Pre-emptive coinfiltration of dexamethasone palmitate emulsion with ropivacaine for postoperative pain in patients undergoing major spine surgery: a study protocol for a prospective, randomised controlled, multicentre trial

Bin Yu,1 Baoguo Wang,2 Niti Shrestha,3, Fang Luo

ABSTRACT

Introduction Patients undergoing major spine surgery usually experience moderate-to-severe postoperative pain. It has been shown that dexamethasone as an adjunct to local anaesthesia (LA) infiltration presented a superior analgesic benefit compared with LA alone in various types of surgeries. However, a recent meta-analysis reported that the overall benefits of dexamethasone infiltration were marginal. Dexamethasone palmitate (DXP) emulsion is a targeted liposteroid. Compared with dexamethasone, DXP has a stronger anti-inflammatory effect, longer duration of action and fewer adverse effects. We hypothesised that the additive analgesic effects of DXP on local incisional infiltration in major spine surgery may have better postoperative analgesic effect, compared with local anaesthetic alone. However, no study has evaluated this so far. The purpose of this trial is to determine whether pre-emptive coinfiltration of DXP emulsion and ropivacaine at surgical site incision will further reduce postoperative opioid requirements and pain scores after spine surgery than that with ropivacaine alone.

Methods and analysis This is a prospective, randomised, open-label, blinded endpoint, multicentre study. 124 patients scheduled for elective laminoplasty or laminectomy with no more than three levels will be randomly allocated in a 1:1 ratio into two groups: the intervention group will receive local incision site infiltration with ropivacaine plus DXP; the control group will receive infiltration with ropivacaine alone. All participants will complete a 3 months follow-up period. The primary outcome will be the cumulative sufentanil consumption within 24 hours after surgery. The secondary outcomes will include further analgesia outcome assessments, steroid-related side effects and other complications, within the 3 months follow-up period.

Ethics and dissemination This study protocol has been approved by the Institutional Review Board of Beijing Tiantan Hospital (KY-2019-112-02-3). All participants will provide a written informed consent. The results will be submitted for publication in a peer-reviewed journals. Trial registration number NCT05693467.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This prospective, randomised, open-label, blinded endpoint trial is designed to compare the postoperative pain relief of incision site infiltration with ropivacaine plus dexamethasone palmitate (DXP) emulsion and ropivacaine alone in adult patients undergoing major spine surgery.
⇒ This study has a strict randomisation system, clear inclusion and exclusion criteria and a rigorous uniform analgesia protocol in both groups.
⇒ This multicentre study will provide a higher level of clinical evidence results.
⇒ The limitation is that this study only uses a single dose of DXP, does not observe the relationship between different doses of DXP and postoperative pain relief. The optimal dose of DXP combined with ropivacaine for incision site infiltration merits further research.

INTRODUCTION

Patients undergoing major spine surgery (such as laminoplasty, single laminectomy and fusion after laminectomy), usually experience moderate-to-severe postoperative pain.12 Inadequate pain control may lead to slower recovery from spine surgery, restricted mobility and decreased patient satisfaction.34 Moreover, at least 10%–30% of patients with acute severe pain subsequently develop chronic pain, which seriously affects patients’ quality of life.56 Therefore, optimal postoperative pain control with minimal side effects (SEs) can allow for reduced complications, faster recovery time and prevent chronic pain, thus improving patient satisfaction.

Currently, pain management after major spine surgery still rely heavily on opioid medications.4 However, they are associated with substantial dose-related SEs including...
constipation, nausea, respiratory depression, urinary dysfunction, gastrointestinal dysfunction and acquired tolerance. Pre-emptive multimodal analgesia has been shown to decrease opioid consumption and optimise postoperative pain management in major spine surgery.

Unlike systemic medications, local administration (such as pre-emptive infiltration of local anaesthetics (LAs)), as a common method of managing postoperative pain in various clinical settings, is associated with minor systemic SEs. It is expected to become one of the ideal choices for multimodal pain management. A recent systematic review has validated the benefits of local infiltration with LAs undergoing lumbar spine surgery by means of early pain perception, postoperative opioid consumptions and time to first analgesia demand. However, the reduction in pain was rather transient and typically occurred in the first two postoperative hours. Even if relatively long-acting LAs such as bupivacaine, levobupivacaine or ropivacaine were used, the analgesic durations were usually less than 24 hours. Hence, many adjuncts (opioids, non-steroidal anti-inflammatory drugs, epinephrine or steroids) combined with LAs have been used for coinfiltration, in an attempt to improve and prolong postoperative pain management. Among them, corticosteroids as adjuncts in incisional/wound infiltrations have been used in various surgical procedures with beneficial results. The analgesic effect of topical corticosteroids is thought to be produced by inhibiting the release of inflammatory mediators. Among various corticosteroids, only methylprednisolone has been reported as an infiltration adjunct with LAs to manage postoperative pain in patients undergoing major spine surgery. Whether methylprednisolone could provide additional postoperative analgesia is still contradictory. Our research team found that coinfiltration of methylprednisolone and ropivacaine provided better analgesic control within postoperative 48 hours after spine surgery, compared with infiltration with ropivacaine alone. However, in view of the short half-life of methylprednisolone (12–24 hours), it is better to choose a more potent, longer-acting glucocorticoid, as an adjunct to infiltrate with LA, to achieve optimal analgesic effect after spine surgery.

Dexamethasone is a potent corticosteroid with a long duration of action of 36–72 hours. Previous literatures have demonstrated that incisional/wound infiltration of dexamethasone with LAs effectively provides enhanced analgesic effects and significantly prolongs the duration of analgesic effects, with a good safety profile, after laparoscopic cholecystectomy, total knee arthroplasty, tonsillectomy and adenoidection, within 24–72 hours. However, a recent meta-analysis confirmed that the overall benefits of additional dexamethasone infiltration on postoperative pain were marginal, below the expected minimal clinically important difference. Dexamethasone palmitate (DXP) emulsion is a liposomal formulation of DXP. Due to its high lipid solubility and predilection for phagocytic cells, DXP is mainly distributed in targeted inflammatory cells and rarely delivered to non-targeted tissues. Therefore, DXP has a stronger anti-inflammatory property compared with free dexamethasone, and its targeting property is associated with lower risk of steroid-related SEs. DXP has been effectively used in pain management for certain types of diseases (musculoskeletal disorders, arthritis, lumbar facet syndrome). Previous studies have reported that the local injection of a mixture of DXP and any LA (eg, tendon, intra-articular and intravitreal injection) did not produce significant crystals, which is safe and effective, without any SEs.

Up to now, no studies have evaluated the additive analgesic effects of DXP on incisional/wound infiltration in major spine surgery. Given that the local inflammatory response to surgical incision is initiated at the same time as the beginning of skin incision, pre-emptive incisional infiltration may be superior to infiltration before wound closure. A prospective, randomised study is needed to compare the postoperative pain relief of incision infiltration with ropivacaine plus DXP emulsion to ropivacaine alone in adult patients undergoing major spine surgery, to provide a simple and feasible strategy for postoperative pain control following spine surgery. We hypothesise that pre-emptive incisional coinfiltration of DXP emulsion with ropivacaine will provide superior postoperative analgesia.

**Objectives**

The primary objective of this trial is to compare the postoperative analgesic effects of incisional coinfiltrating with DXP emulsion and ropivacaine versus ropivacaine alone in adults undergoing major spine surgery.

**Trial design**

This is a prospective, randomised, open-label, blinded endpoint, multicentre clinical study. Participants will be randomly assigned to ropivacaine plus DXP group and ropivacaine alone group at a 1:1 ratio, to compare the superiority of postoperative analgesia. This trial has been registered at ClinicalTrials.gov website under the identifier NCT 05693467. The Consolidated Standards of Reporting Trials patient flow diagram of the clinical trial is illustrated in figure 1, and the trial schedule is shown in online supplemental table 1. This protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials checklist.

**METHODS**

**Study setting**

The trial will be conducted in Beijing TianTan Hospital, Capital Medical University and Sanbo Brain Hospital, Capital Medical University. The first patient will be enrolled in March of 2023. The end of the study will be the last follow-up of the last enrolled patient, and the study is expected to end around September of 2024.

**Eligibility criteria**

**Inclusion criteria**

Patients scheduled for elective laminoplasty or laminectomy with no more than three levels under general
anaesthesia will be consecutively screened for eligibility based on the following criteria:
1. Age 18–64 years.
2. American Society of Anaesthesiologists (ASA) physical status of I–III.
3. Anticipated full recovery and cooperation within 2 hours postoperatively.

**Exclusion criteria**
1. History of spine surgery.
2. Inability to use a patient-controlled analgesia (PCA) pump or comprehend the pain visual analogue scale (VAS, ranging from 0 to 10; 0, no pain; 10, the strongest pain imaginable).29
3. Body mass index (BMI) <15 kg/m² or >35 kg/m².
4. Peri-incisional infection.
5. History of diabetes mellitus and other metabolic diseases.
6. History of severe cardiopulmonary, hepatic or renal dysfunction.
7. Preoperative coagulation abnormalities (activated partial thromboplastin time greater than 1.5 times normal value).
8. History of allergies to any of the study drugs.
9. History of alcohol or drugs abuse (more than 2 weeks), or use of any analgesic within 24 hours before surgery.
10. Use of systemic glucocorticoid within 1 week before surgery.
11. History of psychiatric disorders, chronic neck or back pain.
12. History of radiation therapy and chemotherapy or with a high probability of such treatment postoperatively.
13. Pregnant or breast feeding.
14. Refusal to sign informed consent.

**Withdrawal criteria**
1. Unable to be extubated within 2 hour after surgery.
2. Poor cognitive function within 48 hours after surgery.
3. Have a fever (≥39°C) within 48 hours after surgery.
4. Lost in follow-up.
5. Not perform the planned surgery.
6. Adverse events (AEs, defined as negative or unintended clinical manifestations throughout the study period) force participants to withdraw from the study. Participants who withdraw will be included in the final report of this trial to ensure full transparency.

**Recruitment**
Trained researchers will identify consecutive eligible patients according to the inclusion and exclusion criteria. If patients fulfil the eligibility criteria, a researcher will explain the written consent and relevant information to
the participants 1 day before surgery. Each participant will have enough time to ask questions about the study and decide whether to participate in this study. Then, participants will sign the written consent and have the right to withdraw from this study at any time. The confidentiality of participant records will be protected. All the participants will be asked for permission to share relevant data by the research team. If they withdraw from this study, participants will also be asked whether they agree the use of their data. This trial does not involve the collection of biological specimens.

Randomisation, allocation and blinding

Eligible participants will be randomly allocated to either the intervention group (group A: incision infiltration of ropivacaine and DXP) or the control group (group B: incision infiltration of ropivacaine alone) as per a computer-generated sequence in a 1:1 ratio. A permuted block stratification approach will be used to ensure a balanced distribution of participants based on selected key characteristics and to provide allocation concealment. Three strata will be created based on spinal segment involved in surgery (cervical, thoracic, lumbar, sacral), age (18–29 years, 30–49 years, 50–64 years) and ASA classification (ASA I, ASA II, ASA III), and each recruitment session will be used as a block in the permuted block randomisation procedure with varying block lengths. The randomisation sequence will be generated by a designated researcher who will not be involved in data collection and analysis via a computer-generated list using the RAND function in Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). Whenever differences in the number of participants per group and stratum occur (difference >2 participants), an equal distribution will be achieved by allocating the next participant with a suitable strata combination to the group with fewer participants. The allocation sequence will be placed in a sealed, consecutively numbered envelope. Then, the responsible anaesthesiologist will open the envelope, and prepare the study drugs according to the allocation schedule. The group allocation will be blinded to the participants, outcome assessors and data analysts.

Intervention description

A total of 30 mL solution will be prepared for the two groups with respective study drugs. Group A (intervention group): 1% ropivacaine 7.5 mL (NaiLePin, 10 mg/mL, AstraZeneca AB, Södertälje, Sweden) + DXP 2 mL (4.0 mg DXP/mL is equivalent to 2.5 mg dexamethasone; Mitsubishi Tanabe Pharma Korea) + 0.9% saline 20.5 mL; Group B (controlled group): 1% ropivacaine 7.5 mL + 0.9% saline 22.5 mL. The study solution will be prepared by the anaesthesiologist, and the neurosurgeon will administer the respective study solution at the incision site before skin incision.

Anaesthesia management

During preoperative visits, eligible patients will be instructed on how to rate their pain severity with VAS and how to use PCA pump. After entering the operating room, all patients will be continuously monitored for ECG, blood pressure, pulse oxygen saturation, axillary temperature, end tidal partial pressure of carbon dioxide (PETCO₂) and bispectral index (BIS). Ringers lactate will be infused at the rate of 10 mL/kg for cumulative supplemental loss, and midazolam 0.05 mg/kg will be administered as premedication.

Anaesthesia will be induced with propofol 1.5–2 mg/kg, sufentanil 0.3–0.4 µg/kg and rocuronium 0.6 mg/kg. After endotracheal intubation, patients will be ventilated with air/oxygen (FiO₂) 60% at tidal volume of 6–8 mL/kg, respiratory rate of 10–12/min and total flow 2 L/min to adjust PETCO₂ between 35 and 45 mm Hg. Intraoperative axillary temperature will be maintained between 36°C and 37°C. Anaesthesia will be maintained with sevoflurane 0.4 minimum alveolar concentration (MAC) and propofol 2–4 mg × kg⁻¹ × h⁻¹ to keep BIS values between 40 and 60. Analgesia will be administered by continuous infusion of remifentanil 0.1–0.3 µg × kg⁻¹ × min⁻¹ until the end of surgery. When heart rate (HR) and/or mean arterial pressure increases by 20% above baseline during surgery, remifentanil 0.5 µg/kg will be titrated for analgesia as needed. Meanwhile, the infusion rate of remifentanil will be increased by 0.05 µg × kg⁻³ × min⁻¹. The administration of additional rocuronium will be determined based on the requirements for motor evoked potential monitoring. Vasoactive agents such as esmolol, nicardipine and atropine will be administered as needed, and crystalloid or colloid solutions will be infused according to fluid loss. About 30 min before the end of the surgery, tramadol 100 mg will be administered intravenously to prevent remifentanil-induced hyperalgesia, then ondansetron 8 mg will also be given to prevent nausea and vomiting. No other analgesics and antiemetics will be administered intraoperatively. After surgery, patients will be given 0.05 mg/kg neostigmine and 0.02 mg/kg atropine as needed, to reverse residual neuromuscular blockade. Patients who meet the extubation criteria will be extubated in the operating room and transferred to the Postoperative Anaesthesia Care Unit (PACU). When a modified Aldrete score is ≥9 (0–10), patients will be discharged from the PACU to the surgical wards.

Preemptive incisional infiltration

Prior to skin incision, the neurosurgeon will use a 22-gauge needle to inject the prepared study solution through the entire thickness of the planned incision site. The epidural space and intrathecal space will not be infiltrated. The volume of infiltrated solution per surgical level will be determined by the responsible neurosurgeon according to the thickness of the incision site, up to a maximum of 10 mL per surgical level will be injected. The total volume of infiltrated solution will be recorded by the researcher. The study solution in the intervention group (group A) will contain 0.027% DXP plus 0.25% ropivacaine, while the solution of the control group (group B)
will contain only 0.25% ropivacaine. All other analgesia protocol will be identical between the two groups.

Additional interventions
On arrival at PACU, an electronic analgesia pump containing sufentanil 200 µg and ondansetron 16 mg in 100 mL of 0.9% saline will be connected to each patient. The PCA pump will be set without an initial dose or a background infusion. The pump will only provide a bolus dose when the demand button is pressed (1 mL per bolus, 10 min lock-out time, maximum limit of 8 µg/hour). Pain management will be provided via the sufentanil PCA device for the first 48 hours following surgery. Postoperative pain will be assessed and treated per standard protocols, with the goal of maintaining a VAS ≤ 4 (either VAS during movement or at rest). When patients report their VAS to be greater than 4, or request for analgesia, they will be instructed to press the PCA demand button until pain is relieved. When VAS is still greater than four after pressing the PCA demand button four times, patients will receive supplementary analgesia with oral Tylenol (Mallinckrodt), a combination of 5 mg of oxycodone hydrochloride and 325 mg paracetamol per tablet at a minimum interval of 6 hours.2 After the initial postoperative 48 hours, patients will be prescribed oral loxoprofen 60 mg at a minimum interval of 8 hours with a maximum dose of 180 mg per day as needed, until discharge.33 34 If pain control is still not satisfactory, patients will be allowed to receive oral Tylenol for supplementary analgesia (dose as previously described) until the end of the study (3 months follow-up).

The parameters of the PCA pump (including the total consumption of sufentanil, the number of valid and invalid presses) and whether Tylenol or loxoprofen has been supplemented (including dose and frequency) will be recorded.

Study outcomes
Primary outcome
The primary outcome will be the cumulative consumption of sufentanil within 24 hours after spine surgery via the PCA pump.

Secondary outcomes
Secondary outcome will include the following items:
1. Total consumption of remifentanil during surgery;
2. The cumulative consumption of sufentanil via PCA pump between 24 hours and 48 hours postoperatively.
3. Number of patients without PCA demand, the time of first PCA demand and the total number of PCA presses including both valid and invalid presses.
4. VAS score during movement (VASm) and at rest (VASr) at postoperative 2 hours, 4 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, 3 weeks 1 and 3 months
5. Total consumption of loxoprofen.
6. Total consumption of Tylenol as supplementary analgesia at four postoperative separate periods (0–48 hours, 48 hours–1 week, 1 week–1 month and 1–3 months);
7. Patient satisfaction score (PSS) with pain relief (‘In the time after surgery, how often was your pain well controlled?’; four scales; never, sometimes, usually or always)35 at postoperative 48 hours, 72 hours, 1 week, 2 weeks, 3 weeks, 1 month and 3 months.
8. Postoperative nausea and vomiting (PONV) scores (ranging from 0 to 3; 0=no nausea; 1=mild nausea not requiring treatment; 2=nausea requiring treatment; 3=vomiting)36 and sedation levels using Ramsay Sedation Scale (RSS, ranging from 1 to 6; 1=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)31 at 2 hours, 4 hours, 24 hours, 48 hours and 72 hours after surgery.
9. Wound healing situation assessed by the Patient and Observer Scar Assessment Scale (POSAS) scores (consisting of an Observer and a Patient Scale; the observer scores six items: vascularisation, pigmenta-
tion, thickness, surface roughness, pliability and surface area. The patient scores six items: pain, pruritus, colour, thickness, relief and pliability; all included items are scored on a 10-point scale)31 at 2 weeks, 1 month and 3 months postoperatively.
10. Steroid-related SEs (hyperglycaemia, gastrointestinal bleeding, gastritis, etc) and complications including any cardiac, respiratory, renal, neurologic or infection complications during the hospitalisation.
11. Readmission rate within 3 months after spine surgery.
12. Length of PACU stay.
13. Duration of hospitalisation after surgery (time required from the end of surgery to discharge from the hospital).

Outcome measures and study follow-up
During preoperative visits, a researcher will record preoperative baseline variables including gender, age, BMI, ASA status, type of surgery (laminoplasty or laminectomy) and number of levels and level of spine (cervical, thoracic, lumbar or sacral) to be treated will be recorded. During surgery and PACU stay, responsible anaesthesiologists will collect length of incision (in millimetres), infiltration volume of study solution (in millilitres), total remifentanil dosages, the duration of surgery and anaesthesia, length of PACU stay, perioperative haemodynamic parameters, and blood loss will be collected.

After surgery, a designated researcher who has been well trained and blinded to group allocation, will conduct follow-up at 2 hours, 4 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, 3 weeks, 1 month and 3 months in person or by telephone. The following data will be collected at different time points: cumulative sufentanil consumption within postoperative 24 hours (primary outcome) and between 24 hours and 48 hours postoperatively, VASm and VASr at each follow-up, the first time to PCA button
Data collection and management
The CRFs will be the primary data collection and management tool for the study. The CRFs with code numbers will be conserved in locked file cabinets by the principal investigator (PI) until the end of the study, to protect patient confidentiality. All records containing participant names, or other identifying information (eg, consent forms and contact information forms), will be stored separately from the study records that are identified only by the coded participant number and initials. Only the PI will have access to the files corresponding to the personal data of the participants. All data will be entered into the database (excel form) through double checking by two independent data managers and stored on a computer with password protection. The final database will be handed over to statisticians for statistical analysis. All the information about the identification of participants used for data disclosure or statistical analysis will only appear as code numbers. Special privilege will be required to access the database to acquire personal information with the consent of both the PI and the data monitoring committee. Besides that, only PI and statistical analysts will have access to the database.

Sample size
It is generally recommended that the minimal clinically important difference of postoperative opioid consumption is an absolute reduction of 10 mg intravenous morphine in morphine milligram equivalent of 24 hours opioid consumption.37 The degree of analgesia provided by 1 mg morphine is equal to that by 1 µg sufentanil. Hence, a difference of at least 10 µg in sufentanil consumption within 24 hours postoperatively between groups is considered clinically relevant. Based on the previous study by Li et al, we hypothesise that the SD of sufentanil consumption within 24 hours after spine surgery will be 15 µg.38 PASS V.15 software (NCSS, Kaysville, Utah, USA) was used for sample size calculation, assuming $\alpha=0.05$, $\beta=0.1$ and power=90%, dropout rate=20%, a total of 124 patients will be required in this study ($n=62$ per group).

Statistics
All statistical analyses will be performed by a statistician who is blinded to the entire study. We will use the intention to treat principle for all analyses, that is, all analyses will retain patients in their respective randomised groups. For handling missing data, multiple imputation method will be adopted. The statistical analyses will be carried out using IBM SPSS Statistics software (V.26.0, IBM, USA). All tests will be 2-tailed and $p<0.05$ will be considered as statistically significant. Kolmogorov-Smirnov test will be used to check for normal distribution. Baseline variables will be summarised by group. Normally distributed continuous variables will be stated as means with SD and compared by Student’s $t$-test. Non-normally distributed continuous variables will be stated as medians with IQR and compared by Mann-Whitney U test. Categorical variables will be stated as numbers with percentages and compared by Pearson’s $\chi^2$ or Fisher’s exact tests (when open access
the expected values were <5). The primary outcome will be the total consumption of sufentanil within postoperative 24 hours, which will be compared by Student’s t-test as normal distribution data or by Mann-Whitney U test as non-normal distribution data. For secondary outcomes analyses, the same methods as the baseline variables will be used. Among them, continuous variables will include the consumption of sufentanil between 24 hours and 48 hours postoperatively, VASm, VASr, PSS, PONV scores, RSS and POSAS at different time points, total remifentanil dosages during surgery and loxoprofen dosages, cumulative Tylenol consumption as supplementary analgesia for four separate periods (0–48 hours, 48 hours–1 week, 1 week–1 month and 1–3 months), the first time to PCA button press, length of PACU stay and duration of hospitalisation. Categorical variables will include number of patients without PCA press button, total number of PCA presses, readmission rate and incidence of steroid-related SEs and other complications. In addition, a repeated measures analysis of variance model will be performed to detect the differences in VASm and VASr scores through follow-up period. Multivariate analysis will be used to determine possible confounding factors, such as age, gender, BMI, intraoperative opioid dose, type of surgery, surgical site, number of surgical levels, surgical duration, anaesthesia time, cumulative consumption of intravenous dexamethasone (other glucocorticoids used will be converted to the equivalent doses of dexamethasone) during hospitalisation. Subgroup analysis will be performed to evaluate outcomes in patients based on the site of surgery (age, gender, duration of surgery, preoperative pain severity, cumulative intravenous consumption of dexamethasone).

After completing the evaluation of the first 60 patients of the trial, an interim analysis will be conducted to evaluate trial efficacy and safety. The efficacy of primary outcome and the incidence of steroid-related SEs and other complications will be compared between the two groups, and study discontinuation threshold will be set at p<0.01 using the alphasparring technique (O’Brien-Fleming) for benefit or harm.

Patient and public involvement
Not applicable.

Ethics and dissemination
The study plan is in accordance with ‘Declaration of Helsinki’ and approved by the Ethics Committee of Beijing Tiantan Hospital (KY-2019-112-02-3). The results will be submitted for publication in peer-reviewed journals.

Author affiliations
1Department of Day Surgery, Beijing Tiantan Hospital, Beijing, China
2Department of Anesthesiology, Capital Medical University Sanbo Brain Hospital, Haidian District, Beijing, China
3Department of Pain Management, Beijing Tiantan Hospital, Beijing, China

Twitter Niti Shrestha @NitiShrestha

Contributors BY and BW contributed equally to this work and should be considered co-first authors. BY participated in the study design and drafted the manuscript. BW and FL participated in the study design and performed critical revision of the manuscript. NS drafted and performed critical revision of the manuscript. FL is the principal investigator of the entire study and contributed equally to this work. All authors read and approved the final manuscript.

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ORCIDs
Niti Shrestha http://orcid.org/0000-0001-7360-9747
Fang Luo http://orcid.org/0000-0002-3584-0355

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