# Pre-emptive topical lidocaine 5% plaster for prevention of post-craniotomy pain: a protocol for a multicentred, randomized, triple-blind, placebo-controlled clinical trial

**Lan Meng[1], Zheng Chen[1], Jun Yang[2], Fang Luo[1]**

[1]Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China;
[2]Peking University Third Hospital, Center for Precision Neurosurgery and Oncology, Peking University Health Science Center, Beijing 100191, China.

48% to 69% of patients experience moderate to severe pain during the 48 h after craniotomy.[1] Uncontrolled pain potentiates sympathetic activation, which may elevate arterial and intracranial pressure and result in intracranial haemorrhage. Currently, opiates are commonly used for post-operative analgesia. However, the promising analgesic effects of opiates come at the price of increased incidences of post-operative nausea and vomiting. Non-steroidal anti-inflammatory drugs are not commonly administered mainly because of concern for intracranial bleeding. Pre-operative incisional infiltration and scalp nerve blockage are clinically performed strategies[2]; however, limited evidence is available to support the superiority of the therapeutic benefits of either strategy. Currently, there is a lack of effective, safe, simple and non-invasive approaches for the treatment or prevention of post-craniotomy pain.

Lidocaine 5% plaster (L5P) was first approved for the treatment of neuropathic pain attributed to postherpetic neuralgia. The therapeutic effect of L5P is based on its topical action on the impaired peripheral nerve endings. Transdermal lidocaine blocks the voltage-gated sodium channels of unmyelinated C fibres and small myelinated A-delta fibres so that the transduction of pain nociception is blocked. Recent studies have shown that pre-emptive application of L5P is effective for preventing post-operative pain for percutaneous endoscopic lumbar discectomy and thoracotomy.[3,4] Fiorelli *et al*[4] reported that compared to placebo, pre-emptive L5P scalp analgesia may significantly reduce post-thoracotomy pain intensity and total morphine consumption. Meanwhile, systemic advent events (AEs) have rarely been observed. On the basis of this finding, we believe that pre-emptive scalp analgesia with L5P is a potential approach to help relive post-craniotomy pain. Consequently, to develop an achievable topical (non-invasive) strategy for the prevention of post-craniotomy pain, a randomized, placebo-controlled trial to examine the efficacy and safety of pre-emptive L5P for post-craniotomy pain treatment is needed.

This is a novel protocol for a multicentred, prospective randomized placebo-controlled triple-blind clinical trial. The study protocol has been approved by the local Institutional Review Board (No. KY2020-008-02). The trial registration has been completed at ClinicalTrials.gov (No. NCT 04169854). The pre-emptive topical lidocaine 5% plaster for prevention of post-craniotomy pain (EASY) trial is scheduled to be conducted at the Beijing Tiantan Hospital, Peking University Third Hospital and Peking University International Hospital, three large-scale medical institutions in China specialized in neurosurgery. The study is estimated to start on June 2020 and to last for approximately 24 months. This protocol was developed in accordance with the Standard Protocol Items Recommendations for Interventional Trials guidelines. All patients will sign the consent form.

Patients scheduled for elective craniotomy will be screened based on the following: age of 18 years or older, American Society of Anaesthesiologists status I or II, and informed consent for participation in the trial. Subjects will be excluded who meet the following criteria: allergy to lidocaine or the hydrogel plaster, chronic headache, craniofacial pain or neuralgia, Glasgow Coma Scale less than 15, current or previous cardiovascular or cerebrovascular accident, expected delayed recovery or extubation, uncontrolled arrhythmia, history of intracranial operation, emergency or revision craniotomy, mental

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**Correspondence to:** Prof. Fang Luo, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China
E-Mail: 13611326978@163.com



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illness, psychiatric drug use or alcohol abuse, failure to understand the use of a 100 mm visual analog scale (VAS) or the patient-controlled analgesia.

Computer-generated randomization will be performed by an individual statistician. All participants will be allocated into a masked intervention group or a placebo control group at a ratio of 1:1. A sealed opaque envelope will be used for allocation concealment and kept in a secure locker. The masked intervention group will be equipped with masked lidocaine 5% white hydrogel plasters measuring 10 cm × 14 cm containing 700 mg of lidocaine. The placebo control group will be equipped with plain hydrogel plasters of the same pattern, size, appearance and material as L5Ps but free of lidocaine for maintenance of the blinding. The plasters for both groups will be specifically packaged for this study.

The surgeon, patients and pain physicians will be blinded to the allocation of the study. Emergency unblinding will not occur unless one of the interventions is associated with unexpected excessive AEs such as uncontrollable pain or there are excessive withdrawals. The final decision on unblinding will be authorized by the principal investigator or the Data Monitoring Committee (DMC).

Surgeons will be asked to mark the planned incisions as soon as possible once the informed consent form is signed. For each participant in the masked intervention group, the masked L5P will be applied to cover the marked incision (the plaster will be cut to suit the shape of the incision in advance, if necessary) as well as the head-holder sites. Each participant in the placebo control group will have a masked plain placebo plaster applied to cover the incision mark. In both groups, the plasters will be applied for 12 h at night (from 6:00 PM to 6 AM) and will be removed for 12 h during the day (from 6:00 AM to 6:00 PM).

All craniotomies in this trial will be performed in the morning within 3 h after removing the plasters. General anaesthesia will be induced with propofol (1.5–2.0 mg/kg) and sufentanil (10–15 μg). Neuromuscular blockage will be provided by intravenous cisatracurium (0.2 mg/kg) for tracheal intubation. After intubation, the patients will be ventilated at 6 to 8 mL/kg tidal volume. End-tidal carbon dioxide will be maintained within the range of 28 to 35 mmHg. The mean arterial pressure and heart rate will be maintained within 30% of the baseline values. Analgesic administration will be repeated, extra neuromuscular blockers will be given and intra-operative vasoactive drugs will be used as needed or per the anaesthetist. A loading dose of 0.1 mg/kg morphine will be administered to each participant for post-operative analgesia. Uncontrolled extreme post-operative pain will be treated with an intravenous rescue bolus of 2 mg of morphine.

The primary outcome of this study will be the pain intensity at 24 h after craniotomy. Pain intensity will be evaluated by two independent, well-trained researchers using a 100 mm scale, where 0 mm at the left end represents "no pain" and 100 mm at the right end represents "the greatest imaginable pain."

Secondary outcomes of this study include the following: (1) Pain intensity measured using the 100 mm VAS at 1, 4, 6, 12, 48, and 72 h after craniotomy in both groups. (2) The time interval from the end of craniotomy to the first rescue analgesic administration. (3) Cumulative rescue analgesics consumption within 24, 48, and 72 h after craniotomy. (4) Cumulative intra-operative analgesics consumption. (5) Skin reactions attributed to L5P application. (6) Sleeping scores per the Pittsburgh Sleep Quality Index self-rated questionnaire for the first 3 days after craniotomy.

Combined our clinical experience, previous studies and the placebo effect, a median 100 mm VAS score of 35 at 24 h after craniotomy is predicted for the patients in the placebo control group.[5] According to a recent study, a minimal improvement of 10 mm is declared to be sufficient to signify a clinical difference on a 100 mm VAS. Hence, 80 participants for each group will be needed to detect significance with a two-sided alpha of 0.05 with a power of 85%. Assuming an estimated 10% drop-out rate, a total of 180 participants will be needed for this EASY trial.

Statistical analyses will be performed using SPSS software (version 25.0, IBM, Armonk, NY, USA). Data analyses will be performed in line with the intend-to-treat principle. The Kolmogorov-Smirnov test will be used for normality testing. Continuous variables with normalized distributions will be recorded as the mean and standard deviation and analysed using Student's *t* test. Non-normally distributed data will be recorded as the median (interquartile range) and analysed using the Mann-Whitney *U* test. Categorical variables will be described as the *N* and percentage and compared using the Pearson Chi-square test or Fisher exact test. Sub-group analyses will be conducted to explore any potential differences in the primary outcome by the operation type.

Throughout the trial process, data safety will be monitored by the DMC. A clinical research associate will monitor whether the clinical trial is conducted in accordance with the prescribed protocols and standard operating procedures. The centers make the decisions to change the details of this protocol and announce the persons conducting the trial by written notice after approval by the local Institutional Review Board (IRB). Any AEs or severe AEs will be reported to the DMC by the project investigator within 24 h after occurrence.

There are limitations to our study. One uncontrollable confounder is scalp thickness, which is viewed to be incompletely associated with body weight. As the topical plaster diffuses lidocaine through transdermal contact, the thickness of the scalp does have an impact on permeation. Although body mass index will be considered into the outcome interaction examination, potential confounding factors cannot be avoided. Similarly, the incision shape may vary in line with the operation purpose. As mentioned above, the plaster may be placed obliquely or cut into pieces to suit the shape of the incision. This will inevitably lead to unequal distribution of lidocaine along either side of the incision and cause underlying confounding effects.

## Conflicts of interests

None.

## References


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