Preemptive Infiltration with Betamethasone and Ropivacaine for Postoperative Pain in Laminoplasty or Laminectomy (PRE-EASE): A Study Protocol

CURRENT STATUS: ACCEPTED

Niti Shrestha  
Beijing Tiantan Hospital

Liang Wu  
Beijing Tiantan Hospital

Xianodi Wang  
Beijing Tiantan Hospital

Wenqing Jia  
Beijing Tiantan Hospital

Fang Luo  
Beijing Tiantan Hospital, Capital Medical school

13611326978@163.com Corresponding Author

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SUBJECT AREAS  
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KEYWORDS  
Betamethasone, Diprosan, Preemptive infiltration, Postoperative pain, Laminoplasty, Laminectomy, Protocol
Abstract
Background: Laminoplasty and laminectomy have been used for decades for the treatment of intraspinal space occupying lesions, spinal stenosis, disc herniation, injuries, etc. After these procedures, patients often experience severe postoperative pain at the surgical site. Intense immediate postoperative pain after many spinal procedures makes its control of utmost importance. Preemptive injection of local anesthetics can significantly reduce postoperative pain during rest and movement, however, the analgesic effect is maintained for a relatively short period of time. Whether betamethasone combined with local anesthetic for laminoplasty or laminectomy has better short-term and long-term effects than the local anesthetic alone has not been reported yet.

Method: The PRE-EASE trial is a prospective, randomized, open-label, blinded endpoint, single-center clinical study including 116 participants scheduled for elective laminoplasty or laminectomy, with a 6 months’ follow-up process. Preemptive local infiltration with betamethasone and ropivacaine (treatment group) or ropivacaine alone (control group) throughout the entire thickness of the planned incision site will be performed by the surgeon, prior to making the incision. The primary outcome will be the cumulative butorphanol consumption within the first 48 hours’ postoperative period.

Discussion: This study will add significant new knowledge to the effect and feasibility of preemptive local infiltration of betamethasone for postoperative pain management in laminoplasty and laminectomy.

Trial Registration
Clinicaltrials.gov, NCT04153396. Registered on November 6, 2019

https://www.clinicaltrials.gov/ct2/show/NCT04153396

Administrative Information
Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).
| Trial registration {2a and 2b}. | Clinicaltrials.gov, NCT04153396. Registered on November 6, 2019 https://www.clinicaltrials.gov/ct2/show/NCT04153396 |
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| Author details {5a}         | Niti Shrestha*, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.  
                               | Liang Wu*, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.       
                               | Xiaodi Wang*, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.  
                               | Wenqing Jia, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.      
                               | Fang Luo, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.      |
| Name and contact information for the trial sponsor {5b} | Beijing Municipal Administration of Hospitals Clinical Medicine Development Funding Support                                    |
|                             | Contact information: 008613661058642                                                                                  |
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Introduction

**Background and rationale {6a}**

Laminoplasty and laminectomy have been used for decades for the treatment of intraspinal space...
occupying lesions, spinal stenosis, disc herniation, injuries, etc. After these procedures, patients often experience severe postoperative pain at the surgical site. With currently available systemic analgesics, the drugs related side effects may exacerbate when drug concentration in blood is high, and there may be insufficient analgesia when the blood concentration is low and may also lead to insufficient management of pain at movement.\textsuperscript{1} Intense immediate postoperative pain after many spinal procedures makes its control of utmost importance.\textsuperscript{2} Despite recent advancements in postoperative pain management, there is evidence of inadequate postoperative pain control after spinal surgery, which leads to reduced patient mobility.\textsuperscript{1,2} Early mobilization after spine surgery is vital for reduction of hospital stay, postoperative complications, better performance- based functional tests and patient-reported outcome measures.\textsuperscript{3}

Severe immediate postoperative pain increases the risk of chronic pain, along with the occurrence of nerve injury and the development of neuronal plasticity associated with peripheral and central sensitization.\textsuperscript{4} Central sensitization, an increase in central nervous system excitability, occurs due to the ongoing noxious input,\textsuperscript{5} which leads to alldynia, the perception of pain resulting from a normally non-painful stimuli.\textsuperscript{6} Therefore, reducing postoperative acute pain is vital for the prevention of chronic pain.

At present, several pain controlling methods are available, with opioids being the cornerstone for management of severe acute postoperative pain.\textsuperscript{2,7} However, there are many compelling reasons to avoid opioid in surgical patients due to its numerous side effects.\textsuperscript{8} Methods for systemic administration include: oral analgesics, intermittent intravenous, intramuscular injections, patient-controlled intravenous analgesia, etc.\textsuperscript{1} Nevertheless, the aforementioned methods may have a lot of side effects, and are usually used after the occurrence of pain. Hence, the analgesic effects are sometimes inadequate.

Topical administration options have less systemic side effects. Preemptive injection of local anesthetics can significantly reduce postoperative pain, although the analgesic effect is maintained
for a relatively short period of time. Incidences of technical failure or local anesthetic toxicity from wound catheters were found to be low, in a study by Liu et al., \(^9\) although other reports have raised concerns about probable wound infection from the existence of catheter.\(^{10}\) Furthermore, indwelling catheters come with a risk of complications such as prolapse or obstruction of the catheter. Cost-effectiveness, optimal site for catheter placement, or optimal dosage are also factors to be considered.\(^9\) Techniques such as epidural analgesia and nerve blockade may have a possible high failure rate and not be cost effective, but can deliver better postoperative analgesia.\(^{11,12,13}\) Gurbet et al.\(^1\) reported that preemptive infiltration of bupivacaine or levobupivacaine combined with methylprednisolone, a short-acting glucocorticoid, can effectively control pain after unilateral lumbar laminectomy. However, the above solution has a shorter duration of action, and merely 24-hour postoperative observation was done with only 60 participants. Ersayli et al.\(^{14}\) reported that, compared to infiltration at wound closure, preemptive injection of bupivacaine or bupivacaine-methylprednisolone into muscles near the incisional site provided more effective analgesia after lumbar discectomy, and concluded that, methylprednisolone combined with local anesthetic was not superior to the analgesic effect of local anesthetic alone. However, in the study,\(^{14}\) 75 participants were enrolled with only 15 in each group. Therefore, it is necessary to observe more cases to explore other compatibility of drugs with longer duration of action and stronger analgesic effect.

Betamethasone, a stereoisomer of dexamethasone, is a long-acting corticosteroid, which has longer lasting anti-inflammatory properties because of its partial presence in particulate form in ropivacaine that acts as a local reserve.\(^{15}\) Whether betamethasone combined with local anesthetic for laminoplasty or laminectomy has better analgesic effects than the local anesthetic alone has not been reported yet. Therefore, a detailed study is needed to compare the postoperative analgesic efficacy of preemptive infiltration of betamethasone plus ropivacaine and ropivacaine alone for laminoplasty or laminectomy.
Objectives {7}
We hypothesize that preemptive local infiltration of betamethasone plus ropivacaine helps relieve postoperative pain, reduces the request for postoperative analgesics, and promotes early rehabilitation without significant risks.

Trial design {8}
The PRE-EASE trial is a prospective, randomized, open-label, blinded endpoint (PROBE), single-center clinical study designed to compare the postoperative analgesic efficacy of preemptive wound infiltration of ropivacaine alone and betamethasone plus ropivacaine for laminoplasty or laminectomy. In total, 116 patients will be randomly assigned to the betamethasone-ropivacaine (Treatment) group and the ropivacaine (Control) group at 1:1 ratio. The CONSORT patient flow diagram is presented in Figure 1.

Methods

Participants, interventions and outcomes

Study setting {9}
This is a single centre study which will be conducted from February 2020 – December 2021 at Beijing Tiantan Hospital Capital Medical University, Beijing, China.

Eligibility criteria {10}

Inclusion criteria
Patients scheduled for laminoplasty or laminectomy; American Society of Anaesthesiologists (ASA) classification of I or II; Age 18 to 64 years; Participants with an anticipated full recovery within 2 hours postoperatively.

Exclusion criteria
Patient refusal; Participants who cannot use a patient-controlled analgesia (PCA) device and cannot understand the instructions of a Visual Analogue Score (VAS); Previous history of spinal surgery; Allergy to opioids, betamethasone or ropivacaine; Peri-incisional infection; History of stroke or a major neurological deficit;
Trauma, deformity;
Psychological problems;
Extreme body mass index (BMI) (< 15 or > 35);
History of excessive alcohol or drug abuse, chronic opioid use (more than 2 weeks), or use of drugs with confirmed or suspected sedative or analgesic effects;
Patients using systemic steroids;
Pregnant or breastfeeding;
Preoperative Glasgow Coma Scale < 15;
Participants who have received radiation therapy or chemotherapy preoperatively, or with a high probability to require a postoperative radiation therapy or chemotherapy according to the preoperative imaging.

Who will take informed consent? {26a}

All participants will be provided with a written, informed consent prior to the surgery, that will describe in detail all aspects of the study and withdrawal process. Patients considered eligible for participation in the study will be given a verbal explanation of the written informed consent. Each participant will have sufficient time to decide whether to participate in this study, and will be instructed that they are free to obtain any relevant information, and raise questions they may have regarding the study at any point throughout the study. If the patient is willing to participate, written informed consent will be obtained, before the surgery. Participants will be allowed to withdraw their consent or discontinue participation without any restriction, at any time throughout the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable

Interventions

Explanation for the choice of comparators {6b}

A total of 30 ml solution will be prepared for each group, which will include 0.5ml of compound betamethasone injection (Diprospan® betamethasone propionate 5mg and betamethasone sodium phosphate 2mg) added to 14.5ml of saline and 15ml of 1% ropivacaine (NaiLePin®10mg/ml,
AstraZeneca AB, Sweden), for the Treatment group and 15ml of ropivacaine added to 15 ml of saline for the Control group. The study investigator will be responsible for preparing the respective drugs to be used for preemptive infiltration in these two groups, and the neurosurgeon will infiltrate the planned incision site with the respective study solution, prior to the incision.

**Intervention description {11a}**

**Preemptive infiltration**

A 22-gauge needle will be introduced throughout the entire thickness of the planned incision site by the surgeon, at an angle of 45° to infiltrate the prepared solution. Local infiltration solution in the Treatment Group will consist of betamethasone and ropivacaine with saline, whereas ropivacaine alone will be used with saline in the Control Group. The volume of solution to be used will be based on the length of the incision. It will be determined by the surgeon and recorded by the investigator. All other aspects of the rehabilitation process will be identical between the two groups.

**Anesthesia management**

During preoperative visit, after signing written consent, patients will be taught how to indicate postoperative pain levels based on VAS ranging from 0 (no pain) to 10 (maximal pain). Patients will also be taught how to use PCA device. In the operating theater, each patient will be prepared for continuous blood pressure and heart rate monitoring, peripheral pulse oximetry, bispectral index (BIS system, Covidien/Medtronic, USA) and electrocardiography. Then a peripheral venous cannula will be inserted and an intravenous (IV) infusion of crystalloid solution will be started. Each participant will be pre-medicated with IV midazolam 0.03 mg/kg before the induction of general anesthesia. A standard general anesthesia protocol will be followed, using 0.3-0.4 µg/kg sufentanil, 1.5-2 mg/kg, propofol and 0.2 mg/kg cisatracurium or 0.6mg/kg rocuronium. Anesthesia will be maintained with IV propofol and remifentanil and muscle relaxation will be maintained using IV cisatracurium or rocuronium. After endotracheal intubation, invasive blood pressure will be monitored by placing an arterial line if deemed necessary by the anesthesiologist in-charge. Ventilation will be adjusted as needed to maintain normocapnia. Anesthesia will be maintained with IV propofol and remifentanil and muscle
relaxation will be maintained using IV cisatracurium or rocuronium. Local infiltration of the prepared solution will be performed by the neurosurgeon, before the incision is made. Sufentanil will be administered at certain time points to attenuate potent stress responses and maintain the mean arterial pressure and heart rate fluctuations within the 20% range of baseline. No additional analgesics will be administered intraoperatively. Antihypertensive drugs or Vasoactive drugs will be administered as needed. And crystalloid and colloid solutions will be infused as necessary, by the anesthesiologist in-charge. All intraoperative physical parameters, fluid input and output, and dosage of all drugs will be closely monitored and recorded.

**Additional interventions**

The ongoing continuous infusion of propofol and remifentanil will be stopped right after the suture of the incision. To prevent postoperative nausea and vomiting, 8mg of ondansetron will be administered. Any residual muscle relaxation will be antagonized by atropine and neostigmine. Once the patient is hemodynamically stable, along with the recovery of adequate spontaneous ventilation and satisfactory neurological evaluations, the patient will be extubated and transferred to post-anesthesia care unit. A PCA device containing 10mg butorphanol tartrate injection (HengRui Medical CO., LTD., Jiangsu, China) and 10 mg tropisetron hydrochloride injection (Southwest Pharmaceutical CO., LTD., Chongqing, China) diluted to a total volume of 100 ml with 0.9% Normal saline, will be connected to the patients, for a total duration of 48-hours. The aponâ electronic infusion pumps (ZZB-I-150, APON Medical Technology CO., LTD., Jiangsu, China) will be used for patient controlled analgesia. PCA device will have a bolus dose of butorphanol set at 0.3 mg with a lockout interval of 15 minutes. Both initial dose and background infusion of PCA device will be set at zero. The participants will be advised to push the analgesic demand button when they feel pain. Each press will be recorded by an electronic memory system, including both valid and invalid presses. Invalid presses refer to the press for bolus during the lock-out period. In case of inadequate analgesia 4 times after butorphanol bolus, the bolus dose would be increased gradually with the final maximum dose not exceeding 4 mg per hour. There will be real-time updates of drug dosage, press counts and time of each press, to the iPainfree online recording system. Participants will be allowed to take oral supplementary
acetaminophen 500 to 1000mg every 4 to 6 hours if necessary after 48 hours, until the end of our study.

**Criteria for discontinuing or modifying allocated interventions {11b}**
A detailed recording of all the AEs (adverse events) throughout the course of the study will be properly recorded, closely monitored and reported to the ethics committee as soon as possible, with the intentions of a resolution or stabilization, or even termination of the study if necessary.

**Strategies to improve adherence to interventions {11c}**
All researchers will be trained referring to the same training protocol. Protocol modifications are not to be expected.

**Relevant concomitant care permitted or prohibited during the trial {11d}**
In the immediate 48 hours’ postoperative period, all participants will be provided with butorphanol tartate and tropisetron hydrochloride intravenous PCA device. After 48 hours the participants will be allowed to take oral supplementary acetaminophen 500 to 1000mg every 4 to 6 hours if necessary, until the end of the 6 months’ follow up period.

**Provisions for post-trial care {30}**
Not applicable

**Outcomes {12}**
Clinical and demographic characteristics such as gender, age, weight, BMI, ASA status, type of surgery (laminoplasty or laminectomy), level of spine to be treated (cervical, thoracic, lumbar or sacral), number of levels to be treated (1,2,3, 4 levels or more than 4 levels), Oswestry Disability Index (ODI) will be recorded. After operation; duration of surgery, length of incision (mm) and volume of local anesthesia (ml) injected for preemptive infiltration will be recorded. Postoperative complications such as postoperative pain due to spinal cord or nerve injury, wound infection, wound
hematoma, delirium, serious adverse effects and death may affect the follow-up process. Other complications such as allergic reaction, local or systemic toxicity, changes in wound healing, or increased wound drainage will be closely monitored.

**Postoperative Recording Parameters for up to 48 hours**

The parameters will be recorded at 2, 4, 8, 24, and 48 hours after surgery by a research member, who will visit each patient in person. Pain scores will be measured using VAS score: An 11-point VAS score during movement (VASM) and at rest (VASR) will be recorded as 0 indicating no pain, whereas 10 indicating the most severe pain imaginable.

Time of first analgesic demand will be indicated by the first press of analgesic demand button on PCA device. The time of first analgesic demand, total press count, the cumulative butorphanol dose for four separate periods (0-4, 4-8, 8-24, and 24-48 hours), and total butorphanol dose at 48 hours will be recorded.

Patient Satisfaction Score (PSS) used in this study will comprise points 1-4, based on the study by R. J. Mobbs et al. 17

The Postoperative Nausea and Vomiting (PONV) and Ramsay Sedation Scale (RSS) will also be recorded. PONV will be measured using an ordinal scale, with 0 - no nausea; 1 - mild nausea not requiring treatment; 2 - nausea requiring treatment; 3 - vomiting. RSS will be measured using a 6-point scale to assess sedation levels, with 1 indicating agitated, anxious; 2 - cooperative; 3 - only responds to commands; 4 - strong response to glabellar tapping or noisy stimulants; 5 - weak response to glabellar tapping or noisy stimulants; 6 - no response.

**Postoperative Follow-up Data Recording**

Follow-up will be conducted on day 3, weeks 1, 2, 4, 6 and months 3 and 6 by an experienced research member blinded to the study. All the participants will complete a 6-months follow-up. The postoperative follow-up data recording parameters will also include VAS and PSS.

The World Health Organization Quality of Life-BREF (WHOQOL-BREF) scores will be used to obtain scores for four domains related to quality of life: physical health (7 items), psychological (6 items), social relationships (3 items) and environment (8 items). It will also include two stand-alone questions.
on overall quality of life and satisfaction with health. Each question will be rated on a scale of 1-5 with higher scores signifying better quality of life.

Functional disability will be assessed preoperatively and at 4 and 6 weeks and 3 and 6 months after surgery using the ODI. It includes 10 questions about pain and activities of daily living. Each item has five response categories from no pain related disability (0), to the worst possible pain related disability (100).

Patient Scar Assessment and Observer Scar Assessment Scale (POSAS), comprised of subjective symptoms of pain and pruritus, will be assessed at 6 months postoperatively.

Adverse Events (AEs) such as nausea, vomiting and steroid related adverse effects (gastrointestinal bleeding, gastritis, delayed wound healing, etc.) will be documented for comparison of outcome.

**Primary Outcome**

The primary outcome will be the cumulative butorphanol dose during the 48 hours after surgery via the PCA device.

**Secondary Outcome**

$\text{VAS}_M$ and $\text{VAS}_R$ 2 hours, 4 hours, 8 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, 4 weeks, 6 weeks, 3 months and 6 months after surgery.  
Cumulative butorphanol dose for four separate periods (0-4, 4-8, 8-24, and 24-48 hours), a total press count including both valid and invalid presses, first analgesia demand on the PCA device. 

PSS 2 hours, 4 hours, 8 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, 4 weeks, 6 weeks, 3 months and 6 months postoperatively.  
PONV and RSS 2 hours, 4 hours, 8 hours, 24 hours, 48 hours after surgery.  
WHOQOL-BREF scores preoperatively and 6 months postoperatively.  
Functional disability assessed by ODI scores preoperatively and at 4 weeks, 6 weeks, 3 months, 6 months after surgery.  
Wound healing situation assessed by the POSAS scores at 6 months postoperatively.

**Participant timeline** (**13**)

The enrolment, interventions, assessments and study visits of the PRE-EASE trial is presented in Table 1.

Table 1. Study visits of the PRE-EASE trial
### Study Period

| Time points          | Preoperative | 0d | 2h | 4h | 8h | 1d | 2d | 3d | 1w | Discharged | 2w | 4w | 6w |
|----------------------|--------------|----|----|----|----|----|----|----|----|------------|----|----|----|
| Enrolment            | X            |    |    |    |    |    |    |    |    |            |    |    |    |
| Allocation           | X            |    |    |    |    |    |    |    |    |            |    |    |    |

### Eligibility Screening
- X
- Informed consent X
- Random Allocation X

### Interventions
- Betamethasone plus Ropivacaine X
- Ropivacaine X

### Assessments
- Baseline data X X X
- Intraoperative data X
- Cumulative Butorphanol consumption
- Patients with no Butorphanol X
- Total PCA button press count X
- Time of first analgesia demand X X X X X
- VASM X X X X X X X X X
- VASR X X X X X X X X X
- PSS X X X X X X X X
- PONV X X X X X
- RSS X X X X X
- WHOQOL-BREF X
- ODI X X
- POSAS X X
- AEs
  - Nausea XX XX XX XX
  - Vomiting X X X
  - Gastritis XX XX XX
  - GI bleeding XX XX XX
  - Delayed wound healing XX XX XX

### Sample size {14}

Ersayli et al reported that, total morphine consumption at 24 hour was 13.2 ± 4.1mg after lumbar discectomy for patients who received local wound infiltration of bupivacaine alone just before incision. The analgesic effect of 1mg morphine is the same as that of 3.75~7mg butorphanol. This dose of morphine could be converted into an equianalgesic dose of butorphanol (the conversion factor is 1mg morphine = 3.75~7mg butorphanol). Therefore, we have estimated that total butorphanol
consumption will be about 120.0 ± 90.0mg at 48 hours after laminoplasty or laminectomy for the patients who received preemptive analgesia with local anesthetics.

Nakai et al suggested that local wound infiltration by addition of betamethasone could reduce the dose of analgesics by about 45% in the 24 hours after lumbar discectomy. Therefore, we hypothesize that the cumulative butorphanol consumption during 48 hours after lumbar discectomy will be 120.0 ± 90.0mg in the Control group and 70.0 ± 50.0mg in the treatment group. Based on a 90% power with a two-sided α of 0.05 and a dropout rate of 20%, we have calculated that at least 116 patients (58 per group) will be required.

Recruitment

The PRE-EASE trial team includes two research members from the department of neurosurgery who will be in-charge of the patient recruitment process.

Assignment of interventions: allocation

Sequence generation

Eligible participants will be randomly assigned by a computerized random-number list generator used for randomization (SPSS 20.0), after written consent is obtained.

Concealment mechanism

The study investigator will be responsible for preparing the respective drugs to be used for preemptive infiltration. Only the doctors in charge of the postoperative pain evaluation will be blinded.

Implementation

An experienced sub investigator, not involved in any other aspect of this study, will use SPSS 20.0 to generate a computerized random-number list, which will allocate participants to either one of the two groups. Participants who fulfil the inclusion criteria will be recruited by the neurosurgeons involved in
the PRE-EASE trial. Eligible participants will be randomly assigned to their respective interventions according to the list generated by the computerized random-number list generator.

**Assignment of interventions: Blinding**

**Who will be blinded {17a}**

Only the doctors in charge of the postoperative pain evaluation will be blinded.

**Procedure for unblinding if needed {17b}**

Not applicable

**Data collection and management**

**Plans for assessment and collection of outcomes {18a}**

The primary outcome of interest will be recorded by an electronic memory system, which will include both valid and invalid presses for butorphanol demand in the 48 hours’ postoperative period. The online recording system of the PCA demand will only be accessible to the sub investigators blinded to the study. Secondary outcome will be postoperative patient-reported scores, collected by a group of blinded research members in-charge of the postoperative pain evaluation. At completion of the 6 months’ follow-up data collection, we will perform a data quality audit. An investigator will sample every participant file and check for missing data.

**Plans to promote participant retention and complete follow-up {18b}**

Follow-up will be conducted on day 3, weeks 1, 2, 4, 6 and months 3 and 6 by an experienced research member blinded to the study. All the participants will complete a 6-months follow-up. Follow up data collection will either be done in person during the patient follow up visits or by contacting via telephone. Any participants who do not complete the entire 6 months’ follow-up process due to deviation from intervention, discontinuation for personal reasons, or failure of contact, will not be replaced by other patients. Participants will be allowed to withdraw their consent or discontinue
participation without any restriction, at any time throughout the study and further data associated with the trial will be collected.

**Data management {19}**
The primary outcome will be recorded in an online recording system accessible only to sub investigators blinded to the study. Secondary outcome will be postoperative patient-reported scores, collected by a group of blinded research members in charge of the postoperative pain evaluation. At completion of the 6 months’ follow-up data collection by a blinded research member, we will perform a data quality audit. All data collected will be stored in a secure location by the lead investigator, undisclosed to other research members.

**Confidentiality {27}**
All personal information about the participants will be collected and stored in a secure cabinet by the lead investigators, throughout the duration of the study, to guarantee confidentiality. Only the lead investigator will have access to the files corresponding to the personal data of the participants.

**Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}**
Not applicable

**Statistical methods**

**Statistical methods for primary and secondary outcomes {20a}**
Statistical analyses will be performed using statistical package (SPSS software 25.0). Kolmogorov-Smirnov test will be used to assess normality of variables. Data for normal distribution will be presented as mean ± SEM (Standard Error of Mean). Variables for skewed distributions will be described as median and IQR (Inter Quartile Range). Categorical variables will be expressed as frequencies with percentages.
Comparisons between the groups will be carried out using independent t-test to compare normally distributed data, Mann-Whitney U test to skewed data, and \( \chi^2 \) test or Fisher’s exact test to compare categorical data such as safety analyses with the incidence of AEs. For numerical data collected at different time points throughout the course of 6 months (e.g., PCA cumulative consumption of butorphanol, PONV, RSS, PSS, and ODI), repeated measures analysis of variance will be performed between the two groups. The significance level will be set at \( P<0.05 \).

**Interim analyses {21b}**

Not applicable

**Methods for additional analyses (e.g. subgroup analyses) {20b}**

Prior to statistical analysis, a sub investigator will review the data record forms to check for their legitimacy and identify the missing data.

**Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}**

All researchers will be trained referring to the same training protocol. Protocol modifications will not be expected. Missing intraoperative data, if any, will be obtained from the electronic hospital files. Postoperative evaluation at specified time points are mandatory and missing postoperative data are not to be anticipated. Analyses of all outcomes will be performed according to the intention-to-treat principle, and once enrolled, all participants will be analysed, regardless of the findings.

**Plans to give access to the full protocol, participant level-data and statistical code {31c}**

Data collected will be kept in a secure cabinet. Only the research members and the IRB of Beijing Tiantan Hospital will have access to the files. After the completion of the study, the results will be made public through publication in a scientific journal along with conferences related to neurosurgical anesthesia, and the clinicaltrials.gov website. The data generated or analysed during this study will
be considered to be available from the corresponding author on reasonable request.

**Oversight and monitoring**

*Composition of the coordinating centre and trial steering committee* {5d}

Not applicable

*Composition of the data monitoring committee, its role and reporting structure* {21a}

Not applicable

**Adverse event reporting and harms** {22}

The IRB of Beijing Tiantan hospital will conduct regular inspections of the trial progress. Any adverse events will be recorded, and a thorough assessment of the potential association between the study interventions and the adverse event will be carried out. Serious life threatening adverse events leading to prolonged hospital stay or death, will be reported to the IRB and the PRE-EASE trial will be terminated immediately.

**Frequency and plans for auditing trial conduct** {23}

The IRB of Beijing Tiantan Hospital will be making regular inspections of trial conduct. The inspections will be independent from the investigators and the sponsor.

**Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)** {25}

Protocol modifications are not to be expected.

**Dissemination plans** {31a}

After the completion of the study, the results will be made public through publication in a scientific journal along with conferences related to neurosurgical anesthesia, and the clinicaltrials.gov website.
Discussion
This will be a PROBE study. It will have better application in routine clinical practice, along with the clinical outcomes of a large simple research, which will permit a broader patient population and will include the advantage of randomization and an extensive evaluation of endpoints by blinded experts.

19 To our knowledge, there has been no attempt in the past to infiltrate laminoplasty or laminectomy with a preemptive local administration of betamethasone and ropivacaine. This study will add significant new knowledge to the effect and feasibility of preemptive wound infiltration of betamethasone.

Due to its large particles occluding the blood vessels supplying the spinal cord, betamethasone was previously reported to result in infarction of spinal cord after epidural analgesia. 20 However, we speculate that local peri-incisional infiltration of betamethasone is safe as betamethasone has previously been used for intralesional, 21 local infiltration, 22 intramuscular, 23 and intraarticular injections. 16 Local infiltration of steroid hormones undeniably present the risk of delayed wound healing or local infection. However, we intend on using the lowest possible concentration of betamethasone for local infiltration based on previous literatures, 15, 16, 22, 24 and should therefore be considered safe. Wound healing and infection will be closely observed. The study will be immediately terminated in case of serious adverse reactions by the PRE-EASE trial Management Group.

There are still some limitations regarding our study. Firstly, this is a single-center study, a multi-center study would be helpful in providing a more significant data. In addition to incisional pain, acute pain after laminoplasty or laminectomy may be followed by long-term chronic pain that may not only originate from incisional wound, but may also include neuropathic pain from spinal cord damage and nerve root injury. Another possible limitation of this study is that it will only infiltrate the surrounding tissue of the incision site. Therefore, we would like to suggest a further detailed study, regarding weather local betamethasone injection into the affected nerve roots before closure could be beneficial for postoperative pain after laminoplasty or laminectomy.

Trial Status
This research protocol version 2 (2019/12/22) is approved by the IRB of Beijing Tiantan Hospital Affiliated to Capital Medical University. Recruitment of patients for this PRE-EASE trial will begin in February of 2020, and is expected to complete by the end of 2021.

Abbreviations
PCA (Patient Controlled Analgesia); VASM (Visual Analogue Score during Movement); VASR (Visual Analogue Score during Rest); PSS (Patient Satisfaction Score); PONV (Postoperative Nausea and Vomiting); RSS (Ramsay Sedation Score); WHOQOL-BREF (World Health Organization Quality of Life-BREF Score); ODI (Oswestry Disability Index); POSAS (Patient Scar Assessment and Observer Scar Assessment Scale); AEs (Adverse Events); GI bleeding (Gastrointestinal bleeding); IRB (Institutional Review Board)

Declarations

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Not applicable

Authors’ contributions {31b}

NS, LW and WD contributed equally to this work and should be considered co-first authors. NS, LW and WD drafted and wrote the manuscript. WJ and FL contributed equally in designing the project. FL performed the final revision and approval of the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials {29}

After the completion and following the publication of the PRE-EASE trial, requests for data sharing will be considered by the PRE-EASE trial Management Group.

Ethics approval and consent to participate {24}

This study design was approved by the IRB of Beijing Tiantan Hospital (KY 2019-112-02-1) and in
accordance with the World Medical Association’s “Declaration of Helsinki”. All participants will be provided with a written, informed consent prior to the surgery, that will describe in detail all aspects of the study and withdrawal process. Patients considered eligible for participation in the study will be given a verbal explanation of the written informed consent. Each participant will have sufficient time to decide whether to participate in this study, and will be instructed that they are free to obtain any relevant information regarding the study at any point throughout the study. If the patient is willing to participate, written informed consent will be obtained, before the surgery. Participants will be allowed to withdraw their consent or discontinue participation without any restriction, at any time throughout the study. This PRE-EASE trial protocol has been designed according to the Consolidated Standards of Reporting Trials (CONSORT) recommendations, and the protocol follows the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 statement.

Consent for publication {32}

Not applicable

Competing interests {28}

The authors declare that they have no competing interests.

Author details

Niti Shrestha*, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Liang Wu*, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Xiaodi Wang*, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Wenqing Jia, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Fang Luo, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

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Figures
Figure 1

CONSORT patient flow diagram