Traumatic spinal fractures the fall and rise

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PART 3

POST-OPERATIVE CARE

CHAPTER 6

IS POSTOPERATIVE BRACING AFTER PEDICLE SCREW FIXATION OF SPINE FRACTURES NECESSARY? STUDY PROTOCOL OF THE ORNOT STUDY: A RANDOMISED CONTROLLED MULTICENTRE TRIAL

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Abstract

Background

The most common surgical treatment of traumatic spine fractures is through a posterior approach using pedicle screws and rods. Post-operative treatment protocols including the use of post-operative orthoses however differ between hospitals and surgeons. A three-point hyperextension orthosis is designed to support proper posture and unload the anterior column. Some motion remains when wearing an orthosis and its main value in post-operative treatment is therefore believed to be pain relief and patient confidence. This could consequently shorten recovery time. On the other hand, an orthosis could also lead to muscle weakness and slow down recovery. Any orthosis related complications might also be avoided. Additionally, recent studies on conservative fracture treatment show no difference in radiologic outcomes with or without an orthosis. To date no randomized studies have been performed on the use of post-operative orthoses.

Methods and analysis

Patients undergoing posterior fixation with pedicle screws for a traumatic thoracolumbar fracture (Th7 – L4) will be included in this randomized controlled multicenter noninferiority trial. Forty-six patients will be randomized 1:1 to one of the two parallel groups; one group will wear a post-operative orthosis for 6 weeks followed by 6 weeks of weaning and one group will not wear an orthosis. The primary outcome is pain at 6 weeks reported on NRS. Secondary outcomes consist of pain on other moments, analgesic use, complications and length of hospital stay, quality of life (EQ-5D), back pain related function (ODI) and radiologic outcomes with a follow-up of one year. Orthosis compliance is monitored weekly in the orthosis group.

Ethics and dissemination

The institutional review board (METc VUmc) approved this study on October 11th 2016 under case number 2016.389. After completion of the trial, the results will be offered to an international scientific journal for peer-reviewed publication.

Trial registration

The trial is registered on Clinicaltrials.gov under number NCT03097081 and on trialregister.nl with number NTR6285.

Introduction

A lot of research is currently done involving the best operative and non-operative treatment of traumatic thoracolumbar spine fractures. Both surgical stabilization and the use of orthoses play an important role in the treatment of thoracolumbar fractures. The most common surgical intervention is posterior fixation with pedicle screws and rods. Guidelines on post-operative care remain ambiguous and the role of an orthosis differs depending on hospital and surgeon's preference.[1-3] An orthosis is designed to support proper posture and unload the anterior vertebral column through a three point fixation.[4] It does, however, not provide rigid stability or complete immobilization of the spine.

While operatively treated fractures gain intrinsic stability from the implanted fixation material, an orthosis is still commonly used in postoperative care by many surgeons.[3, 5-9] The additional value is supposed to be pain relief, patient confidence and reducing the load on implanted hardware. An orthosis is not likely to influence hospital stay duration as shorter hospital stay was not observed in one study[10] and even longer hospital stay was reported in another.[11] Other disadvantages are possible orthosis related complications such as muscle atrophy, stiffness, skin irritation, thromboembolism and impaired respiration.[10-12]

Studies that reported not to use an orthosis postoperatively are scarce,[3, 12, 13] while the benefits seem obvious. One study encouraged immediate mobilization without orthosis to allow a more rapid return to activities and avoid complications.[12] Furthermore the authors found that loss of kyphosis correction did not differ from studies that used bracing after surgery. No weaning from the brace could lead to quicker return to daily activities and work which might lead to faster improvement of quality of life and back pain related function while reducing costs for society. Finally, (rare) orthosis related complications are avoided.
The use of an orthosis has been studied post-operatively after lumbar spine surgery for degenerative conditions[14, 15] and for conservative treatment of thoracolumbar fractures.[11, 16, 17] In one study on lumbar surgery for degenerative conditions it was found to promote arthrodesis.[14] No differences were shown concerning pain, adverse events, functional outcomes, radiographic consolidation and kyphotic progression. One study on conservative treatment reported improved pain and functional scores when using a brace compared to physical therapy.[18] A recent systematic review on post-operative bracing showed comparable results for both groups except slightly more kyphosis correction loss and less pseudo arthrosis in the group with post-operative bracing.[3] It has to be noted that this review is probably not reliable to translate into clinical practice as it contains large heterogeneity, combining all types of studies and (operative) treatments.

Possibly due to the fact that there are no clinical studies to date to prove or disprove the additional value after surgical stabilization of thoracolumbar fractures, a post-operative orthosis is still often common practice. The aim of this randomized trial is to make the first evidence based recommendation on postoperative use of an orthosis for posteriorly stabilized traumatic thoracolumbar fractures. We hypothesize that post-operative pain without an orthosis will not be worse compared to post-operative pain with an orthosis. Additionally it is hypothesized that there will be no influence on fracture collapse, kyphosis correction, complications and functional outcomes as compared to post-operative treatment without an orthosis.

Methods and analysis

Study design

The study is set up as a parallel 1:1 group randomized controlled multicenter noninferiority trial. It will take place in the Netherlands in one initiating academic hospital and one participating regional center; VU University medical center Amsterdam (department of traumasurgery and department of orthopedic surgery) and Onze Lieve Vrouwe Gasthuis Amsterdam (department of orthopedic surgery). The study protocol is written according to the SPIRIT guidelines[19] and the study will be reported according to the CONSORT guidelines.[20]

Recruitment

Patients will be initially recruited in one of two participating centers by the treating surgeon once the decision for posterior fixation has been made. Study specific and legal information about the study is given and permission to be contacted by one of the study team members is requested. Within 24 hours patients will be contacted again by their treating doctor or another trained study team member to discuss any further questions and, if applicable, sign informed consent.

Eligibility criteria

Patients between 18 and 65 years of age with a traumatic thoracolumbar (Th7 to L4) fracture that will undergo or have <24 hours ago undergone posterior fixation (short and long segment) using pedicle screws and rods are potentially eligible. Patients with a neurologic injury or psychiatric comorbidity are excluded because it is very likely this influences quality of life outcomes. Further exclusion critera are reported in Table 1.

Table 1. In- and exclusion criteria for the ORNOT trial

Inclusion	Exclusion
- 18 – 65 years - Traumatic fracture Th7 – L4 - Fracture type AO A2 – C - Surgical posterior fixation with pedicle screws	- Inadequate knowledge of the Dutch language to fill in questionnaires - Complete or partial spinal cord injury (ASIA A to D) - (additional) Anterior surgical stabilization through thoracotomy or lumbotomy - Thoracolumbar fracture of non-traumatic etiology (e.g. pathologic, infectious) - Osteoporosis; using bisphosphonates or positive DEXA - ISS ≥ 16 - Brain injury AIS ≥ 4 - Not able to walk before the fracture - Unable to come to the outpatient clinic - Psychiatric comorbidity - Inability to wear an orthosis, e.g.: o BMI > 35 o Thoraco-abdominal wounds o Pre-existing spine deformity which impairs the use of an orthosis

Th: Thoracic, L: Lumbar, ASIA: American Spinal Injury Association score, ISS: Injury Severity Score, AIS: Abbreviated Injury Score, BMI: Body Mass index

Interventions

Two groups are created; one group with a post-operative ORthosis versus a group with NO orThosis (ORNOT), Figure 1. The study intervention is no post-operative orthosis, the orthosis group serves as control while this is the current post-operative protocol. The three point hyperextension orthosis is used which supports vertebra L4 to T7. After the operation, patients have at least 6 hours of bed rest, after which they can try and mobilize as tolerated with the help of a physiotherapist. After this point they are permitted to walk, if tolerated. According to the randomization, this will be done with or without an orthosis. The group randomized to an orthosis is required to wear this when in vertical position (standing, walking, sitting up straight) for 6 weeks, followed by 6 weeks of gradual weaning. Weaning of the orthosis is as tolerated, based on pain and physical condition of the patient. Because potential differences exist between patients in the amount of perceived pain, confidence and range of motion, weaning is a process that is patient specific. The orthosis does not need to be worn when the patient is lying down. The orthosis comes in three standard sizes (S, M, L) and will be adjusted manually to the patient by a specialized nurse. Both groups will receive standard post-operative protocol pain medication if needed and discharge will be based on clinical improvement. Every participant to the study has the right to withdraw from the study at any time without further argumentation.

Patients in the orthosis group are monitored for adherence to their orthosis use. They are asked and reminded several times, to register their weekly orthosis compliance during twelve

weeks on a week diary that is handed out at inclusion. Patients randomized to no orthosis cannot be monitored for their adherence

Primary outcome

The primary outcome parameter is pain at six weeks, measured on the numerical rating scale (NRS) and compared between the two groups. A clinical significant difference is defined as 2 points on the NRS scale. This difference of 2 points is based on previous literature[21, 22] on pain and based on meetings with the hospital's pain exerts. If an orthosis affects post-operative pain, we hypothesize this effect will be the largest at six weeks postoperatively. Effects from the surgery such as wound pain will then mostly be disappeared and the fracture will not yet be fully consolidated which should adequately demonstrate the effect of an (or no) orthosis on back pain. Weaning from the orthosis will also be started at six weeks. The NRS score (with 0-10 range) has shown similar psychometric properties to VAS scores,[21, 23-25] is preferred over the VAS score by patients [26] and has shown applicable to back pain.[27-29] In order to obtain reliable average values and rule out distorted maximum or minimum values, patients are required to fill in the NRS score for four consecutive days, three times a day at each measurement moment (2, 6 and 12 weeks). It has been shown that a composite pain score demonstrates adequate reliability and excellent validity as a measure of average pain. [30] The primary outcome, pain at six weeks, will consequently be the mean of twelve values per patient.

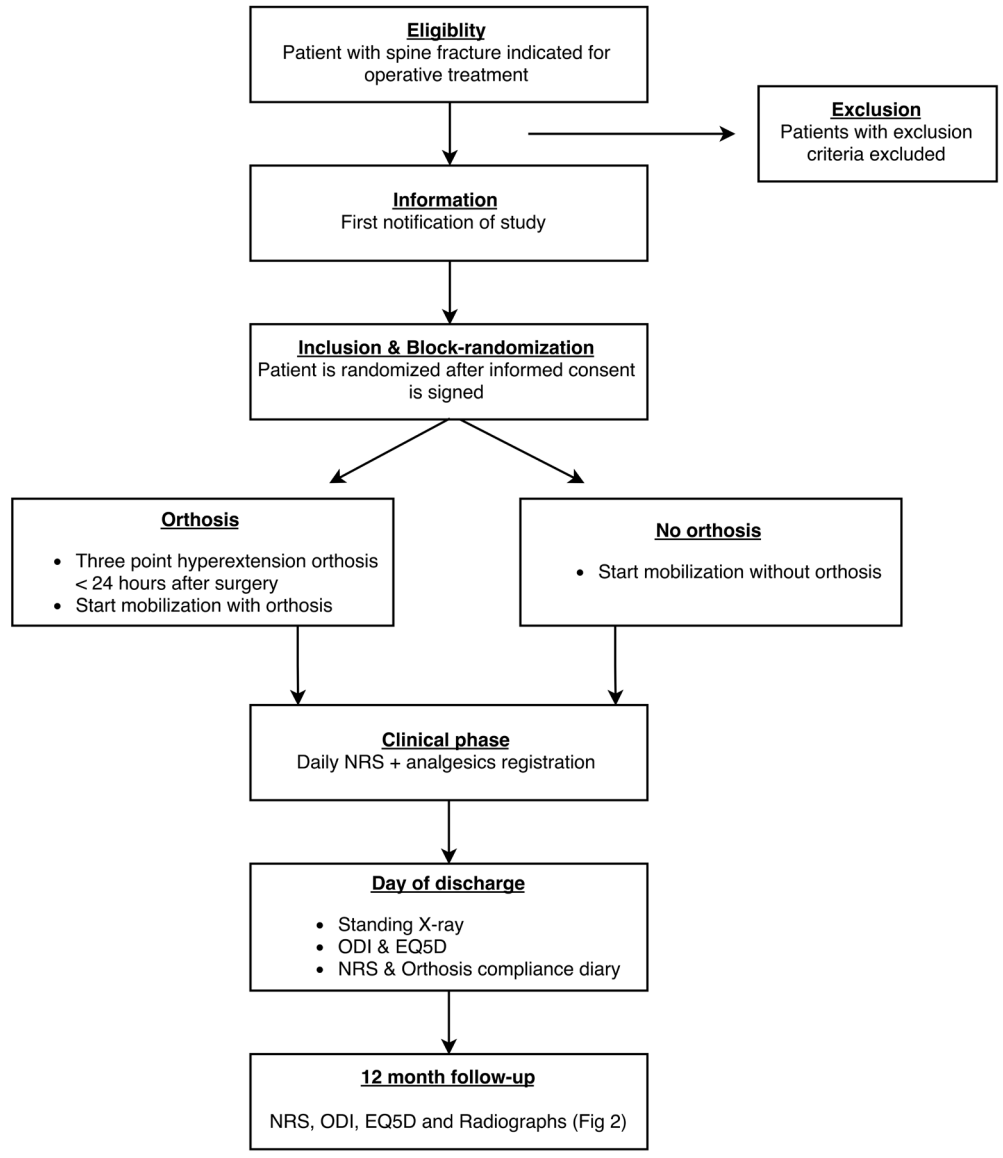
Secondary outcomes

Pain (NRS) on other measurement moments & Analgesics

Pain measured on other moments than the primary moment will function as secondary outcomes (Fig 2). The moment 'day of discharge' is defined as day 1 to (maximum) day 10. Groups will be compared at each moment and the total course of pain development over twelve weeks will be compared.

Analgesics are additionally registered at the pain measurement moments. Patients have to answer whether they at that moment use analgesics for back pain (yes/no), and if yes, what medication (acetaminophen; NSAID; opioids; or a combination). The medication used will be compared between groups.

Figure 1. Flow chart for patients from presentation until final follow-up.



EQ-5D, EuroQuol 5 Dimensions; NRS, Numerical Rating Scale; ODI, Oswestry Disability Index.

Quality of life

Quality of life will be measured (Figure 2) using the EuroQuol 5 Dimensions (EQ-5D-5L) questionnaire which has shown validity for low back pain.[31] The EQ-5D is a standardized measure of health status that consists of five domains; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain can be scored on five levels; no problems, slight problems, moderate problems, severe problems, and extreme problems/unable. Finally the questionnaire consists of a VAS score which can be scored from 1 – 100 to be used as a quantitative measure of general health. An index value of overall health can be calculated for each patient using the five dimension scores and a country specific value set, which is available for the Netherlands. Groups will be compared on domain, VAS and index scores. Furthermore EQ-5D scores will be compared to scores of the Dutch general population[32].

Back pain related function

The Oswestry Disablity Index (ODI)[33] is validated for[27, 34] and will be used to measure condition specific back pain (Figure 2). The 'day of discharge' value will be determined on day 1 to (maximum) day 10. Originally designed for chronic low back pain but due to lack of specific scoring instruments now also often used for evaluation of treated traumatic thoracolumbar fractures.[35] The questionnaire consists of ten questions with each six answer options that are rated from 0 to 5 points from which a summary score is calculated.

Kyphosis and fracture consolidation

Kyphosis will be measured (Figure 2) using the Cobb angle which has proven the best inter- and intraobserver reliability.[36] Defined as the angle between the upper endplate of the vertebra above and the lower endplate of the vertebra below the fractured vertebra. This will be done on CT-scan (mid-sagittal slide) pre-operatively and at follow-up moments on standing X-ray. Follow-up radiographs are made at the discretion of the treating surgeon and generally follow a standard pattern (Figure 2). Fracture consolidation will be assessed at the same time of kyphosis assessment using the same radiographic images. Kyphosis and fracture consolidation measurements will be done at the end of follow-up by an outcome assessor (orthopedic/trauma surgery resident) blinded to patient allocation. Additionally if any implant failure is seen on follow-up radiographs, this will be recorded under complications. In difficult cases an independent experienced spine surgeon will be consulted.

Complications

All complications occurring during the study period from inclusion to final follow-up after one year are registered. Complications are extracted from the hospital information system. Complications will include, but will not be limited to, infections (pulmonary, urinary tract, wound) that are culture proven and/or treated with antibiotics, clinically diagnosed and registered pressure sores, ileus treated with a gastric tube and deep venous thrombosis that is ultrasound proven and medically treated. Complications will be graded according to the Clavien-Dindo grading scale[37].

Hospital stay & return to work

Hospital stay is defined as the amount of days from surgery to discharge. Return to work is defined as the amount of days from surgery to the outpatient appointment on which it is first registered that a patient has returned to work. Results are stratified for patients that have partially returned to work.

Subjective outcomes

After twelve weeks, the group that was randomized to using an orthosis will receive three additional subjective questions accompanying the validated questionnaires. These consist of orthosis satisfaction (yes/no); wishing a post-operative orthosis if another thoracolumbar fracture would occur (yes/no); main benefits of the orthosis (pain relief; confidence; faster healing; reminder to take care; did not help; other (open)).

Orthosis compliance

Additionally the group that was randomized to an orthosis will receive a questionnaire at inclusion on which they are asked to register orthosis compliance. Compliance should be registered weekly, at the end of every week, for twelve weeks. An estimate has to be given of how often the orthosis was worn as it was required by the physiotherapist or doctor. Answers consist of always (100%); most of the time (75%); half of the time (50%); quarter of the time (25%) or never (0%). On every measurement moment of other questionnaires (2,6,12 weeks), patients are also reminded to fill in the pain and compliance forms.

Figure 2. ORNOT study flow diagram (according to SPIRIT guidelines)

	STUDY PERIOD							
	Enrolment	**Allocation**		**Post-allocation**				
TIMEPOINT	**Clinical phase**	**< 24h post operative**	**Day of discharge (day 1 to max. 10)**	**2 wks**	**6 wks**	**12 wks**	**6 mts**	**12 mts**
ENROLMENT:								
Eligibility screen	X							
Informed consent		X						
Allocation		X						
INTERVENTIONS:								
Orthosis		●	—	—	—	●		
No Orthosis		●	—	—	—	●		
ASSESSMENTS:								
Baseline variables	X		●	—	—	—	—	●
Complications	X		●	—	—	—	—	●
Hospital Stay			X					
NRS	X		●	—	—	●		
Analgesics			●	—	—	●		
Radiographs (standing)			X		X	X	X	X
EQ-5D			X			X	X	X
ODI			●	—	—	—	—	●
Return to work				●	—	—	—	●
Subjective outcomes						X		
Orthosis compliance			●	—	—	●		

Wks; weeks, mts; months, NRS; Numerical Rating Scale, ODI; Oswestry Disability Index, EQ5D; EuroQuol 5 Dimensions

Data collection

All data will be collected, coded and stored using Castor EDC (www.castoredc.com), a GCP guideline approved online data capture application. The decoding file will be saved to a local secured hospital drive, only accessible by the principal and coordinating researchers. Data is collected during hospital stay, at specific measurement moments and outpatient appointments

(Figure 2). Questionnaires will be sent by email through Castor. The coordinating investigator (AS) regularly checks if questionnaires are sent and completed, if not, the questionnaire is generally resend within 5 days. If the questionnaire is not completed within one week, the patient is called by the coordinating investigator. Baseline data and secondary outcomes including NRS during hospital stay (standard nursing care) will be extracted from the hospital information system. No additional outpatient appointments will be made for study purposes and radiographic investigations will only be ordered on behalf of necessary treatment by the treating surgeon, although this generally follows a standard schedule. A study flow diagram is shown in Fig. 1 and detailed follow up in Fig. 2. Patients that deviate from intervention are requested to report this on the orthosis compliance form with arguments and to continue reporting outcomes as they would have otherwise.

Intervention assignment

Intervention allocation is computer generated using Castor, randomization is stratified for single or multiple vertebral fractures and treatment center. These variables are used for stratification of randomization because these possibly influence the primary outcome (pain). As this study was not designed to change local daily practice of surgical techniques concerning the approach (minimally invasive versus open (MIS)) or the use of additional transpedicular vertebral body stenting (VBS), patients are stratified for treatment center. Choice of surgical technique is based on patient and fracture characteristics and surgeons preferences in both hospitals. One hospital preferably treats patients minimally invasive and is liberal in the use of VBS (OLVG). The other hospital uses both open and minimally invasive techniques, and is less liberal in the use of VBS (VUMC). Patients can only be randomized by the principal researcher and the coordinating researcher and after informed consent is signed. Allocation is not blinded to patients, researchers and care providers as this is practically not possible. The outcome assessor of kyphosis and fracture consolidation will be blinded to patient allocation.

Sample size

A power calculation based on the primary outcome parameter was done to calculate the required sample size. The primary outcome is pain on NRS score at 6 weeks post-operative. There is currently no literature available that describes the minimal clinical important difference (MCID) for acute traumatic spine fractures. It has however been stated by experts that there is insufficient empirical evidence to set different MICs for acute or chronic low back pain[22]. Based on the expertise of the initiating hospital's pain consulting team (that treats a lot of patients with acute spine fractures) and existing literature[21, 22], a difference of 2 points on NRS score with standard deviation of 2,5 was used as a clinical significant difference. Using these differences, a significance level of α=0,05 and power of β=0,80, it was calculated that

with 21 patients in both groups a power of β=0,82 can be reached. When taking a follow-up loss of 10% into account, the total amount of patients aimed for is 46.

Statistics

Outcomes will be analyzed using IBM SPSS 22. Primary analysis will be done according to both intention-to-treat principle and per-protocol approach, due to the non-inferiority setup.[38-40] Non-compliant patients will not be crossed over the other group as this would probably lead to an overestimation of the no-orthosis group. Depending on the amount of non-compliance of the orthosis it will be decided which analysis is of more importance if they do not lead to the same conclusion.

Categorical data will be displayed as frequencies with proportions. Continuous outcomes will be described as mean with standard deviation and if skewed as median with interquartile range. Normality will be tested visually using a histogram, Q-Q plot and boxplot. Parametric tests will be used if data follows a normal distribution and non-parametric tests otherwise. The primary outcome, average NRS score on six weeks, will be analyzed using an independent t-test or Mann-Whitney U test if skewed.

To compare secondary outcomes at specific time moments, depending on normality, a T-test or Mann-Whitney U test will be used. In case of confounding or effect modification, this will be corrected for using linear regression analysis. To analyze the effect on NRS, ODI and EQ-5D over time a mixed model analysis for repeated measures will be performed. Categorical variables will be analyzed using a Chi^2 test.

Monitoring

Data monitoring is provided by an independent clinical research bureau (Clinical Research Bureau, Amsterdam, the Netherlands) and will take place at pre-defined moments in the initiating center based on study risk classification. Monitoring in the initiating center is deemed sufficient as the study risk has been classified negligible and most inclusions are expected in the initiating center. Monitoring starts after approval of the study by the REC/IRB. Principal researchers will be informed orally and in writing on the results of monitoring. The REC/IRB will be informed annually with a progress report. All (serious) adverse events and serious adverse device events will be reported in due time to, and judged by, the REC/IRB.

Ethics and dissemination

The study protocol has first been approved by the MOVE research institute affiliated with VUmc Amsterdam on July 18th 2016 (protocol number 16.06). Secondly the REC/IRB (METc VUmc) approved the study on October 11th 2016 (case number 2016.389). There has so far been one approved protocol modification consisting of an added center, transforming the

study from single center to multicenter. All protocol modifications will only be done after approval of the REC/IRB. An interim analysis is done after inclusion of the first 20 patients. If a statistical difference of ≥ 3 NRS points between groups is found, the METc will be consulted to judge if premature termination is necessary. The study has been registered in an international and a national trial database, respectively clinicaltrials.gov (NCT03097081) and trialregister.nl (NTR3840). After completion of the trial, the results will be offered to an international scientific journal for peer-reviewed publication.

Discussion

The role of an orthosis in post-operative care of surgically treated thoracolumbar fractures has not yet been studied properly. An essential role of the orthosis in the healing process of these injuries has never been proven, which explains the current subjective use in post-operative care.[2, 3] The beneficial effect can only be scientifically tested by randomizing groups between the use and no use of an orthosis. To our best knowledge, this is the first prospective randomized study on the use of post-operative orthoses.

Patients randomized to an orthosis, might not use it as prescribed. Therefore, weekly monitoring of orthosis compliance is introduced in this study. Some dependence on patients' willingness to truthfully and periodically complete the questionnaires (pain and orthosis compliance) is consequently created. However, despite reminders some missing data cannot be ruled out. A compliance validation study is however currently being planned using temperature sensors to obtain true orthosis compliance data. If this study will start while the current study is still including patients, some will receive an orthosis with a temperature sensor. The validation of the compliance forms will then be reported in the study results and used for final analysis.

While other studies on orthoses for spine fractures usually measure pain only once for each moment,[11, 16, 41] pain measurement in this study consists of several consecutive scores. Even with momentary peaks or missing values, a very reliable average outcome can be computed.

One center was added six months after the first inclusion, changing the study from mono- to multicenter. Introducing some heterogeneity as local operative treatment protocols differ slightly between hospitals due to different standards of surgical practice. This concerns the posterior open versus minimally invasive approach and the additional use of vertebral body stenting.[42] As randomization is stratified for participating center it is unlikely this outcome will be influenced unequally. Furthermore, the number of patients treated with MIS and VBS in each group will be reported and outcomes will be statistically corrected if needed. Additionally, it is likely that these techniques will in the future become standard care, making the results of this study wider applicable. No patients with a psychiatric comorbidity have been included so far and this could considerably influence QOL outcomes. Therefore an additional amendment

that excludes patients with a psychiatric comorbidity to participate in the study is currently under consideration by the IRB.

Conclusion

This prospective randomized non-inferiority study will provide a clear recommendation on the use of a post-operative orthosis after posteriorly stabilized thoracolumbar fractures. If no orthosis is proven to be non-inferior to an orthosis, this could lead to a change in post-operative protocols in which orthoses should not be used routinely. This could result in less unnecessary patient' inconvenience and less costs.

Trial status

The trial has started recruiting patients on November the 29th 2016 and is currently under protocol version 4 designed at August 8th 2017. Recruitment is expected to be complete by the end of 2021.

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