

BMJ Open Pre-emptive scalp infiltration with ropivacaine plus methylprednisolone versus ropivacaine alone for relief of postoperative pain after craniotomy in children (RP/MP vs RP): a study protocol for a randomised controlled trial

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ABSTRACT

Introduction Pre-emptive scalp infiltration with local anaesthetics is the simplest and most effective method to prevent postoperative incisional pain. However, local infiltration of an anaesthetic only provides relatively short-term pain relief. Methylprednisolone (MP) treatment, administered as an adjuvant at the wound site, has been shown to provide satisfactory pain management after lumbar laminectomy. However, there is no evidence regarding the efficacy of MP infiltration for the relief of postoperative pain after craniotomy. Currently, postoperative pain after craniotomy in children is undertreated. Therefore, we aim to investigate whether pre-emptive scalp infiltration with ropivacaine (RP) plus MP is superior to RP alone to improve postoperative pain after craniotomy in children.

Methods and analysis The RP/MP versus RP trial is a prospective, single-centre, randomised, parallel-group study of 100 children aged 8–18 years undergoing intracranial surgery. Participants will be randomly allocated to receive pre-emptive scalp infiltration with either RP plus MP or RP alone. The primary outcome will be the cumulative fentanyl dose administered by patient-controlled intravenous analgesia within 24 hours postoperatively. The secondary outcomes will include postoperative Numerical Rating Scale scores, pain control satisfaction scores, length of stay and adverse events. Data will be analysed by the intention-to-treat principle.

Ethical approval and dissemination The study protocol has been approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (Approval Number: KY 2018-066-02). The results will be disseminated in international academic meetings and published in peer-reviewed journals.

Trial registration number NCT03636165; Pre-results.

BACKGROUND

Until now, the idea that pain management following craniotomy is lacking in children

Strengths and limitations of this study

- Local infiltration only provides relatively short-term pain relief. The analgesic effects of a mixture of steroids and local anaesthetics may last longer. The ropivacaine (RP)/methylprednisolone (MP) versus RP trial is the first prospective randomised controlled study to confirm the analgesic effects of MP administered as an adjuvant as part of pre-emptive scalp infiltration in children undergoing craniotomy.
- Pre-emptive analgesia is defined as a preoperative treatment that is more effective than the same treatment postoperatively. The pre-emptive scalp infiltration blocks the introduction of nociceptive stimulation and inhibits the occurrence of central sensitisation, which provides a better analgesic effect than scalp infiltration before skin closure.
- The RP/MP versus RP trial will investigate whether pre-emptive scalp infiltration with RP plus only a single concentration of MP is superior to RP alone in improving postoperative pain after craniotomy in children. Further studies are needed to determine the optimal concentration of MP. Furthermore, because this trial is a single-centre study, it is necessary to perform multicentre clinical studies to provide higher levels of evidence.

has been rejected. The incidence of postoperative pain and the characteristics of pain after craniotomy in children are still rarely reported. Teo *et al* reported that 42% of children undergoing craniotomy had at least one episode of moderate or severe pain within 72 hours after the procedure.¹ Pain is associated with adverse effects, such as hypertension and agitation, which may increase the risk of secondary intracranial haemorrhage, lead to a prolonged hospital stay and even

increase mortality in children.^{2–4} However, postoperative pain in children has remained overlooked because of the difficulty of pain assessment in children and their limited expressive proficiency.⁵ If postoperative pain cannot be treated appropriately, children with recurrent pain are at a high risk of developing chronic pain after surgery.⁶ Therefore, adequate postoperative analgesia requires further study in children.

Currently, there are limited data describing pain management after neurosurgery in children. Children receiving multimodal analgesia, including strong opioids and non-steroidal anti-inflammatory drugs (NSAIDs), presented low pain intensity after major craniotomies.^{1,7} However, opioid-associated side effects, such as sedation and miosis, can mask early signs of neurological problems. There is also a potential risk of bleeding due to NSAIDs, particularly after craniotomy. Building an optimal pain management plan with a focus on reduction in opioids⁸ and NSAIDs is important.

Pain following craniotomy originates from the surgical incision in the pericranial muscles and soft tissues of the scalp.^{9,10} Scalp infiltration with local anaesthetics is the simplest and most effective method of preventing postoperative incisional pain in paediatric patients.^{11,12} Cercueil *et al* reported that children younger than 2 years of age who received local anaesthetic infiltration had a decreased need for postoperative morphine.¹³ Local infiltration with a single anaesthetic only provides significant pain relief for a brief period, so many patients have significant pain after the local anaesthetics have dissipated. Many studies suggested that scalp infiltration could also improve postoperative pain in patients undergoing craniotomy, but only for the first few hours after surgery.^{14–18} Therefore, an optimal analgesic regimen to induce sufficient and prolonged analgesia is worth exploring to relieve pain in paediatric patients after major neurosurgical procedures.

Continuous incisional infiltration with local anaesthetics may be considered as a pain management method after knee and hip replacement due to improved analgesic efficacy.¹⁹ However, the major complications associated with this technique are mainly caused by catheter withdrawal, dislodgement or occlusion. In recent years, multiple modalities have been introduced to achieve adequate analgesia. The analgesic effects of a mixture of corticosteroids and local anaesthetics introduced into the articular cavity have been reported to be sustained for 3 days after total knee arthroplasty (TKA).²⁰ Meanwhile, according to the American College of Rheumatology, intra-articular (IA) corticosteroid injections may be recommended in people with knee osteoarthritis to provide a short-term reduction in moderate to severe pain.^{21,22} Therefore, corticosteroids administered as an adjuvant may be a good way to prolong the analgesic time of local incisional infiltration.

Methylprednisolone (MP) is a type of glucocorticoid with potent anti-inflammatory effects and a high affinity for its receptor. The topical application of MP has been demonstrated to suppress transmission via C-fibres but

not via A-beta fibres through direct membrane action.²³ Gurava Reddy *et al* suggested that the addition of MP to an injectable analgesic cocktail infiltration for periarticular infiltration in patients undergoing unilateral TKA leads to better postoperative analgesia in the early postoperative period of 24–48 hours.²⁴ Administration of a single IA multidrug, including MP, RP and epinephrine, on the first day following TKA may provide better pain relief during the 5 days following surgery.²⁵ MP administered only at the incision site instead of systemically achieved satisfactory pain management at the end of 24 hours in adults undergoing lumbar laminectomy.²⁶ The local application of MP, with a strong analgesic effect, may further improve the analgesic effect of scalp infiltration. However, there is no evidence regarding the efficacy of pre-emptive scalp infiltration with RP plus MP for relief of postoperative pain after craniotomy in children.

Based on the current literature, we hypothesise that, compared with RP alone, RP plus MP will provide improved postoperative pain management after craniotomy in children aged 8–18 years, and we will perform the following randomised controlled trial.

METHODS AND ANALYSIS

Trial design

The RP/MP versus RP trial is a single-centre, randomised, parallel-group clinical trial of patients scheduled to undergo elective craniotomies and receive pre-emptive scalp infiltration with either RP plus MP or RP alone in a 1:1 group ratio for the two study arms (figure 1). The trial will be conducted at Beijing Tiantan Hospital Affiliated with Capital Medical University. This study, which will begin in December 2018, will have a duration of 1 year.

Objectives

The aim of the RP/MP versus RP trial is to determine whether MP plus RP is superior to RP alone in relieving postoperative pain in children undergoing intracranial surgery.

Eligibility criteria

Patients must meet all of the following criteria to be eligible:

1. Age 8–18 years.
2. Elective craniotomy under general anaesthesia.
3. American Society of Anaesthesiologists (ASA) physical status of I or II.
4. Anticipated full recovery within 2 hours postoperatively.
5. Informed consent provided by the patient's parent(s) and/or legal guardian.

Subjects with one or more of the following conditions will be excluded:

1. History of allergies to any of the study drugs.
2. Chronic opioid use (3 days per week for more than 1 month), use of any painkiller within 24 hours before surgery and steroid use.

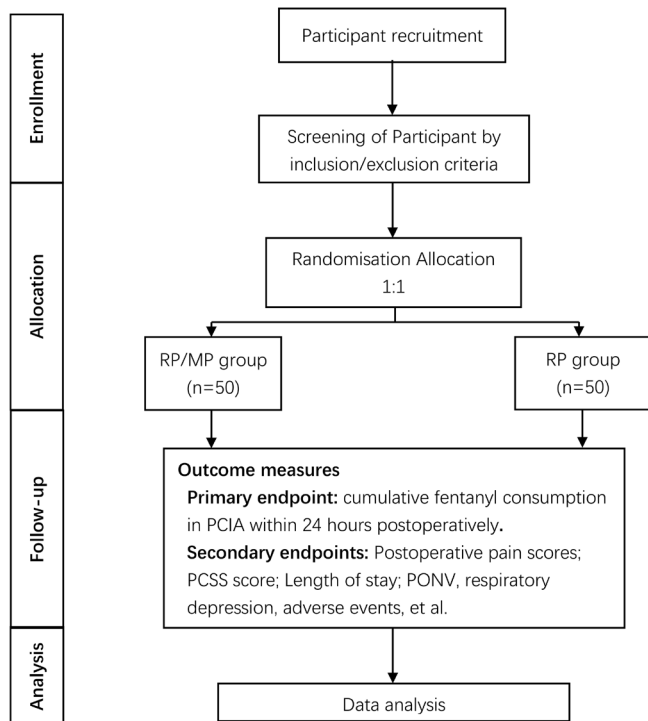


Figure 1 Study flow diagram of the RP/MP versus RP trial. MP, methylprednisolone; PCIA, patient-controlled intravenous analgesia; PCSS, pain control satisfaction score; PONV, postoperative nausea and vomiting; RP, ropivacaine.

3. Psychiatric disorders.
4. Uncontrolled epilepsy.
5. Chronic headache.
6. Peri-incisional infection.
7. Body mass index exceeding the 99th percentile for age.
8. Children who cannot use patient-controlled intravenous analgesia (PCIA) devices.
9. Children who cannot understand the instructions for the pain scales before surgery.

Allocation and blinding

The participants will be randomised into two treatment arms: an experimental group (RP/MP treatment group) and a control group (RP treatment group). The subjects will be allocated to the two arms in a 1:1 ratio using simple randomisation. The randomisation will be organised by the pharmacy department using a computerised randomisation table. The random numbers will be kept in opaque sealed envelopes and opened by an independent anaesthesiologist who will not be involved in the study, and he or she will be responsible for preparing the study drugs in identical syringes labelled only with the drug's serial number. Then, the study drugs will be delivered to the study surgeon performing scalp infiltration. During the study period, the patients and outcome assessors will be blinded to the group randomisation. All other aspects of the perioperative pain protocol will be identical between the two groups.

Interventions

All included patients will be allocated to one of the following two study groups. Patients in the RP/MP group will receive peri-incisional scalp infiltration with miscible liquids consisting of 0.125% MP, 0.2% RP and normal saline miscible liquids.²⁷ Patients in the RP group will receive peri-incisional scalp infiltration with miscible liquids consisting of 0.2% RP and normal saline. The infiltration solution will be prepared by the first anaesthesiologist in a separate operating room. The assigned solution will be injected subcutaneously by the surgeon along the incision and throughout the entire thickness of the scalp before a skin incision is performed. The volume of local infiltration solution will be determined by the surgeon according to the incision length, and the amount of solution used will be recorded by the investigators. The study drug will be supplied as a syringe of liquid, identical in volume but indicated by a letter, for both groups. For the scalp infiltrations, a straight 23G needle will be used.

Anaesthesia induction and management

In the ward, all children will receive midazolam 0.5 mg/kg orally 20 min before being transferred to the operating room. On arrival to the operating room, standard monitoring will be established (pulse oximetry, electrocardiography and non-invasive arterial blood pressure monitoring). Peripheral vascular access will be established while the children are breathing 50% nitrous oxide in oxygen. Anaesthesia will be induced with 2 mg/kg propofol, 0.6 mg/kg rocuronium and 3 µg/kg fentanyl after obtaining intravenous access.

After intubation, anaesthesia will be maintained with sevoflurane (1.5%) and remifentanyl (0.17 µg/kg/h). Ventilation with 60% oxygen and 40% air will be controlled to maintain an end-tidal carbon dioxide (PETCO₂) of 30–40 mmHg. Before proceeding to surgery, the children will receive peri-incisional scalp infiltration performed by the surgeon according to their group allocation. Five minutes after local infiltration, surgery will be performed by the same surgeon. The mean arterial pressure (MAP) and heart rate (HR) will be maintained within 30% of the baseline values with vasoactive drugs. Fentanyl will be administered to attenuate potent stress responses induced by noxious stimuli at certain time points, such as scalp incision or skull drilling. No acetaminophen or other additional analgesics will be administered. The dosage of all drugs and intraoperative physical parameters will be closely monitored and recorded by the investigator.

After surgery, atropine 0.01 mg/kg and neostigmine 0.05 mg/kg will be administered intravenously to antagonise any residual neuromuscular blockade. Extubation will be performed after confirmation of eye opening, adequate spontaneous respiration and purposeful movements. Additionally, all patients will receive tropisetron hydrochloride (0.2 mg/kg to a maximum dose of 5 mg) intravenously.

After extubation, patients will be transferred to the postoperative care unit (PACU). The postoperative

PCIA formulation will be set as fentanyl (20 µg/kg) and tropisetron hydrochloride (0.2 mg/kg) diluted to a total volume of 100 mL in normal saline. The PCIA device will provide a bolus (0.5 µg/kg, 10 min lock-out time), and the maximum dose will be limited to 2 µg/kg per hour.^{28–30} If the patient experiences inadequate analgesia four times after the fentanyl bolus, the bolus dose will be increased to 1 µg/kg, and the maximum dose will be increased to 4 µg/kg per hour. Both the initial dose and background infusion of the PCIA in this study will be set at 0. The button on the analgesic pump will be pressed when the patient reports an Numerical Rating Scale (NRS) score of 4 or more or at the request of the patient or the parent. The modified Aldrete score will be used as an objective assessment tool to guide discharge from the PACU to a ward. A score >9 will be required for discharge.³¹ The MAP, HR and SpO₂ will be monitored for 4 hours in the ward. If vomiting occurs more than twice in 2 min, metoprolamide (2.5–5 mg) will be intravenously injected.

Outcomes

Table 1 provides an overview of the outcomes and assessment time points.

Primary outcome

The primary outcome will be the cumulative fentanyl consumption administered via the PCIA device within 24 hours postoperatively.

Secondary outcomes

Secondary outcomes will include the following aspects:

- ▶ *Postoperative analgesia*: The number of participants who receive no fentanyl, the first time the patient presses the PCIA button, which will be defined as the time from the beginning of the postoperative period to the first administration of analgesics and the total number of times that the patient presses the PCIA button, including effective presses and ineffective presses, will be recorded.
- ▶ *Postoperative pain scores*: A NRS will be administered to assess postoperative pain intensity by a research assistant who will receive specific training regarding the use of this scale and will be blinded to the grouping. The NRS score (0=no pain; 10=the worst possible pain) will be assessed at fixed intervals after the procedure, that is, 2 hours, 4 hours, 8 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, 1 month, 3 months and 6 months after surgery. Significant or moderate pain will be defined as an NRS score ≥4. Severe pain will be defined as a pain score ≥7.
- ▶ *Postoperative recovery*: Patient satisfaction will be assessed by the pain control satisfaction score (PCSS) (0 for unsatisfactory and 10 for very satisfactory) at 24 hours, 48 hours, 72 hours, 1 week, 1 month, 3 months and 6 months after surgery. The length of stay (LOS) will be recorded as the number of nights spent in the hospital after surgery. The times to first water

consumption and oral intake request and scales of oral intake after surgery will also be recorded.

- ▶ *Adverse events (AEs)*: Postoperative nausea and vomiting, respiratory depression, pruritus, hypotension, bradycardia, emergence delirium, oversedation and any signs of local anaesthetic or steroid-associated systemic toxicity within 24 hours postoperatively will be recorded. Respiratory depression will be defined as persistent (more than 1 min) oxygen desaturation of 90%, a respiratory rate of less than 8 breaths min⁻¹ or oxygen desaturation of less than 94% along with a respiratory rate less than 10 breaths min⁻¹ requiring supplemental oxygen to maintain SpO₂ at more than 94% in the absence of clinically obvious upper airway obstruction.³² Emergence delirium will be assessed using the Paediatric Anaesthesia Emergence Delirium scale.³³ Emergence agitation will be considered to correspond to a total score of >12 at any time. Sedation will be assessed using the Ramsay Sedation Scale.³⁴
- ▶ *Vital signs*: HR and MAP will be recorded before anaesthetic induction, after anaesthetic induction, after scalp infiltration, during skull drilling, during dura mater cutting and during skin closure at 2 hours, 4 hours, 8 hours and 24 hours after surgery.
- ▶ *Incision-related AEs*: Related AEs will be assessed, including delayed incisional healing, incisional infection, intracranial infection and scar healing after surgery. The wounds will be assessed using the Wound Healing Score, including skin healing, infection and hair regrowth at 3 and 6 weeks postoperatively.³⁵ To quantify scar healing, Patient and Observer Scar Assessment Scale scores will be assessed at 6 months postoperatively.³⁶ In addition, the time of removal of stitches or surgical drains will also be recorded.
- ▶ *Occurrence of AEs and serious adverse events (SAEs)*: An AE will be defined as any untoward medical occurrence. An SAE will include death, immediately life-threatening conditions, coma, inpatient hospitalisation or prolongation of existing hospitalisation. AEs and SAEs will be observed throughout the study.

Safety

All AEs for which the investigator or the sponsor determines to have a causal relationship with the investigational treatment during the trial will be recorded. An SAE between study enrolment and hospital discharge will be reported to the trial management committee within 24 hours. An SAE report will note the date of occurrence, severity, intensity, relationship with the treatment (or the study), evaluation and outcome. All SAEs will be addressed to resolution or stabilisation. If the patients are harmed as a result of their participation in the trial, they will receive free treatment and adequate compensation. All patients will be under close personal supervision by the outcome assessors until their follow-up visit 6 months after surgery. The chief investigator will be responsible for all AEs reported.

Table 1 Study visits of the RP/MP versus RP trials

Time point	Enrolment		Allocation		Postallocation														
	Preoperative	0 day	Surgery	0 day	2 hours	4 hours	8 hours	1 day	2 days	3 days	1 week	Discharged	2 weeks	3 weeks	1 month	6 weeks	3 months	6 months	
Enrolment																			
Eligibility screen	X																		
Informed consent	X																		
Allocation		X																	
Interventions																			
Methylprednisolone plus ropivacaine		X																	
Ropivacaine		X																	
Assessments																			
Baseline variables	X	X	X																
Intraoperative data			X																
Fentanyl consumption of PCIA							X												
Patients with no fentanyl							X												
PCIA button press times							X												
Time of the first press of the PCIA button							X												
NRS score				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCSS score							X	X	X	X	X	X	X	X	X	X	X	X	X
LOS												X							
Respiratory depression				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pruritus				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypotension				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bradycardia				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Emergence delirium				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RSS score				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PONV				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HR and MAP			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Wound healing score													X						
POSAS																			X
The occurrence of the AEs and SAEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AEs, adverse events; HR, heart rate; LOS, length of stay; MAP, mean arterial pressure; MP, methylprednisolone; NRS, Numerical Rating Scale; PCIA, patient-controlled intravenous analgesia; PCSS, pain control satisfaction score; PONV, postoperative nausea and vomiting; POSAS, Patient and Observer Scar Assessment Scale; RP, ropivacaine; RSS, Ramsay Sedation Scale; SAEs, serious adverse events.

Missing values

Missing data will not be replaced. Mixed models will be used in the analysis of repeated data to avoid deleting subjects with any missing values.

Sample size calculation

According to Ju's article, the total fentanyl consumption during the first 24 hours after surgery was 103.9 (11.5) μg for children who received local infiltration with RP for tonsillectomy and adenoidectomy.³⁷ Maxwell *et al* reported that paediatric craniotomy patients receive approximately 300 $\mu\text{g}/\text{kg}$ of morphine on the first postoperative day.³⁸ This dose of morphine is converted to an equianalgesic dose of fentanyl (the conversion factor is 1 mg morphine=10 μg fentanyl), that is, paediatric craniotomy patients receive approximately 3 $\mu\text{g}/\text{kg}$ of fentanyl on the first postoperative day. Combined with the previous experience of our centre, we hypothesise that the total fentanyl consumption during the first 24 hours after craniotomy will be 110 \pm 30 μg for children who received local infiltration with RP.

Although Ersayli's study did not identify any extra effect of MP in patients undergoing lumbar discectomy,²⁷ this study suggested a trend that local infiltration by MP could reduce the amount of postoperative analgesics in the 24 hours after lumbar discectomy by 20%. We hypothesise that the local application of MP will reduce the dosage of fentanyl by 20%, that is, 88 \pm 30 μg , within 24 hours after paediatric craniotomy.

Therefore, we estimate that the accumulated fentanyl dose after 24 hours will be approximately 110 \pm 30 μg in the RP group and 88 \pm 30 μg in the RP/MP group. Forty patients per group will be needed based on a 90% power with a two-sided α level of 0.05 to show a relative between-group difference of 20% in the composite primary outcome measure. Considering a dropout rate of 20%, a total of 50 patients per arm will be required; thus, the total sample size will be 100 patients in this RP/MP versus RP trial.

Statistical analysis

For descriptive variables, we plan to use the mean and SD to report normally distributed variables and the median and IQR for skewed distributions. Dichotomous and categorical data will be described as the number of patients/episode and percentages. The Kolmogorov-Smirnov Z test will be used to analyse the equality of the distributive functions of the variables.

Endpoint data will be analysed according to the intention-to-treat principle, and all participants will be analysed once enrolled. Baseline characteristics of the children will be compared between groups using the non-parametric Mann-Whitney/Wilcoxon test for continuous data or the χ^2 or Fisher's exact test for categorical data. For numerical data collected more than once (eg, NRS, PCSS, haemodynamic parameters and Wound Healing Score) during the study period, two-way repeated measures analysis of variance on ranks will be performed with time of

measurement as the repeated factor and group as the non-repeated factor. Potential risk factors (eg, age and sex) for moderate or severe postoperative pain after surgery will be identified using univariate analyses. For dichotomous pain descriptors (moderate to severe pain and severe pain), multivariate analysis will be used to determine possible confounding covariates, such as age, body mass index and type of surgery. The results of the regression analyses will be presented as ORs and 95% CIs. Posthoc comparisons will include within-group changes over time and between-group differences at each assessment. A $p<0.05$ will be considered statistically significant. Statistical analyses will be performed with SPSS software, V.23.

DISCUSSION

The RP/MP versus RP trial will be the first rigorous trial to examine the analgesic effects of MP administered as an adjuvant as part of pre-emptive scalp infiltration in children undergoing craniotomy and may provide guidance for paediatric postoperative pain management. We plan to recruit children aged 8–18 years old for the following reasons. Several studies have noted that older children experience more severe postoperative pain than younger children and that pain intensity increases with age.^{39–41} Sowder *et al* found that children with an average age of 5 years tended to receive ibuprofen alone after tonsillectomy; however, older patients with a mean age of 8 years were more likely to receive potent opioids or ibuprofen combined with anaesthetics.⁴² Older children may need more painkillers than younger children because they have different pain thresholds. Berde *et al* also noted that it seems reasonable for children aged over 7 years to receive PCIA because they are at a developmentally mature age.⁴³ Consequently, combined with the characteristics of paediatric pain and postoperative analgesia, we will select school-aged children and adolescents who are able to learn how to use PCIA devices and will not result in deviations from the endpoint due to age.

In this study, 0.2% RP will be administered, and this concentration is generally recommended by the European Society for Paediatric Anaesthesiology (ESPA) Pain Committee.²⁹ In children, 0.025% dexamethasone can be applied locally, which is the most frequently used concentration in clinical practice and provides effective postoperative analgesia during otolaryngology and orthopaedic surgery.^{37–44} The potency of dexamethasone, however, is five times stronger than that of MP.⁴⁵ The calculated concentration of topical MP used in this study is 0.125%, and this concentration is similar to that used in adults.²⁷ There is no significant difference in the concentration of topical glucocorticoids used between children and adults, and the amount injected may vary depending on weight. Therefore, 0.125% MP will be used in this study, as this dose is safe and effective for children.

This study has several limitations. First, we will use single doses of MP as an adjuvant to local anaesthetics,

which are often used and identified in clinical practice. Further studies with different local doses of methylprednisolone as an infiltration adjuvant may be warranted to determine the optimal topical concentration to achieve the best analgesic effect and minimise the risk of side effects. In addition, this study is also a single-centre trial. Therefore, it is necessary to perform multicentre clinical studies with a larger sample size to provide higher levels of evidence.

In summary, the results from the RP/MP versus RP trial may provide an effective method to alleviate postoperative pain after craniotomy in older children and provide a significant contribution to the development of paediatric multimodal analgesia.

ETHICS AND DISSEMINATION

Ethical and legislative approvals

The RP/MP versus RP trial is registered at ClinicalTrials.gov with the trial identification number NCT 03636165. The trial methods and results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.⁴⁶ Amendments to the protocol will only be made by an academic committee and approved by the Institutional Review Board at Beijing Tiantan Hospital Affiliated to Capital Medical University. Signed informed consent will be obtained from the patient's parent(s) and/or legal guardian (see online supplementary file 1). If a child is able to express himself or herself in writing, the child will be invited to sign a simplified child assent form (see online supplementary file 2) appropriate to his or her capacity for expression. All changes will be recorded. Any change will be applied to all subsequent patients, and the registration record will be updated.

Publication plan

Scientific statements and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study, with the consent of the principal investigators and the methodologist. The co-authors of the report and the publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. Rules regarding publication will follow international recommendations, and publications will be submitted to peer-reviewed journals.⁴⁷

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protocol and will participate in the follow-up for this trial. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Patient consent for publication Obtained.

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Data sharing statement Substantive protocol amendments will be reported, reviewed and approved by the local medical ethical committee before application. The frequency of monitoring visits will be determined by the site enrolment rate. Rules on publication will follow international recommendations.

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