

# Pre-Emptive Incision-Site Infiltration with Ropivacaine Plus Dexamethasone for Postoperative Pain After Supratentorial Craniotomy: A Prospective Randomized Controlled Trial

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**Background:** Incision-site infiltration with local anesthetics prevents pain on incision site, but pain relief is limited to the first few postoperative hours. Dexamethasone as an adjuvant to local infiltration successfully achieves better postoperative pain relief; however, this has not been studied in craniotomy patients yet.

**Study Design and Methods:** This is a prospective, single-center, blinded, randomized, controlled trial included patients aged between 18 and 64 years, ASA physical status of I–II, scheduled for elective supratentorial tumor craniotomy under general anesthesia. We screened patients for enrollment from April 4, 2019 through August 15, 2019. The final study visit of the last patient was conducted on February 13, 2020. We randomly assigned eligible participants (1:1) to either the dexamethasone group who received incision-site infiltration of 0.5% ropivacaine plus 0.033% dexamethasone (N=70) or the control group who received 0.5% ropivacaine alone (N=70). Primary outcome was the cumulative sufentanil consumption ( $\mu\text{g}$ ) within 48 hours postoperatively. Primary analysis was performed based on the modified intention-to-treat (MITT) principle.

**Results:** Baseline characteristics were similar between the groups ( $p>0.05$ ). Sufentanil consumption during the first 48 hours postoperatively was 29.0 (10.7)  $\mu\text{g}$  in the dexamethasone group and 38.3 (13.7)  $\mu\text{g}$  in the control group (mean difference  $-9.3$ , 95% CI  $-13.4$  to  $-5.1$ ;  $p<0.001$ ). There was no serious adverse effect directly associated with incision-site infiltration or local dexamethasone use.

**Conclusion:** The addition of dexamethasone to pre-emptive incision-site infiltration with the local anesthetic can reduce about 27% of opioids consumption and the postoperative pain scores within 72 hours after craniotomy.

**Trial Registration:** ClinicalTrials.Gov (NCT03618264).

**Keywords:** postoperative pain, craniotomy, dexamethasone, incision-site infiltration, randomized controlled trial

## Introduction

After craniotomy, 55–69% of patients experience moderate to severe pain, most frequently within the first 48 postoperative hours.<sup>1,2</sup> Inadequate analgesia may lead to postoperative complications, such as arterial hypertension, intracranial hemorrhage, prolonged hospital stay and increased mortality.<sup>3</sup> Moreover, acute postoperative pain is associated with an increased risk of chronic pain.<sup>4,5</sup> Therefore,

optimal analgesic treatment is essential for improving the quality of pain management after craniotomy.

Systemic analgesics, such as opioids, are the mainstay of treatment for post-craniotomy pain. However, given the various side effects of systemic opioids such as postoperative nausea and vomiting (PONV), sedation, respiratory depression and interference with neurological assessments, the minimization of reliance on opioids while exploring multimodal approaches with nerve blockade or incision-site infiltration using local anesthetics and smaller doses of opioid supplements is paramount.<sup>6–9</sup>

Pain following craniotomy is thought to be primarily superficial, suggesting a more somatic than visceral origin, that arises from the pericranial muscles and soft tissues of the scalp.<sup>10</sup> Incision-site infiltration with local anesthetics such as bupivacaine and ropivacaine prevents pain on incision site and can be a promising postoperative pain management technique for craniotomy.<sup>11–15</sup> However, an earlier study found that, incision-site infiltration with a single anesthetic could only provide a relatively satisfactory pain relief during the first 2 postoperative hours, despite the addition of adrenaline.<sup>15</sup> Moreover, attempts to prolong the blockade of local anesthetics by increasing dosage have provided conflicting data regarding their safety, mainly because of toxicity. The development of new drugs has also been suboptimal.

Dexamethasone is an inexpensive synthetic glucocorticoid that has a strong anti-inflammatory effect with a long half-life of 36 to 72 hours. Several randomized controlled trials evaluating the analgesic effects of adding dexamethasone to local infiltration have concluded that dexamethasone alone or as an adjuvant to local infiltration successfully achieves better pain relief after total knee arthroplasty (TKA), tonsillectomy, endodontic treatments and cesarean section.<sup>16–19</sup> Meanwhile, no serious side effects from the local use of dexamethasone have been observed in previous studies. However, to our knowledge, no other literature exists comparing the effects of dexamethasone incorporated into local infiltration along with local anesthetics after craniotomy. Therefore, this prospective, randomized, controlled study aiming to compare postoperative pain relief during the first 48 hours following supratentorial craniotomy was conducted. We hypothesized that pre-emptive incision-site infiltration of ropivacaine plus dexamethasone could improve pain relief after craniotomy when compared with ropivacaine alone.

## Materials and Methods

Ethics approval was obtained from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (KY2018-034-02). All participants were provided with a verbal explanation of the written informed consent and had signed the written informed consent to participate in the study during a preoperative visit, one day prior to the surgery. This study was registered prior to patient enrollment at ClinicalTrials.Gov website (NCT03618264, Principal investigator: Fang Luo, Date of registration: August 7, 2018). The trial was conducted in accordance with the World Medical Association's "Declaration of Helsinki", the principles of good clinical practice and relevant regulatory requirements. There were no substantial changes to the main study protocol after commencement of the recruitment process. The trial protocol has previously been published elsewhere.<sup>20</sup>

## Study Design and Participants

This was a prospective, single-center, blinded, randomized, controlled trial, conducted at Beijing Tiantan Hospital, Capital Medical University. Patients were eligible for participation if they met the following inclusion criteria: between 18 and 64 years of age and American Society of Anesthesiologists (ASA) physical status of I-II, scheduled for elective supratentorial tumor craniotomy under general anesthesia, who were required to fix their head in a head clamp intraoperatively, had a 2 hours postoperative anticipated return of consciousness, orientation as well as cooperation, and could thereby correctly recognize and express the degree of pain. Exclusion criteria included patients with a history of craniotomy, psychiatric disorders, uncontrolled epilepsy or chronic headache, expected delay in extubation or had no plan to extubate, who were unable to use a patient-controlled analgesia (PCA) device or understand the instructions of a numeral rating scale (NRS), who had extreme body mass index (BMI) ( $< 15$  or  $> 35$ ), allergic to opioids, dexamethasone or ropivacaine, with a history of excessive alcohol or drug abuse, chronic opioid use (of more than 2 weeks), or the use of drugs with confirmed or suspected sedative or analgesic effects, who were pregnant or breastfeeding, with symptomatic cardiopulmonary, renal, or liver dysfunction or history of diabetes, a preoperative Glasgow Coma Scale (GCS)  $< 15$ , suspected intracranial hypertension, peri-incisional infection, who had received radiation therapy and chemotherapy preoperatively or with a high probability to require a postoperative radiation

therapy and chemotherapy based on preoperative imaging. Participants were withdrawn from the study under the following circumstances: were not awake 2 hours after surgery, had a delayed extubation and underwent early revision within the first 48 hours, which affected the assessment of outcome measures. In addition, participants were allowed to withdraw voluntarily at any stage of the trial, for any reason.

## Randomization and Masking

Eligible participants were randomly assigned (1:1) to either the dexamethasone group or the control group, via SPSS version 22.0 (International Business Machines Inc., USA). Opaque, sealed, sequentially numbered envelopes were used to ensure allocation concealment; which included the participants' screening order outside and their assigned group inside. Before surgery, the envelope was opened by the study investigator in charge of the surgery, and the patient was assigned to undergo corresponding local infiltration. Participants were enrolled by a dedicated research nurse who was not involved in the collection of primary outcome data.

Patients, nurses, surgeons and anesthesiologists in charge of the postoperative period and pain evaluation were blinded to group assignment; except in case of serious adverse events (SAEs) potentially related to the study treatment that required unmasking. The pharmacist in charge was allowed to unmask drug allocation only in case of SAEs. The respective drugs to be used for incision-site infiltration were prepared by an independent study investigator in the two groups: 10 mg dexamethasone, 150 mg ropivacaine diluted to a total volume of 30 mL in 0.9% saline in the dexamethasone group,<sup>16,20</sup> and 150 mg ropivacaine diluted to a total volume of 30 mL in 0.9% saline in the control group. The concentration of ropivacaine was 0.5% in both groups. Both syringes contained clear fluid, appeared identical and were labelled as "study drug".

## Procedures

On arrival in the operating room, standard monitoring of blood pressure (BP), heart rate (HR), electrocardiography, pulse oximetry (SpO<sub>2</sub>) and bispectral index (BIS) were continuously performed. Intravenous (IV) midazolam at 0.05 mg kg<sup>-1</sup>, sufentanil at 0.3–0.5 µg kg<sup>-1</sup>, propofol at 1.5–3 mg kg<sup>-1</sup> and cisatracurium at 0.2 mg kg<sup>-1</sup> were used for induction of anesthesia. Mechanical ventilation was adjusted at 60% oxygen and 40% air to maintain an end-

tidal partial pressure of carbon dioxide at 30–40 mmHg. Anesthesia was maintained with 4 to 8 mg kg<sup>-1</sup> hour<sup>-1</sup> propofol and 0.1 to 0.3 µg kg<sup>-1</sup> min<sup>-1</sup> remifentanyl intravenously. Additional doses of vasoactive drugs were administered to maintain baseline levels within the 20% of the baseline.

5 minutes before head fixation, local infiltration of the study solution was performed by the neurosurgeon in charge of the craniotomy at each pin-insertion site used for skull clamp placement. Subsequently, the same solution was infiltrated with a 22-gauge needle introduced into the skin at a 45° angle throughout the entire thickness of the scalp along the planned incision site, by the same neurosurgeon. The total volume of the study solution used for each patient was determined by the neurosurgeon based on the length of the incision and recorded by the investigator.

Patients were extubated after satisfactory hemodynamic, respiratory and neurologic evaluations were achieved. Additionally, 4 mg of ondansetron was administered to prevent PONV and patients were transferred to the post-anesthesia care unit (PACU). A PCA device (ZZB-I-150, Apon Medical Technology Co., Ltd., Jiangsu, China) containing 200 µg of sufentanil and 16 mg of ondansetron, diluted to a total volume of 100 mL in 0.9% saline. The PCA device provided a bolus of 2 µg sufentanil on demand, followed by a 10 min lockout interval; the maximum dose was limited to 8 µg per hour. Both the initial dose and background infusion of the PCA pump were set to 0. Patients pushed the PCA demand button when an NRS of 4 or more was reported and repeated until pain was relieved. Insufficient post-operative analgesia was defined as NRS score exceeding 4 after the maximum dose of sufentanil was administered with the PCA device. All aspects of the rehabilitation process were identical between the two groups.

## Outcomes

Primary outcome was the cumulative sufentanil consumption (µg) via PCA pump within 48 hours postoperatively.

Secondary outcomes included the following aspects: first analgesia demand indicated by participants pressing the PCA demand button; NRS scores (0 indicating no pain, 10 indicating the most severe pain imaginable) and patient satisfaction scale (PSS) scores (0 indicating unsatisfactory, and 10 indicating very satisfactory) at 2 hours, 4 hours, 8 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, 1 month, 3 months and 6 months postoperatively; PONV scores (0, absent; 1, nausea not requiring treatment; 2, nausea requiring

treatment; and 3, vomiting) within 48 hours postoperatively; Wound healing score<sup>21</sup> (total score of 3, excellent wound healing; score 4–5, good wound healing; and score 6+, sub-optimal wound healing) at 3 weeks and 6 weeks postoperatively; Patient and Observer Scar Assessment Scale (POSAS) scores<sup>22</sup> at 6 months postoperatively; the times of emergency reduction of BP within 48 hours postoperatively; postsurgical duration of hospitalization.

Safety assessments included steroid-induced complications such as wound infection, wound hematoma, impaired wound healing, chest infection or gastric ulcers during hospitalization. All the adverse events (AEs) were closely monitored and promptly treated. The research team verified suspected AEs where possible. Unrelated AEs were not recorded.

Follow-up evaluations were conducted by experienced research members who were blinded to the study.

## Statistical Analysis

Based on previous studies and our clinical experience at the study center,<sup>13</sup> we estimated that the cumulative postoperative sufentanil consumption in participants who received pre-emptive incision-site infiltration with 0.5% ropivacaine would be approximately  $100 \pm 50$   $\mu\text{g}$ , and the postoperative pain intensity or analgesic requirements would be reduced by 30–50% with the addition of dexamethasone.<sup>16,18,19,23</sup> Thus, we hypothesized that the sufentanil dose within 48 hours postoperatively in the dexamethasone group would be  $70 \pm 50$   $\mu\text{g}$ . PASS V.11 software (NCSS, Kaysville, Utah, USA) was used. To detect such a reduction with 90% power at an  $\alpha$  level of 0.05, 62 participants were required in each group. Considering a 10% withdrawal rate, the sample size was 70 in each group; the total sample size was 140 patients for this trial.

Primary analysis was performed based on the modified intention-to-treat (MITT) principle. We also prespecified a sensitivity and consistency analysis within the per-protocol (PP) population. Analyses of secondary outcomes were exploratory in nature, and therefore p values and confidence intervals were provided with no adjustments for multiple comparisons. Treatment effects were presented as risk ratios (RRs) or mean differences, with 95% confidence interval (CI). Two-tailed analyses were conducted, and a p-value of  $\leq 0.05$  was considered statistically significant. We further evaluated the consistency of treatment effect on primary outcome among 7 prespecified subgroups.

Safety analyses were compared in the safety data set with the incidence of AEs using Chi-square test or Fisher's exact test, according to actual treatment received.

All statistical analyses were performed by statisticians who were masked to the entire allocation and intervention process. Data analysis was performed using the SPSS version 22.0.

## Results

We screened patients for enrollment from April 4, 2019 through August 15, 2019. The final study visit of the last patient was conducted on February 13, 2020. Out of 251 patients initially assessed for eligibility, 111 (44%) patients were excluded (primarily because they did not meet one or several inclusion criteria or declined to participate); 140 (56%) patients were eligible for inclusion. We randomly assigned 70 patients to receive ropivacaine plus dexamethasone and 70 patients to receive ropivacaine alone. All participants received the allocated drug in compliance with the protocol, and were included in the MITT analysis of the primary outcome. Sixty-eight patients in the dexamethasone group and 65 patients in the control group completed the 6-month follow-up and were included in PP analysis. Figure 1 shows the trial profile.

## Baseline Characteristic

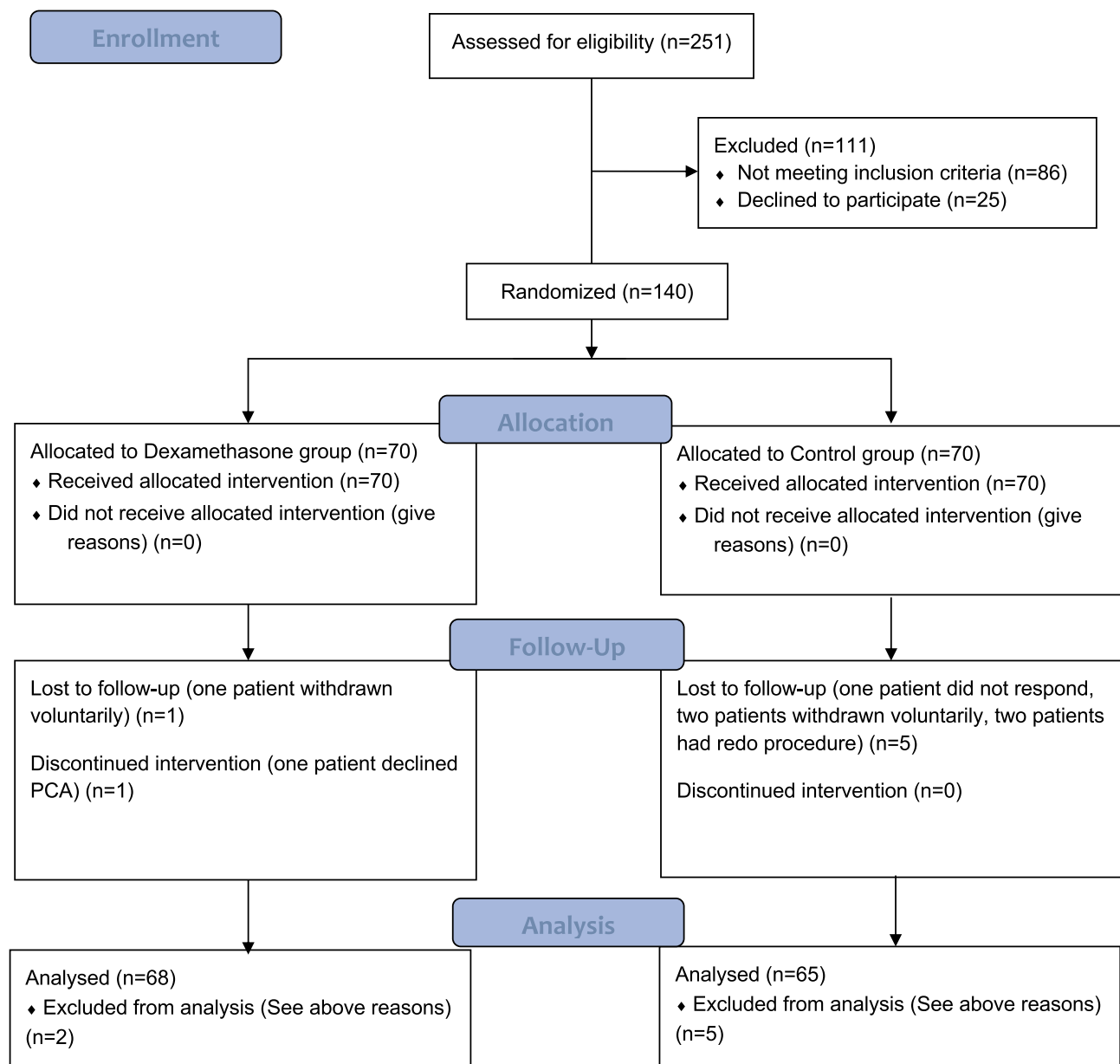
Demographic data and surgical variables of the two groups are shown in Table 1. Baseline characteristics were well balanced between the groups. Moreover, there were no statistically significant differences in HR (Figure 2A) and MAP (Figure 2B) intraoperatively and postoperatively between the groups (Figure 2). Eighty-three (59.3%) patients (40 patients in the dexamethasone group and 43 patients in the control group) received perioperative intravenous glucocorticoid ( $p=0.606$ ).

## Primary Outcome

As shown in Table 2, dexamethasone as an adjuvant to pre-emptive incision-site infiltration significantly reduced sufentanil consumption during the first 48 hours postoperatively: 29.0 (10.7)  $\mu\text{g}$  in the dexamethasone group vs 38.3 (13.7)  $\mu\text{g}$  in the control group ( $p<0.001$ ). Additionally, sensitivity analysis performed in the PP population also showed significant difference in primary outcome between the two groups ( $p<0.001$ ).

## Time of First PCA Demand

Estimated median of the first analgesia demand time indicated by participants pressing the PCA demand button was 16 hours in the dexamethasone group and 12 hours in the control group. However, analgesia demand time on the



**Figure 1** Trial profile.

PCA device did not differ by type of intervention (hazard ratio [HR] 0.86, 95% CI 0.59 to 1.20; Log-rank  $p=0.40$ ; [Figure 3](#))

## Postoperative Pain and Analgesia Satisfaction

[Figure 4A](#) and [4B](#) show the NRS and PSS score distribution of patients after surgery. Within the first 72 postoperative hours, 69 (49.3%) patients (16 patients in the dexamethasone group and 53 patients in the control group) suffered from moderate to severe pain which was

determined by  $\text{NRS} \geq 4$  scores; the difference was statistically significant (risk ratio 0.3, 95% CI 0.2 to 0.5,  $p < 0.001$ , as shown in [Table 2](#)). The pain scores ([Figure 4A](#)) decreased after 1 week postoperatively; 8 (6%) patients (4 patients in the dexamethasone group and 4 patients in the control group) were found to have chronic pain at 3 months and 6 months postoperatively. On the 2 hours, 4 hours, 8 hours, 24 hours, 48 hours and 72 hours postoperative periods, NRS scores of the control group were higher than those of the dexamethasone group [mean difference (95% CI); 0.7 (0.4 to 0.9), 0.6 (0.3 to

**Table 1** Baseline Characteristics

Variables	Participants, No. (%)		
	Dexamethasone Group (n=70)	Control Group (n=70)	p value
<b>Demographic data</b>			
Age, mean (SD), y	49.6(12.0)	47.2(12.4)	0.239
BMI, mean (SD), kg/cm <sup>2</sup>	24.2(2.6)	24.0(3.2)	0.665
Sex			0.612
Male	38(54.3)	35(50.0)	
Female	32(45.7)	35(50.0)	
ASA physical status			0.866
1	32(45.7)	34(48.6)	
2	38(54.3)	36(51.4)	
<b>Surgical variables</b>			
Tumor pathology <sup>a</sup>			0.401
Astrocytoma	17(24.3)	9(12.9)	
Oligodendroglioma	4(5.7)	6(8.6)	
Glioblastoma	5(7.1)	11(14.3)	
Meningioma	35(50.0)	32(47.1)	
Metastatic tumors	2(2.9)	2(2.9)	
Others	7(10.0)	10(14.3)	
Tumor diameter, mean (SD), cm	4.4(1.6)	4.1(1.4)	0.354
Location of incision			0.470
Frontal	12(17.1)	19(27.1)	
Temporal	5(7.1)	7(10.0)	
Fronto-temporal	25(35.7)	19(27.1)	
/pterional			
Parietal	7(10.0)	4(5.7)	
Others <sup>b</sup>	26(37.1)	26(37.1)	
Length of incision, mean (SD), cm	18.0(1.9)	17.5(2.4)	0.198
Area of incision, mean (SD), cm <sup>2</sup>	36.0(5.6)	34.2(8.1)	0.140
Amount of local anesthetic, mean (SD), mL	24.2(3.8)	24.2(4.1)	0.947
Dose of ropivacaine, mean (SD), mg	121.0(19.0)	121.0 (20.5)	0.947
Dose of dexamethasone, mean (SD), mg	8.0(1.2)		
<b>Intraoperative variables</b>			
Opioids dosage			
Sufentanil, mean (SD), µg	37.4(5.9)	37.5(7.4)	0.995
Remifentanil, mean (SD), mg	2.4(1.0)	2.7(1.4)	0.089

(Continued)

**Table 1** (Continued).

Variables	Participants, No. (%)		
	Dexamethasone Group (n=70)	Control Group (n=70)	p value
Propofol dosage, mean (SD), g	1.5(0.5)	1.7(0.7)	0.115
Duration of surgery, mean (SD), h	3.8(1.0)	3.8(1.7)	0.911
Duration of anesthesia, mean (SD), h	4.8(1.0)	4.9(1.9)	0.588
<b>Numbers of perioperative IV glucocorticoid</b>	40(57.1)	43(61.4)	0.606

**Notes:** <sup>a</sup>The 2016 World Health Organization classification of tumor of the central nervous system. <sup>b</sup>Other locations included occipito-temporal, fronto-parietal, temporo-parietal, parieto-occipital.

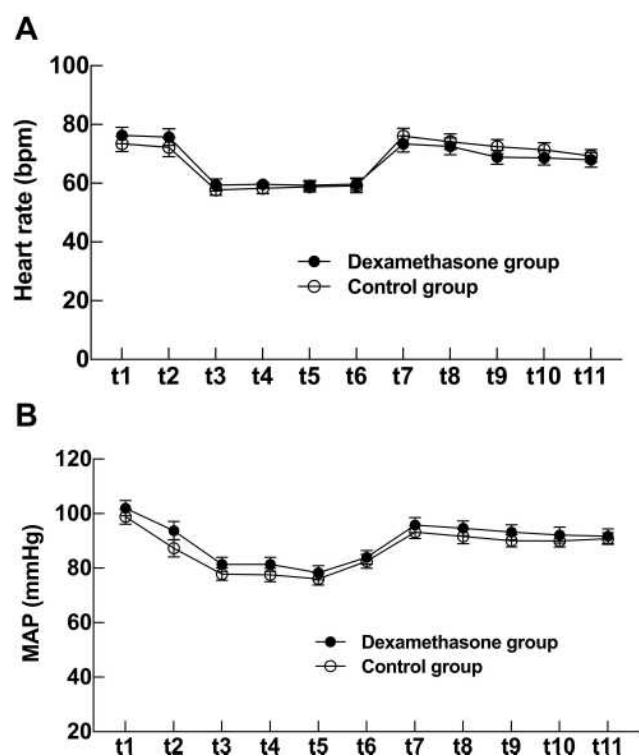
**Abbreviations:** BMI, body mass index; ASA, American Society of Anesthesiologists; IV, intravenous.

1.0), 1.1 (0.8 to 1.4), 1.4 (1.1 to 1.8), 1.2 (0.9 to 1.6) and 1.4 (1.0 to 1.7), respectively;  $p < 0.001$ ] (Figure 4A). The minimum median of PSS scores at each time point after surgery was more than 6.5 points (Figure 4B). The PSS scores were higher in the dexamethasone group than that in the control group on the 2 hours, 4 hours, 8 hours, 24 hours, 48 hours and 72 hours [mean difference (95% CI); 0.4 (0.2 to 0.7), 0.4 (0.1 to 0.8), 1.0 (0.7 to 1.3), 1.4 (1.0 to 1.7), 1.2 (0.9 to 1.5) and 0.4 (0.1 to 0.7), respectively;  $p < 0.05$ ].

## Wound Healing Situation

At 3 weeks postoperatively, 97 (69%) patients (53 patients in the dexamethasone and 44 patients in the control group) were reported to have very good wound healing. At 6 weeks postoperatively, the wound healing improved and a total of 92 (66%) patients achieved excellent wound healing. Three patients (4.3%) out of 70 in the control group suffered suboptimal wound healing at 6 weeks; whereas, zero patient in the dexamethasone group suffered suboptimal wound healing.

At 6 months postoperatively, a high objective evaluated outcome with a median objective general score of 2.2 was recorded. Moreover, there was a statistically significant difference between the two groups at 6 months (dexamethasone group 8.2 (0.8) vs control group 9.4 (2.8), mean difference -1.1, 95% CI, -1.9 to -0.4;  $p = 0.003$ ).



**Figure 2** Perioperative heart rate (HR) and mean arterial pressure (MAP).  
**Notes:** Data were mean with 95% CI over the study period. There were no statistically significant differences in the perioperative HR and MAP. t1: before anesthetic induction, t2: after anesthetic induction, t3: scalp infiltration, t4: skull drilling, t5: mater cutting, t6: skin closure, t7: 2 hours after surgery, t8: 4 hours after surgery, t9: 8 hours after surgery, t10: 24 hours after surgery, t11: 48 hours after surgery.

Meanwhile, patients were also highly satisfied with their scar appearance, with a median patient general score of 2.2. However, there was no statistically significant difference between the two groups in Patient Scar Assessment Scale (PSAS) at 6 months. There was one patient with wound infection in the control group and none in the dexamethasone group.

## Subgroups

The reduction of sufentanil consumption with ropivacaine plus dexamethasone incision-site infiltration was generally consistent across all prespecified subgroups, within the first 48 hours postoperatively (Figure 5). There were no significant interactions in any of the 7 predefined subgroups ( $P > 0.10$  for all comparisons).

## Safety

The average volume of local anesthetic used for each patient was 24.2 mL, which was equivalent to 121 mg of ropivacaine and 8 mg of dexamethasone. The expected but unrelated AEs, such as complications of surgery, could not

be attributed to study interventions. No SAEs or drug reactions were recorded during the study, which were directly associated with incision-site infiltration or local dexamethasone use.

## Discussion

This is the first large-scale clinical trial examining the analgesic efficacy of dexamethasone as an adjuvant to pre-emptive incision-site infiltration in patients scheduled for elective supratentorial craniotomies. When compared to ropivacaine alone, pre-emptive incision-site infiltration with ropivacaine plus dexamethasone (average 8 mg) could reduce about 27% of sufentanil consumption via PCA within the first 48 hours after craniotomy. It could also improve the postoperative pain scores within 72 hours after craniotomies and improve patient satisfaction. However, the addition of dexamethasone to pre-emptive incision-site infiltration had no long-term effect on recovery, such as the duration of hospital stay.

The location of surgical incision (infratentorial vs supratentorial) could affect the incidence and severity of postoperative pain. Pain scores after supratentorial craniotomy are generally lower than those reported after posterior fossa procedures because of the relatively low muscle dissection.<sup>24</sup> Subtemporal and suboccipital craniotomies yield a higher incidence of postoperative pain. Therefore, in order to minimize the influence of confounding factors that may result in high heterogeneity of the characteristics of postoperative pain, this study only included supratentorial craniotomies. Previous studies have demonstrated a common mechanism of incisional pain, which involves inflammatory mediators released after tissue damage directly stimulating the peripheral nociceptors; abnormal activation transmitted by A $\delta$  and C-fibers causes local pain after tissue injury.<sup>25,26</sup> Glucocorticoids inhibit inflammatory responses by blocking factors such as bradykinin, prostaglandin and leukotriene, thereby reducing inflammation levels and accompanying signs and symptoms.<sup>27</sup> Therefore, this innovative combination of local anesthetics and dexamethasone is theoretically expected to consistently reduce incisional pain in other types of surgeries.

Although local infiltration of dexamethasone has not been used for incision-site infiltration after craniotomy yet, several clinical trials have reported the short-term benefits of the addition of dexamethasone to local infiltration analgesia in endodontic practices<sup>18</sup> and tonsillectomy in pediatric patients.<sup>28</sup> Despite the high heterogeneity in the design and quality of these randomized trials, the analgesic

**Table 2** Primary Outcome and Postoperative Recovery Situation

Variable	Participants, No. (%)			
	Dexamethasone Group (n=70)	Control Group (n=70)	Mean Difference or RR (Estimate 95% CI)	p value
<b>Primary outcome</b>				
Sufentanil consumption within 48 hours postoperatively, mean (SD), µg	29.0(10.7)	38.3(13.7)	−9.3(−13.4 to −5.1)	<0.001
<b>Secondary outcomes</b>				
Moderate to severe pain within 72 hours	16(22.8)	53(75.7)	0.3(0.2 to 0.5) <sup>a</sup>	<0.001
PONV, median (IQR), scores				
2 h	0(0–1)	0(0–0)		0.123
4 h	0(1–1)	0(0–1)		0.798
8 h	0(0–1)	0(0–1)		0.859
24 h	0(0–1)	0(0–1)		0.132
48 h	0(0–0)	0(0–0)		0.800
Duration of hospital stay, median (IQR), days	14(12–15)	14(12–16)		0.294
<b>Wound healing</b>				
Wound healing scores at 3 weeks				0.014
Suboptimal (6+)	0(0)	7(10.0)		
Very good (4–5)	53(75.5)	44(62.9)		
Excellent (3)	16(24.5)	19(27.1)		
Wound healing scores at 6 weeks				0.221
Suboptimal (6+)	0(0)	3(4.3)		
Very good (4–5)	21(30.0)	24(34.3)		
Excellent (3)	49(70.0)	43(61.4)		
POSAS scores at 6 months, mean (SD)				
Objective scar rating	2.2(0.5)	2.2(0.4)	0(−0.2 to 0.2)	1.000
OSAS	8.2(0.8)	9.4(2.8)	−1.0(−1.7 to −0.4)	0.003
Patient satisfaction	2.3(0.5)	2.2(0.4)	0(−0.1 to 0.2)	0.367
PSAS	8.8(1.1)	9.2(2.1)	−0.4(−1.2 to 0.1)	0.155

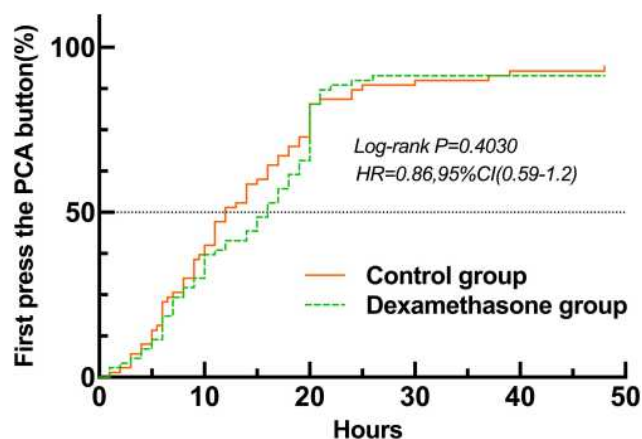
**Note:** <sup>a</sup>This value is risk ratio (RR).

**Abbreviations:** SD, standard deviation; IQRs, interquartile ranges; PCA, patient-controlled analgesia; PONV, postoperative nausea/vomiting; POSAS, Patient and Observer Scar Assessment Scale; OSAS, Observer Scar Assessment Scale; PSAS, Patient Scar Assessment Scale.

efficacy of dexamethasone appears to be definite. We demonstrated statistically significant differences in analgesic consumption within the first 48 hours after surgery. In addition, the reduction in sufentanil consumption was generally consistent across all prespecified subgroups. Moreover, there was no significant difference in the number of patients receiving systemic glucocorticoids. In addition to reducing the consumption of analgesics, there was a significant difference in NRS pain scores of greater than 1 point, especially in the 8 hours, 24 hours, 48 hours and 72 hours postoperative periods, which could be clinically important.<sup>29</sup> The duration of the analgesic effect is

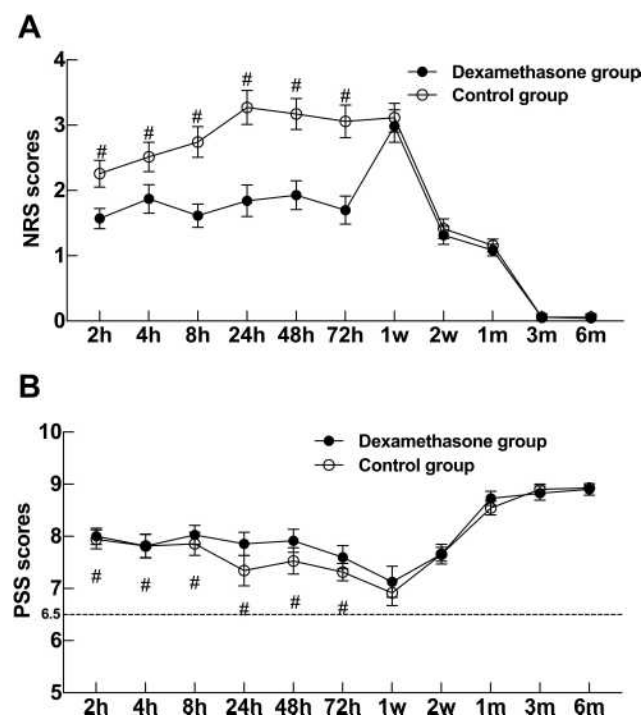
consistent with the physiological effects of dexamethasone, which remains for 36–72 hours in the human body. Such a duration of effect seems to be sufficient to relieve pain after craniotomy, as it has been reported by previous studies that postcraniotomy pain peaks within the first 48 h.<sup>1,2</sup>

In this study, the duration of the analgesic effects of dexamethasone was 2–3 days following craniotomy, which is consistent with previous reports.<sup>16,30</sup> Several studies have reported that the analgesic effects of pre-emptive local infiltration of dexamethasone alone only last 16–24 hours after endodontic treatment, cesarean section, tonsillectomy and



**Figure 3** Kaplan-Meier estimation of the first analgesia demand press time among patients who were given dexamethasone as an adjuvant (dexamethasone group) or ropivacaine alone (control group) to pre-emptive incision-site infiltration.

adenoidectomy.<sup>18,19,31</sup> Certainly, incisional pain is only one type of postoperative pain.<sup>32</sup> The short-term analgesic effect of dexamethasone alone or as an adjuvant to local infiltration is definite on incisional pain, but might be ineffective on other types of postoperative pain. However, the characteristics of postoperative pain in different types of surgeries vary greatly.<sup>33,34</sup> These reasons might explain the inconsistency in



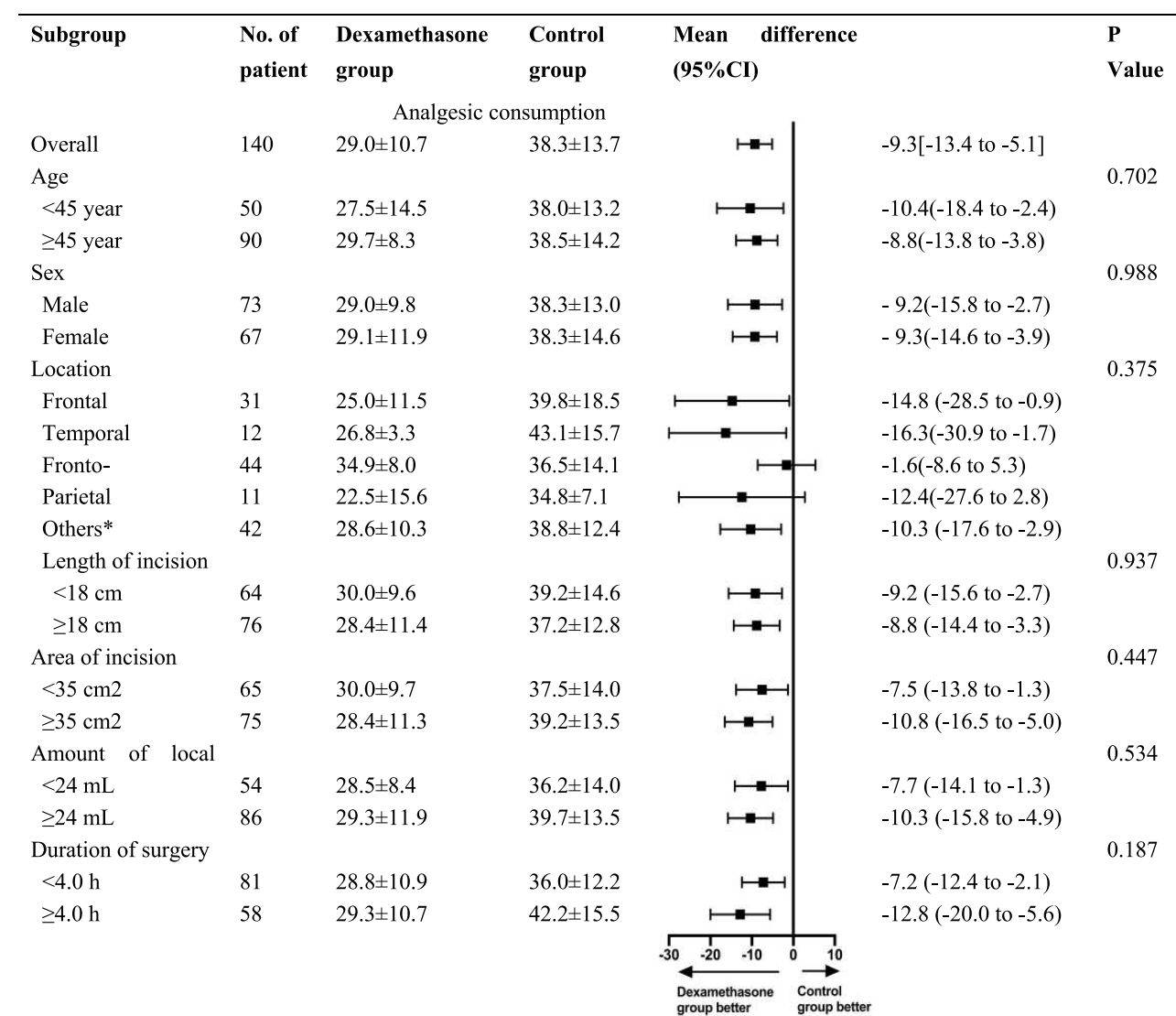
**Figure 4** Postoperative numerical rating scale (NRS) (A) and patient satisfaction scale (PSS) (B) scores.

**Notes:** Data are shown as mean with 95% CI over the study period; #Represents statistically significant ( $p < 0.05$ ).

conclusions regarding the duration of action of dexamethasone when administered locally, alone or when mixed with local anesthetics, after different types of surgeries.

Glucocorticoid treatment complications, such as peptic ulcer, increased wound infection, and impaired wound healing, are often associated with long-term systemic use.<sup>35–37</sup> More patients in the dexamethasone group (70%) achieved excellent wound healing than those in the control group (61%). Moreover, there was a lower wound infection rate in the dexamethasone group (0%), compared to the control group (0.7%, 1 patient). Although we did not find any adverse effects of dexamethasone on wound healing and infection, the current study is not powered for the possible side effects of the treatment. Therefore, the results of local infiltration of dexamethasone on wound healing and infection should be taken with caution.

Despite our significant findings, this study has a few limitations. First, this was a single-center study, and therefore, the generalizability of our outcomes must be established with large scale, multicentric randomized controlled trials. Second, the results of this dexamethasone study do not apply to other types of steroids.<sup>39</sup> There are significant differences in the half-life and anti-inflammatory effects of various steroids. Third, we found a discrepancy between the estimated sufentanil consumption (100  $\mu\text{g}$ ) and the actual sufentanil consumption (38.3  $\mu\text{g}$ ) in the control group within the first 48 hours after craniotomies. The main reason may be because we only selected patients with supratentorial tumors; thus, the number of patients experiencing moderate to severe pain (37%) may have been significantly lower than previous reports (55–69%).<sup>1,2</sup> Nevertheless, we can still guarantee the power of this study to be greater than 90% for the primary outcome. However, this reduction in the addition of dexamethasone might not really be clinically relevant based on clinical experience. Fourth, the use of painkillers at home was not considered in this study, which might have affected the severity of pain during follow-up. Fifth, we did not monitor blood glucose concentration and concentrations of dexamethasone. Finally, we had selected a single dose of dexamethasone for addition. We selected the dose that was previously reported to be safe in this setting.<sup>16</sup> Needless to say, clinical trials on dose-dependent effects of dexamethasone need to be conducted in the future, to determine the optimal dose. The addition of other long-acting adjuvants should also be explored.



**Figure 5** Mean differences in primary outcome of the prespecified subgroups. The reduction in sufentanil consumption within the first 48 hours after craniotomy with pre-emptive incision-site infiltration with the ropivacaine plus dexamethasone group (dexamethasone group), when compared with the ropivacaine alone group (control group), was consistent across all prespecified subgroups. There were no significant interactions in any of the 7 predefined subgroups ( $P>0.10$  for all comparisons). \*Other locations included occipito-temporal, fronto-parietal, temporo-parietal, parieto-occipital.

## Conclusions

The addition of dexamethasone to pre-emptive incision-site infiltration with local anesthetic can reduce about 27% of opioids consumption and the postoperative pain scores within 72 hours after craniotomies. Further exploration of the ideal combination of local anesthetics and glucocorticoids is expected to provide an effective strategy for the prevention of incisional pain.

## Abbreviations

MITT, modified intention-to-treat; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists physical status; PCA, patient-controlled analgesia; NRS, numeral

rating scale; BMI, body mass index; GCS, Glasgow Coma Scale; SAEs, serious adverse events; BP, blood pressure; HR, heart rate; SpO<sub>2</sub>, pulse oximetry; BIS, bispectral index; IV, Intravenous; PONV, postoperative nausea/vomiting; PACU, post-anesthesia care unit; PSS, patient satisfaction scale; RSS, Ramsay Sedation Scale; POSAS, Patient and Observer Scar Assessment Scale; AEs, adverse events; IQRs, interquartile ranges; RRs, risk ratios; CI, confidence interval; PP, per-protocol.

## Data Sharing Statement

Raw data were generated at Beijing Tiantan Hospital, Capital Medical University. Individual participant data that underlie

the results reported in this article, after de-identification (text, tables, figures and appendices) are available. Derived data supporting the findings of this study are available from the corresponding author Fang Luo on request.

## Ethics Approval and Informed Consent

Ethics approval was obtained from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (KY2018-034-02). Written informed consent has been obtained from all patients before inclusion in the study.

## Acknowledgment

We thank the patients who participated in this trial. We also thank Apon Medical Technology Co., Ltd., Jiangsu, China for lending the PCA pump equipment.

## Author Contributions

CMZ and SHW contributed equally to this work and should be considered co-first authors. FL, CMZ and NJ did the literature search and were responsible for the study design. Study conduction and data collection were led by SHW. Study analysis and figure generation were done by CMZ, supervised by YSP. Writing of the paper was led by FL and CMZ with assistance from NJ and YSP. FL conceived the idea for this study and secured funding. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval for the version to be published, and agree to be accountable for all aspects of the work.

## Funding

This research was supported by Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. XMLX201707). The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had complete access to all the data in the study; all the co-authors were responsible for making the final decision to submit for publication.

## Disclosure

The authors declare that they have no conflicts of interest.

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