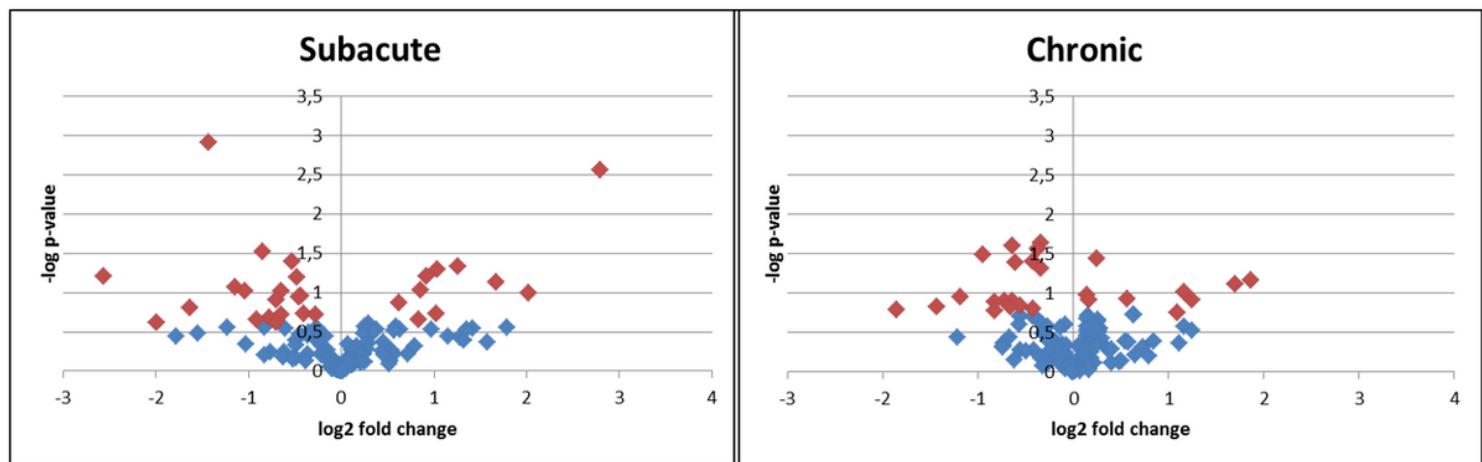


Figure 3

miRNA screening pre and post ESWT in the different treatment groups. Almost 40 potential candidates could be detected which will be further analyzed.

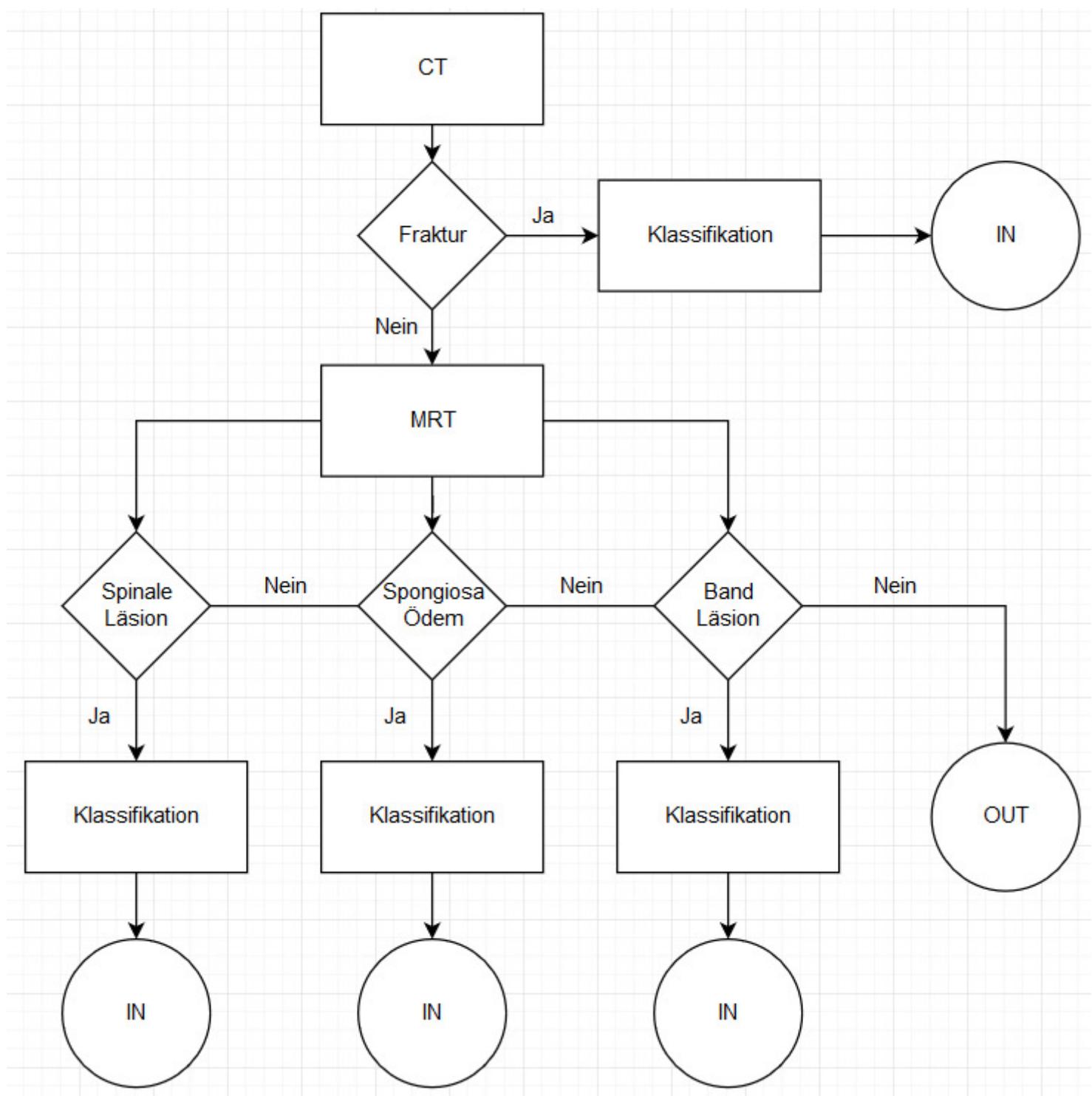


Figure 4

Fracture classification for study inclusion/exclusion according to CT and/or MRI scans.

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