

Combined extracorporeal shock wave lithotripsy and endoscopic treatment for pain in chronic pancreatitis (SCHOKE Trial): study protocol for a randomized sham-controlled trial

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Abstract

Background: Pain is the primary symptom of chronic pancreatitis (CP) and remains a considerable therapeutic challenge. In patients with obstruction of the pancreatic duct, including stones and strictures, endoscopic treatment with or without preceding extracorporeal shock wave lithotripsy (ESWL) have been used for pancreatic duct decompression. The rationale for these procedures is based on the assumption that obstruction of the pancreatic duct leads to ductal hypertension and pain. However, clinical pain symptoms correlate poorly with pancreatic duct morphology and the evidence for pancreatic duct decompression as an effective treatment for pain is based on case-series and comparison between different procedures, while no randomised prospective sham-controlled trials are currently available. The SCHOKE trial is a randomized sham-controlled trial designed to determine if pancreatic duct decompression is an effective treatment for pain in patients with CP.

Methods: The SCHOKE trial is a randomized, single-blinded, parallel-group, sham-controlled trial designed to evaluate the effect of combined ESWL and endoscopic treatment for pain in patients with CP. In total, 106 adult patients with painful CP and pancreatic duct obstruction will be randomized to combined ESWL and subsequent endoscopic treatment or corresponding sham procedures. The primary outcome is pain relief during the 3 months post-randomization period as documented in a pain diary. Secondary outcomes include quality of life and functional scores, patient's global impression of change, change in use of analgesics, frequency of hospitalization and complications. Standard follow-up is at 3 and 6 months after randomization. In an experimental sub-study, quantitative sensory testing obtained before and after intervention will be used to obtain information on central pain processing and to develop models for prediction of treatment outcome.

Discussion: The SCHOKE trial investigates if pancreatic duct decompression, obtained by combined ESWL and endoscopic treatment, is effective for pain treatment in patients with CP.

Trial registration: ClinicalTrials.gov, NCT03966781. Registered on 25th May 2019.

Introduction

Pain is the primary symptom of chronic pancreatitis (CP) and remains a considerable therapeutic challenge [1]. In patients with pathological changes of the pancreatic duct, including stones and strictures, endoscopic treatment with or without preceding extracorporeal shock wave lithotripsy (ESWL) and surgery have been used with varying success to treat pain [2–4]. The rationale for such invasive procedures is based on the hypothesis that obstruction of the pancreatic duct leads to ductal hypertension and pain [5, 6]. However, clinical pain symptoms correlate poorly with pancreatic ductal morphology, as assessed on cross-sectional imaging [7, 8], and the response to endoscopic or surgical treatment is unpredictable, with long term response rates ranging from 30–60% [3, 9, 10]. Also, the evidence for these treatments are based on case-series and comparison between different procedures, while no randomised prospective sham controlled trials have evaluated the effectiveness of invasive

treatments for pain in CP [9–11]. Additionally, a marked placebo effect has been observed in most trials of painful CP and this, together with the natural history of disease, needs consideration when treatment effects are evaluated [12–14]. Therefore, the evidence for invasive treatments for pain in CP treatments can be questioned [14].

Recent meta-analyses have documented that non-specific effects of invasive procedures are generally large; particularly in the field of pain-related conditions and for endoscopic based therapies [15, 16]. For example, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (biliary or pancreatic sphincterotomy or both) has for many years been considered the state-of-the-art treatment for patients with abdominal pain due to suspected sphincter of Oddi dysfunction. However, a high quality randomized controlled trial (RCT) showed that patients who had no sphincterotomy at ERCP, and who were blinded to their treatment, reported as much pain relief as those who underwent sphincterotomy [17, 18]. These findings challenge conventional wisdom and underscore the necessity of appropriately conducted RCTs including a sham procedure, when the effectiveness of invasive procedures is evaluated [14].

Albeit endoscopic treatment or surgery are widely used for pain in CP they are only effective in a subset of patients [4, 9, 19, 20]. An improved understanding of the mechanisms underlying pain in CP suggest that the pain aetiology in most patients is multifactorial and, in addition to the proposed mechanical mechanisms for pain (ductal obstruction/hypertension), a large body of evidence support a “neuropathic pain phenotype” with abnormal processing in the peripheral and central neural pathways [6, 21, 22]. Invasive procedures will not be effective in neuropathic pain, and can even be considered harmful [14]. This likely explains the variable response to endoscopic and surgical treatments and underline an unmet need for biomarkers to identify responders to the different treatment modalities.

Quantitative sensory testing (QST) can be used to investigate the state of the pain system. The technique is based on the rationale that different neural pathways and networks can be explored using standardized stimulation with simultaneous recording of the evoked pain response by psychophysical and/or objective methods [23]. Due to spinal convergence between visceral afferents from the pancreas and somatic afferents from the T10 skin dermatome, somatic QST can be reliably used to assess if the pain system is locally sensitized by nociceptive input from the pancreas (segmental sensitization) [24, 25]. However, in many patients with chronic pain, the pain system has become dysfunctional and undergone widespread sensitization, which is evident as abnormal responses (hyperalgesia) to stimuli applied in areas remote to the pancreas [26]. Taken together, QST profiling based on testing in several dermatomes together with specific test paradigms (temporal summation and assessment of descending inhibition) can be used to determine whether patients have abnormal central pain processing or evidence of segmental or widespread sensitization [27–29].

Methods

The study protocol is reported in accordance with the Standard protocol items: recommendation for interventional trials (SPIRIT) guidelines (Supplementary Table 1: SPIRIT checklist).

Study hypothesis and aim

The hypothesis of the study is that pancreatic duct decompression following ESWL and endoscopic treatment induce short term (3 months) and mid-term (6 months) pain relief in patients with CP compared to a sham procedure. In addition, we hypothesize that QST can be used to predict the outcome of treatment. Hence, patients with evidence of widespread sensitization of central pain pathways are hypothesized to have a worse outcome to ESWL and endoscopic treatment compared to patients with no evidence of widespread sensitization.

Study design and setting

Randomized, single-blinded, single-centre, parallel-group, sham-controlled, prospective trial designed to evaluate the effect of combined ESWL and endoscopic treatment for pain in adult patients with CP. The study will be conducted at the tertiary care academic institute Asian Institute of Gastroenterology, Gachibowli, Hyderabad, India.

Inclusion Criteria

- A diagnosis of chronic calcific pancreatitis diagnosed using the Mayo Clinic diagnostic criteria [30]. Both diabetic and non-diabetic patients will be allowed to enter the study.
- Age \geq 18 years.
- Chronic abdominal pain characteristic for CP with a pain intensity >3 VAS on a 0-10 VAS and meet the criteria for chronic pain (pain \geq 3 days per week for at least 3 months).
- Obstruction of the pancreatic duct due to intraductal stones with dilatation of the duct proximal to the obstruction, as determined by magnetic resonance cholangiopancreatography (MRCP) or abdominal computed tomography (CT).
- The patients must be able to read and understand the provided informed consent.
- Patients must personally sign and date informed consent document indicating that he/she has been informed of all pertinent aspects of the trial.
- Patients should be willing to comply with the scheduled visits, clinical and experimental assessment plans, and other trial procedures.

Exclusion Criteria

- Patients with any clinically significant laboratory abnormalities that in the opinion of the investigator may increase the risk associated with trial participation or may interfere with the interpretation of the trial results.
- Previous history of pancreatic surgery, ESWL or ERCP

- Patients with a pancreatic stricture on cross-sectional imaging prior to study enrolment
- Active alcohol or illicit drug dependencies.
- Patients with evidence or history of medical or surgical disease of importance for this study as judged by the investigator.
- Patients must not suffer from painful conditions other than CP that make them unable to distinguish the pain associated with CP from chronic pain of other origin.
- Presence of pancreatic head mass, multiple strictures, large ascites, large fluid collections.

Interventions

Patients will be randomly allocated to either combined ESWL and endoscopic treatment or sham treatment.

Combined ESWL and endoscopic treatment

Patients enrolled in the active treatment group will be subjected to ESWL followed by ERCP. ESWL will be conducted under epidural anaesthesia. For epidural anaesthesia, bupivacaine will be used to block the 6-12 thoracic spinal segments. The patient's eyes will be lightly covered during the procedure. Once epidural anaesthesia is achieved, the patient will be given a light sedation and ESWL will be performed using a third generation Dornier dual focus lithotripsy system (Dornier Delta 3, Dornier MedTech GmbH, Germany) providing a maximum of 5000 shocks at the rate of 90 shocks per minute over a maximum period of 2 days. After lithotripsy, stone fragments will be removed during an ERCP procedure. An endoscopic pancreatic sphincterotomy will be performed and complete stone removal will be attempted with subsequent stenting of the pancreatic duct in the presence of a pancreatic stricture (not detected on MRCP prior to enrolment) or in case of incomplete stone removal. In case of a pancreatic duct stenting patients will undergo a new ERCP procedure after 6 months for stent exchange or removal (after completion of all study assessments). When complete runoff of contrast material is observed after removal of the stent and an extraction balloon can be passed through the pancreatic duct, endoscopic treatment is considered completed and further stenting will be stopped. Persistent strictures will be treated by repeated endoscopic dilations and sequential insertion of new stents in agreement with the European Society of Gastrointestinal Endoscopy (ESGE) guidelines [31].

Sham treatment

In the sham/control group, patients will be given a transient superficial pin-prick sensation to give the feeling of epidural anaesthesia prior to sham ESWL. Subsequently, the lithotripsy machine will be switched on, without establishing any form of contact with the patient's body. The patient's eyes will be lightly covered all along the procedure. Following sham ESWL, patients will be subjected to sham ERCP with duodenal intubation of the endoscope and examination of the papillary area, but no pancreatic ductal intervention will be performed.

Concomitant medication

Patients will be instructed not to change their regular pain treatment during the trial period. Regular pain treatment will be recorded twice, at the screening visit and the last visit. Rescue pain medication, taken on an “as needed basis”, is allowed throughout the trial period and its use will be documented and quantified in the pain diary.

Outcomes

The study consists of a clinical and an experimental part. The clinical part of the study aims to investigate the pain-relieving effects of combined ESWL and endoscopic treatment in patients with painful CP in comparison with sham treatment. The experimental part of the study aims to evaluate if QST profiles obtained prior to ESWL and endoscopic intervention can be used for prediction of treatment outcome.

Primary Clinical Endpoint

The primary clinical endpoint is pain relief. Average and maximal daily clinical pain intensity scores will be recorded in a patient pain diary based on a 0-10 visual analogy scale (VAS), with registration of the baseline pain intensity scores the week prior to intervention and weekly recordings continued for a 3 months period after intervention. Mean values of pain scores will be calculated over 1 week to adjust for day-to-day variability in pain intensity. The difference in pain scores between patients receiving active treatment (ESWL and ERCP) and sham treatment are compared, with the primary comparison of average pain scores 3 months after intervention. Weekly telephone interviews from a study co-ordinator will be undertaken to facilitate accurate registration and compliance pain score.

Secondary Clinical Endpoints

- Difference in pain scores between groups after 6 months.
- The ratio of responders versus non-responders defined by a decrease in the average clinical pain score (VAS) of 30% after 3 and 6 months compared to baseline.
- Difference in number of pain free days between groups after 3 and 6 months.
- Change in analgesic consumption (if used) after 3 and 6 months compared to baseline.
- Total number of hospitalizations during the study period.
- Difference in quality of life using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30) between groups after 3 and 6 months.¹⁵
- Difference in pain and physical functioning composite scores of the modified brief pain inventory-short form (mBPI-sf) between groups after 3 and 6 months.¹⁶
- Difference in depression and anxiety scores of the Hospital Anxiety and Depression scale between groups after 3 and 6 [32].
- Patient Global Impression of Change (PGIC) after 3 and 6 months.¹⁸
- Assessment of complications to interventions during the study period.

Experimental endpoints

The following experimental pain measures will be employed prior to intervention as well as 24-48 hours and 3 months after intervention to characterize changes in pain processing induced by the assigned procedures:

- Muscle pressure stimulation (pancreatic viscerotome [T10 ventral and dorsal] and control areas [C5, L1 and L4]).
- Bone pressure stimulation (tibia bone)
- Temporal summation to repetitive pinprick stimulations of the pancreatic area (T10) and control area [dominant forearm]).
- Conditioned pain modulation (CPM).

Sample size determination

The study is powered to detect a minimal difference between groups of 30% on the average clinical pain score 3 months after intervention [33]. On the basis of an assumed SD of 45%, we determine that a study with 48 patients per group is needed to provide a power of 90% (to allow for secondary endpoints) with the use of a 2-sided significance level of 0.05 [34]. To allow for a 10% dropout rate the sample size is set at 106 patients.

Randomization, blinding and treatment allocation

A computer-generated pseudo-random code will be used to assign patients to treatment (randomization). A block randomization will be used, allowing 6 patients at the time to be randomized at equal proportions for sham procedures or combined ESWL and endotherapy, no stratification of randomization will be applied. The allocation sequence will be generated by a biostatistician who won't be involved in the administration of treatment or recording of data. Randomization of patients into the two groups will be done by a physician who won't have access to the clinical data of the patients.

The patients will be blinded to the treatment received. The patients in the sham procedure will be provided a superficial needle prick with a sterile needle to mimic epidural anaesthesia. Then the ESWL instrument will be started so that the patients hear the sounds to get an auditory perception that the treatment is being provided. The eyes will be covered and if the patient wishes they will be given light sedation. The operator cannot be blinded due to the nature of the study. However, the principal investigator and the statistician will be blinded to the treatment arms.

In case of an emergency that necessitates knowledge of the randomization, the individual procedure assignment for each patient will be available. The codes will be available at the study centre in sealed envelopes, stored in a locked and secure area accessible only to those individuals authorized by the investigator. This procedure allows unblinding of individual subjects, without revealing codes of the entire study. The investigator will be able to determine which procedure a patient was given by opening the

sealed envelope with the corresponding randomization number. The investigator must state the reason why the code was broken on the envelope, date and sign it. At the end of the study, all sealed and unsealed envelopes must be accounted for.

Outcome measures

At baseline the following assessment parameters will be registered (figure 1): age and gender, aetiology and duration of CP, past history of acute pancreatitis, current alcohol and smoking status, the presence of complications to CP including exocrine pancreatic insufficiency and diabetes mellitus, cross-sectional imaging results, current medications including analgesics as well as past history of endoscopic and surgical treatment. Data will be collected using a paper case report form and later entered into an electronic database with double data entry check.

The follow up duration is 6 months from randomization with scheduled visits after 3 months (primary study period) and 6 months (follow-up). The questionnaires and pain diary used for collection of clinical endpoints are described in the previous sections 'primary and secondary endpoints'. In addition, QST profiles will be recorded prior to intervention as well as 24-48 hours and after 3 months after intervention. A schedule for the study assessment parameters is provided in figure 1.

Quantitative sensory testing

Repetitive pinprick stimulation (temporal summation): Recording of temporal summation to repetitive pinprick stimulations in the pancreatic and control area (midline volar site of dominant forearm) will be employed using a 256 nm Von Frey Hair (Pin-Prick Stimulatoren, MRC Systems GmbH, Heidelberg, Germany). Pain ratings using a 0-10 NRS scale will be obtained after a single application, and after the last application in a series of ten repetitive stimuli with an inter-stimulus interval of 1 second. For accurate timing of the stimuli the procedure is guided by an auditory signal using a metronome. The difference between the last and the first pain rating of the ten stimuli will be recorded as the temporal summation score.

Muscle pressure stimulation: The pressure pain detection threshold (PDT) and pain tolerance threshold (PTT) will be determined for the following skin dermatomes: C5 (clavícula), Th10 ventral (upper epigastric area – pancreatic viscerotome), Th10 back (pancreatic viscerotome), L1 (anterior superior iliac crest) and L4 (the quadriceps 15 cm above the patella). All lateralized pressure stimulations will be applied on the patient's dominant side. An electronic pressure algometer (AlgoMed, Medoc Ltd, Ramat Yishai, Israel) with a probe surface area of 1 cm² will be used for the pressure stimulations. Pressure will be increased in two separate sessions at a rate of 30 kPa per second until the PDT or PTT is reached. The assessment parameter is the pressure at the predefined sensory threshold measured in kPa.

Cold pressor test the dominant hand is immersed in an ice-chilled water bucket (2.0°C ± 0.3°C). The patient will be told to remove the hand from the water after 2 minutes of immersion or sooner if the pain is intolerable. The patients rate the pain intensity for every 10 seconds during the cold pressor test using a

0-10 VAS rating scale. If the patient withdraws their hand sooner than two minutes, due to intolerable pain, the VAS will be considered to be 10 for the remaining period of time and the time for withdrawal of the hand will be noted.

Conditioned pain modulation (CPM): CPM is a clinically measurable form of descending pain modulation that can be induced experimentally by a conditioning stimulus (the cold pressor test) and quantified by applying a “test-pain” (pressure stimulation on the non-dominant quadriceps musculature 4 cm above the patella) before and after the conditioning stimulus [35]. The difference in pressure stimulus intensity (PTT) before and after the cold pressor test provides a quantitative index of the CPM capacity in the individual patient. The techniques used for pressure stimulation and cold pressor test described above will be combined to measure CPM.

Pancreatic imaging

Cross-sectional imaging (CT and MRCP) will be used to evaluate the pancreatic morphology prior to study enrolment based on usual clinical practice. All patients enrolled in the study will have their imaging parameters reviewed and described by an expert radiologist.

Statistical analysis

The primary analysis of clinical endpoints will be by intention-to-treat, meaning that all randomized patients are included in their initially assigned study arm, regardless of adherence to the study protocol. Experimental endpoints will be by per-protocol, meaning that only patients completing the experimental setup will be included. A repeated measures linear mixed effects model will be used for the primary analysis and will include terms for treatment group, assessment time point (week) and the interaction of treatment with assessment time point. Summary statistics of pain scores will be provided for the individual time points, the difference in pain scores between groups after 3 months is considered the primary efficacy parameter. Subgroup and covariate analyses will be performed, if applicable. Subsequent analyses directed at the secondary, experimental, and safety endpoints are analysed using appropriate statistics including mixed effect models, Fisher’s exact tests, and Student’s t-tests or Wilcoxon rank-sum tests as appropriate. The predictive value of the QST profiles will be analysed using logistic regression models.

We plan to conduct an interim analysis after approximately one third of patients (n=40) have been randomized and completed 6 months follow-up, using a two-sided significance test with the O’Brien–Fleming spending function and a type 1 error rate of 5 percent. An independent statistician, blinded for the treatment allocation, will perform the interim analysis. The statistician will report to an independent Data safety monitoring board (DSMB). The DSMB will have unblinded access to all data and decide on the continuation of the trial and will report to the internal review board of the Asian Institute of Gastroenterology. If there is a highly significant difference in improvement in pain in the treatment arm, then all subsequent patients will be subjected to this. The trial will not be stopped in case of futility, unless the DSMB during the course of safety monitoring advice otherwise.

Monitoring and safety

Prior to the trial initiation, a DSMB comprising of a neurologist, an anaesthesiologist, and a statistician (*all from outside the study centre*) will be constituted. The DSMB will conduct periodic monitoring to ensure that the protocol and good clinical practice standards are followed. The monitors may review source documents to confirm that data recorded on case report forms are accurate. The investigator and institution will allow the DSMB and appropriate regulatory authorities direct access to source documents to perform this verification. The trial site may be subject to review by the institutional review boards and/or to quality assurance audits performed by the DSMB, and/or to inspection by appropriate regulatory authorities. The DSMB will also conclude on the planned interim analysis.

The ESWL and ERCP procedures on patients with CP are currently used in daily clinical practice and participation in the study is not expected to be associated with an increased risk of adverse events compared to standard clinical care. Following ESWL we have observed mild erythema at the site of stimulation. There has been very infrequent incidence of acute pancreatitis after the procedure. Since ERCP is associated with an increased risk of post-procedure acute pancreatitis, means to decrease this risk (rectal indomethacin and pre-procedural IV fluids) will be used in high risk patients.

Discussion

Pain is the primary symptom of CP and associated with a poor health related outcome including reduced life quality, disability and increased health resource utilization [36–38]. Unfortunately pain treatment is unsatisfactory in a large proportion of patients and generally based on low quality evidence in particular for invasive treatments (endoscopy and surgery) [14]. The SCHOKE trial is the a randomized sham-controlled trial designed to determine if pancreatic duct decompression is an effective approach for obtaining pain relief in patients with CP. According to current guidelines, invasive procedures are recommended for pain treatment in the context of CP and some practitioners even advocate for surgical treatment in the early phase of CP [39–41]. However, neither surgery or endoscopic therapy have been thoroughly evaluated in sham controlled trials [14]. The present study will, for the first time, provide sham controlled evidence for the effectiveness of pancreatic duct decompression as a remedy to relieve pain in CP.

The mechanisms responsible for pain in patients with CP are multifactorial and thus it is to be expected that no treatment can effectively relieve pain in all patients [42]. Identification of biomarkers that link pain mechanisms with specific treatment modalities is therefore an unmet need in the field, but unfortunately there are few personalized approaches to pain treatment in CP at this time [29]. For example, the presence, severity and temporal nature of pain correlate poorly with imaging findings and, as such, imaging can only be used to identify cases where an invasive based treatment is technically feasible, but it cannot be used to determine if patients will benefit from the planned treatment [7,8,43]. A QST protocol designed for characterization of pancreatic pain has previously shown effectiveness for the prediction of analgesic outcome in patients with CP and may serve as a useful biomarker for endoscopic treatment

efficacy as well [24]. The SCHOKE trial therefore includes a QST testing paradigm specifically developed to assess and characterize pain in CP [29].

In conclusion, the SCHOKE trial is a randomized sham-controlled trial that investigates whether pancreatic duct decompression is effective for obtaining pain relief in patients with painful CP.

Trial Status

Ethical approval has been obtained and the trial was registered with clinical.trials.gov on May 25th, 2019 (NCT03966781). The first patient is expected to be randomized by November 1st, 2019 and recruitment is expected to be completed November 1st, 2020.

Protocol version: November 4th, 2019.

Abbreviations

CP: chronic pancreatitis; CPM: conditioned pain modulation; CT: computed tomography; BPI: brief pain inventory; DSMB: data safety monitoring board; ESWL: extracorporeal shock wave lithotripsy; ERCP: endoscopic retrograde cholangiopancreatography; IRB: institutional review board; MRCP; magnetic resonance cholangiopancreatography; QST: quantitative sensory testing; VAS; visual analogue scale; RCT: randomized controlled trial; SPIRIT: Standard protocol items: recommendation for interventional trials

Declarations

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The SCHOKE trial is an investigator-initiated trial. Financial support is sought from relevant funds. Sponsors will have no influence on the design of the study, data collection, results or publication.

Availability of data and materials

Patients are coded by a numeric randomization code (anonymized) and only the principal investigators have access to this code. The source data are kept by the project leader for 15 years at the datacenter of the Asian Institute of Gastroenterology. All data generated or analyzed during this study will be included in the published results.

Authors' contributions

SSO drafted the manuscript. AMD and RT co-authored the writing of the manuscript. All authors participated in the design of the study and critically assessed the study design, edited the manuscript and read and approved the final manuscript.

Ethics approval and consent to participate

The study will be conducted in accordance with the principles of the Declaration of Helsinki. The internal review board (IRB) of the Asian Institute of Gastroenterology has approved the protocol (AIG/IEC28/04.2017-03). Informed consent will be obtained from all participating patients in oral and written form prior to randomization.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

TIMEPOINT	STUDY PERIOD				
	Enrolment	Allocation	Primary study period		Follow-up
	Week -1	0	Week 1	Month 3	Month 6
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
ESWL & ERCP			X		
Sham treatment			X		
ASSESSMENTS:					
Baseline variables ^a		X			
Primary outcome ^b	←—————→				X
Secondary outcomes ^c		X		X	X
Experimental outcomes ^d		X	X	X	

Figure 1

a Baseline variables: age, gender, aetiology and duration of CP, history of acute pancreatitis, current alcohol and smoking status, complications to CP including EPI and diabetes mellitus, cross-sectional imaging results, medications including analgesics, past history of endoscopic and/or surgical treatment

b Primary outcome: Pain scores documented in a weekly pain diary based on a 0-10 VAS

c Secondary outcomes: Pain scores after 6 months, >30% pain relief, number of pain free days, analgesic consumption, frequencies of hospitalizations, quality of life (EORTC-QLQ-C30), pain and physical functioning composite scores (mBPI-sf), anxiety and depression scores, patients' global impression of change, complications

d Quantitative sensory testing assessment parameters