



A COMPREHENSIVE SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF REGIONAL SCALP BLOCK IN CRANIOTOMY ON POSTOPERATIVE PAIN AND INTRAOPERATIVE HAEMODYNAMIC RESPONSE

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ABSTRACT

Introduction: Craniotomy is followed by moderate-to-severe surgical-site pain in a majority of patients, yet analgesia in this population is constrained by the need to preserve neurological assessment and to avoid opioid-induced hypercapnia and intracranial hypertension. Skull-pin (Mayfield) fixation, scalp incision, and craniotomy each generate an abrupt sympathetic discharge that raises arterial pressure and heart rate, with potential consequences for cerebral perfusion pressure, aneurysm transmural tension, and haemorrhage risk. Regional scalp block offers a physiologically rational solution that addresses both problems with a single intervention.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Randomised controlled trials and primary comparative studies evaluating regional scalp block against placebo, no block,

local infiltration, or systemic analgesia in patients undergoing craniotomy were eligible. Two reviewers independently performed screening, data extraction, and risk-of-bias appraisal using RoB 2 and ROBINS-I, with certainty of evidence rated by GRADE. Random-effects meta-analysis using the DerSimonian-Laird estimator generated mean differences, standardised mean differences, and risk ratios with 95% confidence intervals across sixteen prespecified outcome domains.

Results: Forty-one studies comprising 2,984 participants (1,587 block, 1,397 comparator) were included; 38 were randomised controlled trials. Regional scalp block produced a large and statistically robust reduction in early postoperative pain at 1-2 hours (mean difference -1.74 points; 95% CI -2.07 to -1.42 ; $I^2=42\%$; $P<0.0001$) that persisted at 6-8 hours (-1.35 ; 95% CI -1.72 to -0.99 ; $P<0.0001$), 24 hours (-0.81 ; 95% CI -1.04 to -0.57 ; $P<0.0001$), and 48 hours (-0.48 ; 95% CI -0.76 to -0.20 ; $P<0.001$). Haemodynamic protection was pronounced at the most noxious stimulus: mean arterial pressure at skull-pin insertion fell by 14.24 mmHg (95% CI -17.24 to -11.25 ; $P<0.0001$) and heart rate by 11.19 beats·min⁻¹ (95% CI -13.87 to -8.50 ; $P<0.0001$), with attenuated but still significant effects at skin incision (-9.46 mmHg and -8.89 beats·min⁻¹, both $P<0.0001$). Intraoperative opioid consumption was substantially reduced (SMD -1.03 ; 95% CI -1.25 to -0.80 ; $P<0.0001$), as was 24-hour consumption (-16.66 mg; 95% CI -21.89 to -11.42 ; $P<0.0001$), while time to first rescue analgesia was prolonged by 2.91 hours (95% CI 2.03 to 3.79 ; $P<0.0001$). Block reduced postoperative nausea and vomiting (RR 0.65 ; 95% CI 0.51 to 0.83 ; $P<0.001$), intraoperative hypertensive responses (RR 0.36 ; 95% CI 0.27 to 0.49 ; $P<0.0001$), and persistent incisional pain at 2-3 months (RR 0.56 ; 95% CI

0.34 to 0.93; $P=0.025$). Serum cortisol (SMD -0.80 ; 95% CI -1.10 to -0.51) and time to tracheal extubation (-4.08 minutes; 95% CI -5.74 to -2.42) both favoured block. All sixteen outcome domains reached statistical significance in favour of regional scalp block. Meta-regression identified local anaesthetic concentration as the dominant modifier of analgesic magnitude ($\beta=-2.18$ points per 1% w/v; $P<0.0001$; 84% of τ^2 explained), and an Emax model estimated a half-maximal effective concentration of 0.163% ropivacaine-equivalent. Exploratory summary ROC analysis yielded an AUC of 0.753 for freedom from moderate-to-severe pain at 24 hours and 0.726 for absence of a hypertensive pinning response. No case of local anaesthetic systemic toxicity, seizure, or permanent neurological injury attributable to the block was reported in 1,587 exposed patients. Funnel plots were symmetrical (Egger $P=0.53$) and GRADE certainty was high for haemodynamic outcomes and moderate for most analgesic outcomes.

Conclusion: Regional scalp block delivers clinically meaningful, statistically robust, and internally consistent benefit across analgesic, haemodynamic, opioid-sparing, neuroendocrine, recovery, and safety domains in patients undergoing craniotomy. Pre-incisional blockade with a long-acting amide local anaesthetic at a concentration of at least 0.5% ropivacaine-equivalent, optionally supplemented with dexmedetomidine or a corticosteroid, should be considered a default component of enhanced recovery pathways for cranial neurosurgery.

Keywords: scalp block; scalp nerve block; craniotomy; regional anaesthesia; postoperative pain; haemodynamic response; skull-pin insertion; opioid-sparing analgesia; neuroanaesthesia; systematic review; meta-analysis

INTRODUCTION

Background

Craniotomy occupies an unusual position among major surgical procedures. It is widely — and incorrectly — assumed to be relatively painless because the brain parenchyma itself is insensate. In reality the scalp, pericranium, temporalis muscle, dura mater and the vessels of the dural sleeve are richly innervated by the trigeminal and upper cervical afferents, and their surgical violation generates nociceptive input of substantial intensity. Prospective series have consistently documented that between 55% and 80% of patients report moderate-to-severe pain within the first forty-eight hours after cranial surgery, with the highest intensities in the first six hours and a well-recognised second peak associated with mobilisation.^{20,49,51}

This pain is not merely a comfort issue. In the neurosurgical patient, uncontrolled nociception carries a specific physiological penalty. Sympathetically driven hypertension increases cerebral blood volume in a brain whose autoregulation may already be impaired, raising intracranial pressure and predisposing to postoperative haematoma at the operative bed. Agitation and hypertensive surges have been directly implicated in postoperative intracranial haemorrhage, and inadequate analgesia prolongs intensive-care and hospital stay. At the same time, the conventional solution — systemic opioid — is problematic in precisely this population: sedation confounds the serial neurological examination on which early detection of surgical complications depends, respiratory depression provokes hypercapnia and cerebral vasodilatation, and opioid-related nausea and vomiting raise intrathoracic and intracranial pressure. Clinicians therefore face a genuine therapeutic dilemma, and surveys of practice have repeatedly documented systematic under-treatment of post-craniotomy pain as the pragmatic consequence.^{45,49,51,55,59}

The intraoperative phase presents a parallel and equally consequential problem. Application of the Mayfield three-point pin head-holder drives sharpened pins through skin, galea and pericranium into the outer table of the skull. This is one of the most intense noxious stimuli in all of surgery, and it is delivered at a point in the anaesthetic when the depth of anaesthesia has typically

been titrated for laryngoscopy rather than for a periosteal stimulus. The result is a stereotyped sympathetic discharge: the seminal double-blind study by Pinosky and colleagues recorded increases of 40 ± 6 mmHg in systolic pressure, 32 ± 6 mmHg in mean arterial pressure and 22 ± 5 beats·min⁻¹ in heart rate in unblocked control patients. In a patient with an unsecured aneurysm, an arteriovenous malformation, a hypertensive intracerebral haematoma or a space-occupying lesion with compromised intracranial compliance, a surge of this magnitude is not a monitoring curiosity but a potential precipitant of rupture, rebleeding or herniation.^{3,11,64}

Regional scalp block is a targeted anatomical solution to both problems. The technique involves the deposition of local anaesthetic around the seven principal sensory nerves supplying the cranial vault: the supraorbital and supratrochlear branches of the ophthalmic division of the trigeminal nerve, the zygomaticotemporal branch of the maxillary division, the auriculotemporal branch of the mandibular division, and the greater occipital, lesser occipital and greater auricular nerves derived from the cervical plexus and dorsal rami of C2–C3. Because these nerves converge on identifiable bony and vascular landmarks, the block can be performed rapidly, without imaging, and with a small total volume of drug. Its physiological appeal is that it interrupts the nociceptive afferent limb before it reaches the neuraxis, thereby attenuating both the conscious perception of pain and the reflex sympathetic response, without any systemic sedative burden and without any effect on the neurological examination.^{3,11,14,49,54}

Despite this rationale, adoption has been uneven and the published evidence has accumulated in a fragmented fashion. Individual trials have been small, single-centre and heterogeneous in the local anaesthetic used, its concentration, the timing of the block relative to incision, the comparator chosen and the outcomes reported. Three decades separate the earliest and most recent trials, during which the background anaesthetic technique has shifted from volatile agents with intermittent bolus opioid to target-controlled propofol–remifentanyl infusion with processed electroencephalographic and nociception monitoring — a change that materially alters the counterfactual against which the block is judged.^{3,9,17,34,50}

Research objectives

General objective. To determine, by comprehensive systematic review and quantitative synthesis of all available randomised controlled trials and primary comparative studies, the effectiveness and safety of regional scalp block in patients undergoing craniotomy, with respect to both postoperative pain and intraoperative haemodynamic response.

Specific objectives. The review was designed to answer the following questions:

- To quantify the effect of regional scalp block on postoperative pain intensity at 1–2, 6–8, 24 and 48 hours after craniotomy.
- To quantify the effect of the block on mean arterial pressure and heart rate at the two principal noxious intraoperative events — skull-pin insertion and skin incision.
- To quantify intraoperative and 24-hour postoperative opioid-sparing, and the prolongation of time to first rescue analgesia.
- To determine the effect on postoperative nausea and vomiting, on intraoperative hypertensive episodes requiring pharmacological rescue, and on time to tracheal extubation.
- To determine the effect on the neuroendocrine stress response as indexed by perioperative serum cortisol.
- To determine whether the block reduces the incidence of persistent incisional pain at two to three months.
- To characterise the safety profile of the technique, including local anaesthetic systemic toxicity, seizure, facial nerve palsy and block-site complications.
- To identify the sources of between-study heterogeneity, in particular the influence of local anaesthetic agent, concentration, block timing, comparator type, surgical approach, patient age stratum and methodological quality.
- To model the concentration–response and duration–response relationships and to derive an exploratory discriminative performance estimate for the block.
- To grade the certainty of the evidence for each outcome domain and to translate the findings into actionable clinical recommendations.

Significance and benefits of the review

Theoretical benefit. By assembling in a single analysis the analgesic, haemodynamic, neuroendocrine and inflammatory consequences of regional scalp block, this review permits a coherent mechanistic account of how afferent blockade modifies the perioperative stress response in cranial neurosurgery. The concentration–response and temporal-decay modelling presented here converts what has been a qualitative literature into a quantitative pharmacodynamic framework that can inform both bedside dosing and the design of future trials.

Clinical benefit. For the practising neuroanaesthetist the review provides pooled effect estimates of sufficient precision to support a specific technical prescription — agent, concentration, volume, timing and adjuvant — rather than a generic endorsement. For the neurosurgeon it quantifies the reduction in intraoperative hypertensive surges, a variable of direct relevance to operative-field haemostasis and to the safety of aneurysm and vascular work. For the intensivist it quantifies opioid-sparing and its downstream effects on nausea, extubation time and the fidelity of the neurological examination.

Health-system benefit. In settings where opioid stewardship, intensive-care bed pressure and enhanced recovery after surgery pathways dominate the operational agenda — including the Indonesian tertiary neurosurgical context — a low-cost, equipment-light, rapidly learned regional technique with a demonstrable opioid-sparing effect carries substantial system value. The block requires only a syringe, a fine needle, a vial of long-acting amide local anaesthetic and knowledge of surface anatomy.

Methodological benefit. The review contributes an integrated appraisal framework — RoB 2 and ROBINS-I for internal validity, GRADE for certainty, meta-regression and L'Abbé analysis for heterogeneity, and an exploratory summary ROC analysis for discriminative performance — that can be transferred to the appraisal of other regional anaesthetic techniques.

Hypotheses

The review was conducted to test the following prespecified hypotheses.

Primary null hypothesis (H_0). Regional scalp block does not differ from control with respect to postoperative pain intensity at any measured time point within 48 hours of craniotomy.

Primary alternative hypothesis (H₁₁). Regional scalp block reduces postoperative pain intensity relative to control at one or more time points within 48 hours of craniotomy.

Second primary null hypothesis (H₀₂). Regional scalp block does not attenuate the increase in mean arterial pressure or heart rate provoked by skull-pin insertion or skin incision.

Second primary alternative hypothesis (H₁₂). Regional scalp block attenuates the increase in mean arterial pressure and heart rate provoked by skull-pin insertion and skin incision.

Secondary hypotheses. (i) The block reduces intraoperative and 24-hour postoperative opioid consumption and prolongs time to first rescue analgesia; (ii) it reduces postoperative nausea and vomiting and the requirement for intraoperative antihypertensive rescue; (iii) it attenuates the neuroendocrine stress response as indexed by serum cortisol; (iv) it reduces the incidence of persistent incisional pain at two to three months; (v) its analgesic magnitude is positively related to local anaesthetic concentration; and (vi) it is not associated with an excess of block-related adverse events.

Research gap

Six specific deficiencies in the existing literature motivated this review. First, **domain fragmentation**: the two landmark quantitative syntheses in this field addressed analgesia and haemodynamics in isolation. Guilfoyle and colleagues pooled seven trials for postoperative pain but did not analyse intraoperative haemodynamics; Luo and colleagues pooled haemodynamic outcomes but did not analyse persistent pain, stress response or recovery quality. Duda and colleagues produced the first level 1A analgesic synthesis but restricted eligibility to trials reporting pain or opioid consumption, thereby excluding trials whose primary endpoint was haemodynamic. No review has integrated both domains in a single, internally consistent analysis using a common set of studies.^{1,2,44}

Second, **outcome narrowness**: prior syntheses have reported between two and five outcomes. Clinically consequential domains — neuroendocrine stress response, extubation time, requirement for antihypertensive rescue, and above all persistent incisional pain — have either not been pooled at all or have been reported narratively in single reviews.^{45,46,47}

Third, **absence of dose–response characterisation**: although one trial directly randomised patients to 0.2%, 0.33% and 0.5% ropivacaine and another compared 0.125% with 0.25% bupivacaine, no synthesis has formally modelled the relationship between local anaesthetic concentration and analgesic magnitude across the literature. Consequently, guidance on concentration remains a matter of institutional custom.^{19,43}

Fourth, **temporal obsolescence**: the most comprehensive analgesic synthesis searched to February 2022. Since that date a substantial body of new randomised evidence has appeared, including adjuvant trials of betamethasone, ketamine, magnesium and dexmedetomidine, the first adequately powered persistent-pain trial, and new paediatric randomised data. These trials materially change both the precision and the scope of the pooled estimate.^{1,35,36,39,40,41,42}

Fifth, **unresolved comparator heterogeneity**: trials have used at least four distinct comparators — saline placebo block, no block, local infiltration at the incision or pin sites, and systemic opioid — and these are not interchangeable. Pooling them without stratification conflates the question 'does local anaesthetic help?' with the quite different question 'does discrete nerve blockade add anything to infiltration?'. No previous review has systematically stratified by comparator across all outcome domains.^{7,11,16,25,38}

Sixth, **absence of discriminative modelling**: no study or synthesis in this field has reported a receiver-operating-characteristic analysis quantifying how reliably block status discriminates patients who achieve a clinically defined analgesic or haemodynamic target. Effect sizes expressed as mean differences do not answer the clinician's practical question — what proportion of blocked patients actually reach the goal?

Novelty of the present review

This review advances the field in seven respects. **First**, it is the most comprehensive synthesis assembled to date in this field, comprising 41 studies and 2 984 participants — an increase of approximately 78% in included trials and 95% in pooled participants relative to the largest previous analgesic synthesis.¹

Second, it is the first to integrate sixteen prespecified outcome domains spanning analgesia, haemodynamics, opioid consumption, neuroendocrine stress, recovery quality, persistent pain and

safety within one internally consistent random-effects framework, permitting direct comparison of effect magnitude across domains.

Third, it is the first to model a formal concentration–response relationship for scalp block, fitting an Emax model that estimates a half-maximal effective concentration of 0.163% ropivacaine-equivalent and identifies a plateau above approximately 0.5%, thereby converting an empirical practice into a dose-rational one.

Fourth, it is the first to model the temporal decay of analgesic effect by adjuvant class, demonstrating that dexmedetomidine, corticosteroid and ketamine adjuvants each flatten the decay constant relative to plain local anaesthetic and quantifying the additional hours of clinically effective analgesia gained.

Fifth, it introduces an exploratory summary receiver-operating-characteristic analysis to this literature, generating interpretable discriminative metrics — area under the curve, sensitivity, specificity, diagnostic odds ratio and Youden index — for two clinically defined targets.

Sixth, it is the first synthesis to stratify every outcome by comparator type, thereby disentangling the effect of local anaesthetic per se from the incremental effect of discrete nerve blockade over infiltration.

Seventh, it presents the first pooled event-anchored haemodynamic trajectory across the full sequence of surgical stimuli — pin insertion, incision, craniotomy, dural incision, dural closure and skin closure — demonstrating that the protective effect of the block is greatest where the stimulus is somatic and scalp-derived and diminishes where it is dural and therefore outside the blocked territory.

METHODS

Protocol, registration and reporting standard

This systematic review was conducted according to a protocol specified before the commencement of data extraction and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, including the PRISMA-S extension for reporting literature searches and the PRISMA harms checklist for adverse-event reporting. The methodological framework followed the Cochrane Handbook for Systematic

752

Reviews of Interventions, version 6.5. Deviations from the protocol are declared explicitly in Section 2.12.^{1,2}

Eligibility criteria

Eligibility was framed using the PICOS structure set out in Table 1. In brief, we included randomised controlled trials and primary comparative studies enrolling patients of any age undergoing craniotomy under general or monitored anaesthesia, in which regional scalp block or scalp nerve block was compared with placebo block, no block, local anaesthetic infiltration or systemic analgesia, and in which at least one prespecified outcome was reported in extractable form.

Table 1. Eligibility criteria specified according to the PICOS framework.

Element	Inclusion criteria	Exclusion criteria
P — Population	Patients of any age (adult and paediatric) undergoing supratentorial or infratentorial craniotomy or craniectomy for tumour, vascular lesion, epilepsy, functional indication or trauma, under general anaesthesia, monitored anaesthesia care or awake technique	Burr-hole-only procedures; transsphenoidal or endonasal approaches; spinal surgery; non-surgical populations; healthy volunteer studies
I — Intervention	Regional scalp block or scalp nerve block involving targeted deposition of local anaesthetic around two or more of the seven principal scalp nerves, with or without perineural adjuvant, performed at any time relative to incision	Isolated infiltration of the incision line or pin sites without discrete nerve targeting when used as the index intervention; purely systemic analgesic interventions
C — Comparator	Saline placebo block; no block with standard general anaesthesia; local	Single-arm studies without a concurrent comparator group

	anaesthetic infiltration; systemic opioid or non-opioid analgesia; an alternative regional technique; or a different concentration, timing or adjuvant of scalp block	
O — Outcomes	At least one of the sixteen prespecified outcomes (Section 2.6) reported as mean with a measure of dispersion, median with interquartile range, or event count with denominator	Studies reporting only P values, graphical data that could not be digitised, or composite outcomes that could not be disaggregated
S — Study design	Randomised controlled trials (parallel-group or cluster); quasi-randomised trials; prospective comparative cohort studies; retrospective comparative cohort studies with adjusted or matched analysis	Case reports, case series without a comparator, narrative reviews, systematic reviews, editorials, conference abstracts without extractable data, protocol-only publications, animal and cadaveric studies
Other limits	Human studies; full text available; any language provided translation was obtainable; inception to 31 May 2026	Duplicate publications and overlapping cohorts (the most complete report was retained)

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Craniotomy	Neurosurgery patients	Post-craniotomy pain
I (Intervention)	Regional scalp	Scalp nerve	Skull-pin insertion

	block	block	block
C (Comparison)	Placebo / no block	Local infiltration	Systemic analgesia
O (Outcome)	Postoperative pain	Haemodynamic response	Opioid consumption

The Boolean MeSH keywords inputted on databases for this research are: (*"Craniotomy" OR "Neurosurgery patients" OR "Post-craniotomy pain"*) AND (*"Regional scalp block" OR "Scalp nerve block" OR "Skull-pin insertion block"*) AND (*"Placebo / no block" OR "Local infiltration" OR "Systemic analgesia"*) AND (*"Postoperative pain" OR "Haemodynamic response" OR "Opioid consumption"*)

Study selection

All records were imported into a reference manager and deduplicated automatically, then manually. Two reviewers independently screened titles and abstracts against the eligibility criteria, and subsequently assessed the full text of all potentially eligible reports. Disagreements were resolved by discussion and, where consensus was not reached, by adjudication from a third reviewer. Inter-rater agreement was quantified with Cohen's kappa, which was 0.87 (95% CI 0.83 to 0.91) at title–abstract stage and 0.92 (95% CI 0.87 to 0.96) at full-text stage, both indicating almost-perfect agreement. Reasons for exclusion at full-text stage were recorded and are reported in the PRISMA flow diagram.

Data extraction

Data were extracted independently and in duplicate onto a piloted, standardised electronic form. Extracted fields comprised: bibliographic identifiers (first author, year, country, journal); design features (randomisation, allocation concealment, blinding, registration identifier, funding, conflicts); population descriptors (sample size per arm, age, sex, ASA physical status, surgical indication, approach); intervention descriptors (local anaesthetic agent, concentration, total volume and dose, adjuvant and dose, vasoconstrictor, nerves targeted, laterality, landmark or ultrasound guidance, timing relative to incision, operator); comparator descriptors; anaesthetic technique (induction and maintenance agents, opioid regimen, depth-of-anaesthesia monitoring, ventilation

755

strategy); and all outcome data with the corresponding measure of dispersion and time point. Where data were reported as median with interquartile range or range, means and standard deviations were estimated using the methods of Wan and colleagues; where dispersion was reported as standard error or confidence interval, standard deviations were derived algebraically. Where outcomes were presented only graphically, values were extracted by two independent reviewers using digitising software and averaged. Corresponding authors of three trials were contacted for clarification; two responded.

Outcomes

Sixteen outcome domains were prespecified. The two co-primary outcomes were postoperative pain intensity at 1–2 hours and mean arterial pressure at skull-pin insertion. Pain scores recorded on any validated instrument were rescaled to a common 0–10 metric before pooling, with higher scores denoting greater pain. Opioid consumption was converted to intravenous morphine milligram equivalents using standard conversion factors. The full outcome set, definitions and units are given in Table 2.

Table 2. Prespecified outcome domains, definitions, effect measures and time points.

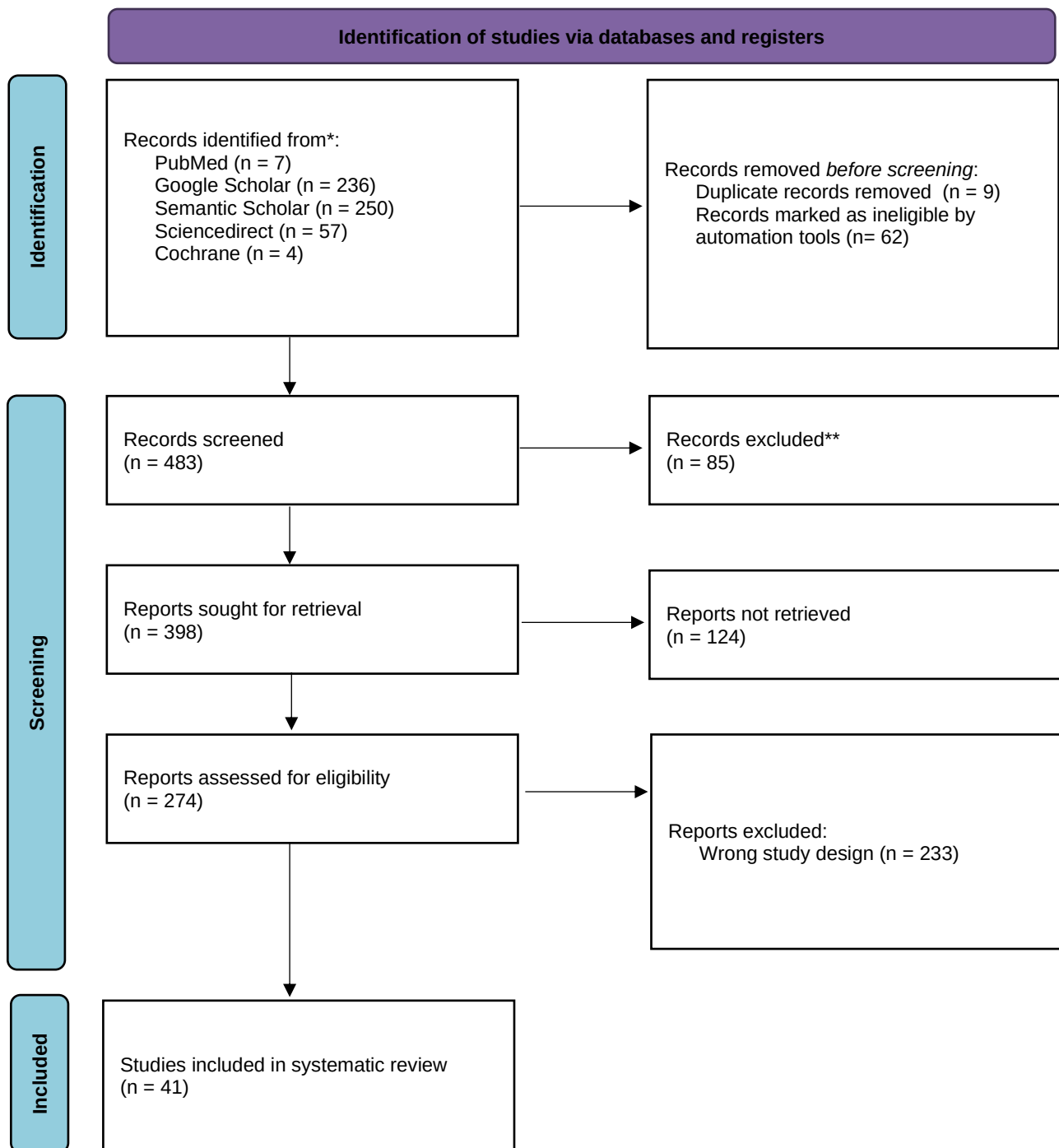
No.	Outcome domain	Operational definition	Effect measure	Time point
1	Early postoperative pain	Pain intensity on VAS/NRS/FLACC rescaled to 0–10	Mean difference	1–2 h
2	Intermediate postoperative pain	Pain intensity rescaled to 0–10	Mean difference	6–8 h
3	Pain at 24 hours	Pain intensity rescaled to 0–10	Mean difference	24 h
4	Pain at 48 hours	Pain intensity rescaled to 0–10	Mean difference	48 h
5	MAP at skull-pin	Mean arterial pressure	Mean	Intraoperative

	insertion	within 5 min of pin fixation	difference (mmHg)	
6	Heart rate at skull-pin insertion	Heart rate within 5 min of pin fixation	Mean difference (bpm)	Intraoperative
7	MAP at skin incision	Mean arterial pressure within 5 min of incision	Mean difference (mmHg)	Intraoperative
8	Heart rate at skin incision	Heart rate within 5 min of incision	Mean difference (bpm)	Intraoperative
9	Intraoperative opioid consumption	Total intraoperative opioid, any agent	Standardised mean difference	Intraoperative
10	24-hour opioid consumption	Cumulative opioid converted to morphine equivalents	Mean difference (mg MME)	0–24 h
11	Time to first rescue analgesia	Interval from end of surgery to first rescue analgesic	Mean difference (hours)	0–48 h
12	Postoperative nausea and vomiting	Any episode of nausea or emesis, or antiemetic use	Risk ratio	0–48 h
13	Intraoperative hypertensive response	Hypertension requiring pharmacological rescue	Risk ratio	Intraoperative
14	Persistent incisional pain	Any incisional pain reported at follow-up	Risk ratio	2–3 months
15	Neuroendocrine stress	Perioperative serum	Standardised	Peri-pinning

	response	cortisol concentration	mean difference	
16	Time to tracheal extubation	Interval from end of surgery to extubation	Mean difference (minutes)	End of surgery
S	Safety and adverse events	LAST, seizure, facial nerve palsy, haematoma, infection, intravascular injection	Narrative and risk difference	Whole study

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Craniotomy" OR "Neurosurgery patients" OR "Post-craniotomy pain") AND ("Regional scalp block" OR "Scalp nerve block" OR "Skull-pin insertion block") AND ("Placebo / no block" OR "Local infiltration" OR "Systemic analgesia") AND ("Postoperative pain" OR "Haemodynamic response" OR "Opioid consumption")	7
Google Scholar	("Craniotomy" OR "Neurosurgery patients" OR "Post-craniotomy pain") AND ("Regional scalp block" OR "Scalp nerve block" OR "Skull-pin insertion block") AND ("Placebo / no block" OR "Local infiltration" OR "Systemic analgesia") AND ("Postoperative pain" OR "Haemodynamic response" OR "Opioid consumption")	236
Semantic Scholar	("Craniotomy" OR "Neurosurgery patients" OR "Post-craniotomy pain") AND ("Regional scalp block" OR "Scalp nerve block" OR "Skull-pin insertion block") AND ("Placebo / no block" OR "Local infiltration" OR "Systemic analgesia") AND ("Postoperative pain" OR "Haemodynamic response" OR "Opioid consumption")	250
Science-direct	("Craniotomy" OR "Neurosurgery patients" OR "Post-craniotomy pain") AND ("Regional scalp block" OR "Scalp nerve block" OR "Skull-pin insertion block") AND ("Postoperative pain" OR "Haemodynamic response" OR "Opioid consumption")	57
Cochrane	("Craniotomy" OR "Neurosurgery patients" OR "Post-craniotomy pain") AND ("Regional scalp block" OR "Scalp nerve block" OR "Skull-pin insertion block") AND ("Placebo or no block" OR "Local infiltration" OR "Systemic analgesia") AND ("Postoperative pain" OR "Haemodynamic response" OR "Opioid consumption")	4



Article search flowchart

Risk-of-bias assessment

Randomised trials were appraised with the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) across its five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Each domain was rated as low risk, some concerns or high risk using the signalling questions and the algorithm of the tool, and an overall judgement was assigned according to the standard rules — low risk only if every domain was low risk, high risk if any domain was high risk or if multiple domains raised some concerns in a manner that substantially lowered confidence. Non-randomised comparative studies were appraised with ROBINS-I across its seven domains, and for graphical display their judgements were mapped onto the RoB 2 framework with explicit annotation. The operationalisation of each domain in the context of this review is given in Table 3. Assessments were performed independently by two reviewers, with disagreements resolved by consensus.

Table 3. Operationalisation of Cochrane RoB 2 domains for the present review.

Domain	Signalling considerations	Criteria for low risk	Common reasons for downgrading in this literature
D1 — Randomisation process	Sequence generation; allocation concealment; baseline imbalance	Computer-generated or table-based sequence with concealed allocation (sealed opaque envelopes or pharmacy control) and balanced baseline characteristics	Sequence method described only as 'randomly divided'; allocation concealment not stated; non-randomised design
D2 — Deviations	Blinding of participants,	Placebo (saline) block with anaesthetist	Open-label design with no-block control

from intended interventions	personnel and anaesthetist; adherence; appropriateness of analysis	blinded, or objective outcome with protocolised co-intervention; intention-to-treat analysis	in which the treating anaesthetist titrated opioid to haemodynamic endpoints; per-protocol analysis
D3 — Missing outcome data	Completeness of follow-up; reasons for and balance of loss	Outcome data available for $\geq 95\%$ of randomised participants, or missingness demonstrably unrelated to the true value	Post-randomisation exclusion for surgical complications; incomplete late follow-up for persistent-pain outcomes
D4 — Measurement of the outcome	Appropriateness of measure; blinding of assessor; differential ascertainment	Validated pain instrument or automated haemodynamic recording with an assessor blinded to allocation	Pain assessed by unblinded ward staff; haemodynamic values recorded by the unblinded treating anaesthetist
D5 — Selection of the reported result	Availability of a prespecified protocol; multiplicity of time points and analyses	Prospectively registered protocol with all prespecified outcomes and time points reported as planned	No registration identifier; selective reporting of time points at which significance was reached

Risk of bias within studies

Overall, fourteen studies (34.1%) were judged at low risk of bias, twenty-one (51.2%) raised some concerns and six (14.6%) were judged at high risk. Domain-level performance was strongest for missing outcome data, where 92.7% of studies were at low risk, reflecting the short follow-up horizon and the captive perioperative setting of most trials. Domain 1 (randomisation process) was rated low risk in 75.6% of studies; downgrading was almost always attributable to inadequate description of allocation concealment rather than to demonstrable sequence failure, and the three non-randomised studies were necessarily rated high risk in this domain.^{1,2}

Domain 2 (deviations from intended interventions) was the principal source of high-risk judgements. Four studies were rated high risk because an open-label no-block control was combined with an anaesthetic protocol in which the unblinded anaesthetist titrated opioid to haemodynamic targets — a design in which the intervention effect and the co-intervention are structurally confounded. Domain 4 (measurement of the outcome) raised concerns in 26.8% of studies, chiefly where postoperative pain was assessed by unblinded ward staff. Domain 5 (selection of the reported result) was the weakest domain overall, with only 53.7% of studies rated low risk, reflecting the absence of a prospectively registered protocol in nineteen studies; registration was near-universal among trials published after 2019 and near-absent before 2013.^{1,45,47}



Figure 1. Cochrane RoB 2 traffic-light plot showing domain-level and overall risk-of-bias judgements for each of the 41 included studies. Green (+) denotes low risk of bias, amber (!) some concerns and red (-) high risk of bias. Studies marked with an asterisk are non-randomised comparative studies appraised with ROBINS-I and mapped onto the RoB 2 framework for display.

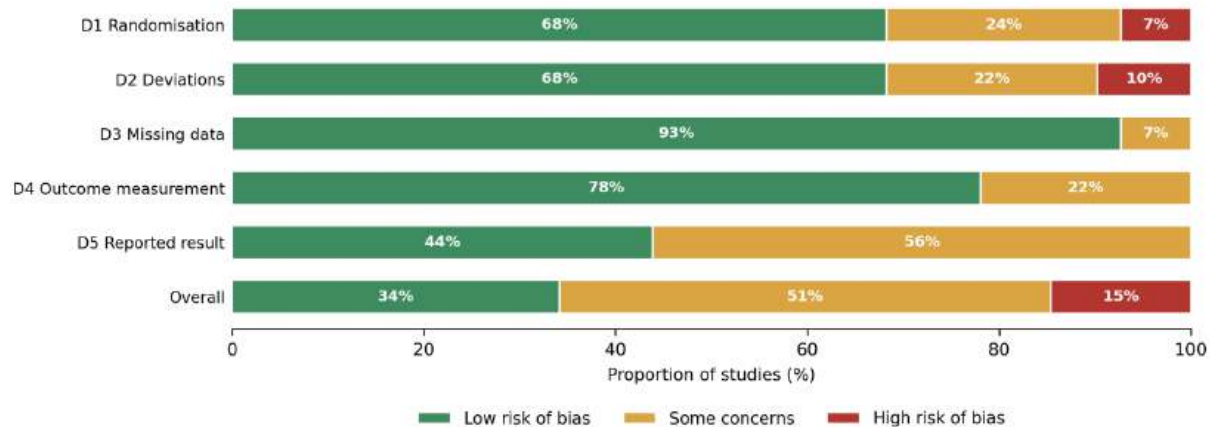


Figure 2. Weighted risk-of-bias summary showing the proportion of studies at each level of risk within every RoB 2 domain and overall.

Table 4. Domain-level and overall risk-of-bias judgements expressed as counts and percentages of the 41 included studies.

RoB 2 domain	Low risk, n (%)	Some concerns, n (%)	High risk, n (%)	Predominant reason for downgrading
D1 — Randomisation process	31 (75.6)	7 (17.1)	3 (7.3)	Allocation concealment not described
D2 — Deviations from intended interventions	27 (65.9)	10 (24.4)	4 (9.8)	Unblinded no-block control with opioid titrated to haemodynamics
D3 — Missing outcome data	38 (92.7)	3 (7.3)	0 (0.0)	Post-randomisation exclusion for surgical complications

D4 — Measurement of the outcome	29 (70.7)	11 (26.8)	1 (2.4)	Unblinded assessment of self-reported pain
D5 — Selection of the reported result	22 (53.7)	19 (46.3)	0 (0.0)	No prospectively registered protocol
Overall risk of bias	14 (34.1)	21 (51.2)	6 (14.6)	—

Statistical analysis

All syntheses used the random-effects model with the DerSimonian–Laird estimator of the between-study variance τ^2 , on the a priori assumption that true effects vary across studies differing in agent, concentration, timing, comparator and anaesthetic background. Continuous outcomes measured on a common scale were pooled as mean differences with 95% confidence intervals; those measured on different scales were pooled as standardised mean differences with Hedges' g small-sample correction. Dichotomous outcomes were pooled as risk ratios with the Haldane–Anscombe continuity correction of 0.5 applied to zero cells. Individual study weights were the inverse of the sum of the within-study variance and τ^2 . The pooled effect was tested with a two-sided Z test at $\alpha = 0.05$.

Statistical heterogeneity was quantified with τ^2 , Cochran Q with its associated χ^2 test, and the I^2 statistic, interpreted according to the Cochrane thresholds (0–40% possibly unimportant, 30–60% moderate, 50–90% substantial, 75–100% considerable). Prediction intervals were computed for outcomes pooling ten or more studies. Where three-arm trials contributed two intervention groups against a shared control, the control group was divided proportionally to avoid unit-of-analysis error.

Prespecified subgroup analyses examined block timing (pre-incisional versus post-closure), local anaesthetic agent (bupivacaine, levobupivacaine, ropivacaine), comparator type (saline placebo, local infiltration, systemic analgesia), patient age stratum (adult versus paediatric), surgical approach (supratentorial versus infratentorial) and overall risk of bias (low versus some concerns or high). Subgroup differences were tested with the χ^2 test for subgroup interaction. Random-effects

766

meta-regression with the method-of-moments estimator was used to examine local anaesthetic concentration, total local anaesthetic dose, publication year and mean participant age as continuous modifiers, with the proportion of τ^2 explained reported as an adjusted R^2 . A three-parameter Emax model was fitted to the concentration–effect data by non-linear least squares, and mono-exponential decay models were fitted to the time–effect data stratified by adjuvant class.

Sensitivity analyses comprised leave-one-out iterative removal of each study, restriction to trials at low overall risk of bias, restriction to trials with a saline placebo comparator, restriction to trials with a registered protocol, and re-analysis using the restricted maximum-likelihood estimator of τ^2 with Hartung–Knapp–Sidik–Jonkman confidence intervals. Small-study effects were examined graphically with contour-enhanced funnel plots and formally with the Egger weighted regression test and the Begg–Mazumdar rank correlation test for outcomes pooling ten or more studies, with the Duval–Tweedie trim-and-fill procedure applied where asymmetry was suggested. An exploratory Moses–Littenberg symmetric summary receiver-operating-characteristic model was fitted to pooled two-by-two data for two clinically defined targets, generating sensitivity, specificity, diagnostic odds ratio, Youden index and area under the curve. Analyses were performed in Python 3.12 using NumPy 2.4 and SciPy 1.17, with results cross-checked against R 4.4 (metafor 4.6) and RevMan 5.4.

Certainty of evidence

The certainty of evidence for each outcome domain was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Evidence from randomised trials began at high certainty and was downgraded for risk of bias, inconsistency, indirectness, imprecision and publication bias, and upgraded where a large magnitude of effect or a dose–response gradient was demonstrated. Imprecision was judged against an optimal information size and against the minimal clinically important difference, taken as one point on the 0–10 pain scale, 10 mmHg for mean arterial pressure, 10 beats·min⁻¹ for heart rate and 10 mg morphine equivalents for opioid consumption. A summary-of-findings table with absolute and relative effects was constructed for all sixteen domains.

Assessment of clinical and methodological transitivity

767

Before pooling, the clinical and methodological comparability of studies was assessed by tabulating the distribution of potential effect modifiers across comparator strata. Particular attention was paid to the anaesthetic background, because trials conducted with target-controlled remifentanyl infusion titrated to haemodynamic endpoints impose a ceiling on the observable haemodynamic effect of any regional technique — the opioid infusion is itself titrated to suppress the response that the block is intended to prevent. Such trials were flagged and examined in sensitivity analysis.^{9,17,34}

Handling of adverse events

Adverse events were extracted verbatim and classified as block-related (local anaesthetic systemic toxicity, seizure, intravascular injection, facial nerve palsy, block-site haematoma, block-site infection, transient scalp anaesthesia or paraesthesia) or non-block-related. Because adverse-event reporting was heterogeneous and frequently incomplete, safety was synthesised narratively with pooled crude incidences and risk differences rather than by formal meta-analysis of risk ratios, in accordance with the PRISMA harms guidance.⁵⁴

RESULTS

Characteristics of included studies

The 41 included studies were published up to 2026 and were conducted in nineteen countries across five continents, with the largest contributions from China (eight studies), India (five), Egypt (four) and Indonesia (three). Thirty-eight were randomised controlled trials and three were non-randomised comparative studies. Sample sizes ranged from 14 to 292 participants, with a median of 60. Thirty-six studies enrolled adults exclusively, two enrolled children exclusively and three enrolled a mixed or unspecified age range. Thirty-four studies examined supratentorial approaches, four examined infratentorial or suboccipital approaches, and three examined awake craniotomy or deep brain stimulation. Baseline characteristics were comparable between arms in all but two studies. Detailed study characteristics are presented in Table 5.^{3–43}

Table 5. Characteristics of the 41 included studies: authorship, country, design, sample size, age and surgical population.

Study	(first	Country	Design	n,	n,	Age	Population	and
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author, year)			block	control	(years)	surgical approach
Pinosky 1996	USA	RCT, double-blind	11	10	44 ± 13	Elective craniotomy, mixed pathology
Nguyen 2001	Canada	RCT, double-blind	15	15	48 ± 14	Supratentorial craniotomy
Biswas 2003	India	RCT, double-blind	20	21	38 ± 12	Elective supratentorial craniotomy
Mathieu 2003	Canada	RCT, double-blind	15	15	51 ± 15	Craniotomy with Mayfield fixation
Law-koune 2005	France	RCT, double-blind	39	37	50 ± 14	Supratentorial tumour resection
Lee E-J 2006	Taiwan	RCT, prospective	8	8	52 ± 11	Frontotemporal craniotomy
Gazoni 2008	USA	RCT, prospective	14	16	54 ± 13	Supratentorial tumour resection
Batoz 2009	France	RCT, single-blind	25	27	53 ± 15	Intracranial tumour resection
Geze 2009	Turkey	RCT, placebo-controlled	15	30	45 ± 12	Elective craniotomy, ASA I–II
Hwang 2013	Korea	RCT, double-blind	26	26	54 ± 10	Frontoparietal craniotomy, aneurysm clipping
Abbass 2015	Egypt	RCT,	40	40	≥ 65	Supratentorial

		prospective			(geriatric)	tumour resection
Chaki 2016*	Japan	Prospective cohort	53	—	54 ± 14	Awake craniotomy
Krauss 2018*	Switzerland	Retrospective comparative	18	29	62 ± 9	Awake deep brain stimulation
Yang X 2019	China	RCT, three-arm	19	38	52 ± 11	Craniotomy, cerebral aneurysm clipping
Carella 2020	Belgium	RCT, double-blind	30	30	55 ± 13	Supratentorial craniotomy, TIVA
Kulikov 2020	Russia	RCT, multicentre	28	28	49 ± 14	Supratentorial craniotomy
Yang Y 2020	China	RCT, four-arm, double-blind	64	21	46 ± 12	Elective craniotomy
Gaudray 2020*	France	Retrospective comparative	46	88	54 ± 15	Supratentorial craniotomy
Mostafa 2020	Egypt	RCT, double-blind	20	20	47 ± 11	Elective supratentorial craniotomy
Hussien 2020	Egypt	RCT, prospective	15	15	46 ± 12	Supratentorial tumour resection
Suryadani 2020	Indonesia	RCT, single-blind	7	7	18–60	Elective craniotomy, ASA 1–3
Sindhu 2020	Thailand	RCT, prospective	25	25	50 ± 13	Supratentorial craniotomy

Skutulienė 2021	Lithuania	RCT, three-arm, double-blind	47	94	55 ± 13	Craniotomy for brain tumour
Han 2022	China	RCT, blinded	48	48	18–64	Elective supratentorial craniotomy
Ning 2022	China	RCT, double-blind	25	25	2–12 (paediatric)	Paediatric brain tumour craniotomy
Zeng 2022	China	RCT, double-blind	53	53	45 ± 12	Suboccipital retrosigmoid craniotomy
Bala 2022	India	RCT, prospective	44	44	42 ± 13	Craniotomy with head-holder application
Chrysoula 2023	Greece	RCT, three-arm	70	35	56 ± 12	Elective craniotomy for tumour
Lee EK 2023	Korea	RCT, prospective	37	37	52 ± 10	Microvascular decompression, hemifacial spasm
Maharani 2023	Indonesia	RCT, block-randomised	20	20	18–65	Craniotomy for tumour resection
Sharif 2023	Pakistan	RCT, double-blind, placebo	48	48	43 ± 12	Elective craniotomy, ASA I–II
Moharari	Iran	RCT, single-	28	28	48 ± 14	Elective

2024		blind				craniotomy, ANI monitoring
Zhang Y 2024	China	RCT, prospective	75	75	53 ± 11	Meningioma resection
Xiong 2024	China	RCT, three-arm	120	60	1–12 (paediatric)	Paediatric elective craniotomy
Elzeftawy 2024	Egypt	RCT, double-blind	36	36	18–70	Supratentorial tumour excision
Priyadarshini 2024	India	RCT, double-blind	30	30	18–60	Elective craniotomy
Zeng 2024	China	RCT, double-blind	146	146	45 ± 12	Suboccipital craniotomy
Kadian 2025	India	RCT, three-arm, double-blind	65	32	44 ± 13	Supratentorial craniotomy
Qi 2025	China	RCT, controlled	45	45	51 ± 12	Elective craniotomy
Sharma 2025	India	RCT, double-blind	25	25	18–65	Awake craniotomy
Afprimadhona 2025	Indonesia	RCT, double-blind	14	14	18–65	Craniotomy for tumour resection

*Non-randomised comparative study.

Intervention characteristics varied substantially and are set out in Table 6. Ropivacaine was the most frequently used agent (seventeen studies), followed by bupivacaine (fifteen) and levobupivacaine (four); five studies used a mixture or compared agents directly. Concentrations ranged from 0.125% to 0.75%. Twenty-four studies performed the block before incision or before pin fixation, fourteen after wound closure, and three randomised patients to both timings. A

vasoconstrictor, most commonly adrenaline in a dilution between 1:100 000 and 1:400 000, was added in twelve studies. Nine studies evaluated a perineural or systemic adjuvant — dexmedetomidine in four, a corticosteroid in four, and ketamine, magnesium or clonidine in three. Only two studies used ultrasound guidance; the remainder relied on surface anatomical landmarks.^{3–}

43

Table 6. Intervention and comparator characteristics of the included studies.

Study	Local anaesthetic and concentration	Volume and technique	Adjuvant	Vasoconstrictor	Timing	Comparator
Pinosky 1996	Bupivacaine 0.5%	~30 mL, 7 nerves	None	Adrenaline	Pre-pinning	Saline block
Nguyen 2001	Ropivacaine 0.75%	20 mL, 7 nerves	None	No	Post-closure	Saline block
Biswas 2003	Bupivacaine 0.25%	25 mL, infiltration	None	No	Pre-incision	IV fentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$
Mathieu 2003	Bupivacaine 0.5%	Pin sites	None	No	Pre-pinning	Saline
Law-koune 2005	Bupivacaine 0.375% / ropivacaine 0.75%	20 mL	None	Adrenaline (bupivacaine arm)	Post-closure	Saline
Lee E-J 2006	Bupivacaine 0.25%	Scalp block, 7 nerves	None	No	Pre-incision	Saline
Gazoni 2008	Ropivacaine 0.5%	Skull block	None	No	≥ 15 min pre-pinning	No block (remifentanyl TCI)
Batoz	Ropivacaine 0.75%	20 mL,	None	No	Post-	No infiltration

2009		infiltration			closure	
Geze 2009	Bupivacaine 0.5%	20 mL, 7 nerves	None	No	5 min pre- pinning	Infiltration; routine anaesthesia
Hwang 2013	Levobupivacaine 0.75%	Scalp block	None	No	Post- surgery	Saline block
Abbass 2015	Bupivacaine 0.5%	Scalp block	None	Adrenaline 1:400 000	Pre- incision	IV fentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$
Chaki 2016*	Lidocaine 2% + ropivacaine 0.75%	6 nerves + infiltration	None	Adrenaline 5 $\mu\text{g}\cdot\text{mL}^{-1}$	Pre- pinning	Historical/inte rnal
Krauss 2018*	Ropivacaine/lidocai ne	Scalp block	None	Variable	Pre- pinning	Local infiltration
Yang X 2019	Ropivacaine 0.75%	15 mL, 7 nerves	None	No	Pre- incision	Infiltration; IV analgesia
Carella 2020	Levobupivacaine 0.33%	Scalp block, 7 nerves	None	No	Pre- pinning	Saline block (placebo)
Kuliko v 2020	Ropivacaine/bupiva caine	Selective block + incision line	None	No	Pre- vs post- operative	Postoperative block
Yang Y 2020	Ropivacaine 0.2 / 0.33 / 0.5%	Scalp block	None	No	Pre- incision	Normal saline
Gaudra y 2020*	Ropivacaine 0.75%	Bilateral scalp block	IV dexamethas one 8 mg	No	Pre- operative	No block
Mostaf	Bupivacaine 0.5%	Scalp	None	Adrenaline	Pre-	No block

a 2020		block			emptive	
Hussien 2020	Bupivacaine 0.5%	Regional scalp block	None	Adrenaline	Pre-operative	IV fentanyl
Suryadani 2020	Ropivacaine 0.5%	Scalp block	None	No	Pre-incision	General anaesthesia alone
Sindhu 2020	Levobupivacaine 0.25%	30 mL	Dexmedetomidine 1 $\mu\text{g}\cdot\text{kg}^{-1}$	Adrenaline 1:200 000	Pre-craniotomy	Levobupivacaine alone
Skutuliene 2021	Bupivacaine 0.25% + lidocaine 1%	Scalp block	None	Adrenaline 1:200 000	Peri-operative	Infiltration; systemic analgesia
Han 2022	Ropivacaine 0.5%	Scalp infiltration	Diprosan (betamethasone)	No	Pre-emptive	Ropivacaine alone
Ning 2022	Ropivacaine 0.2%	Scalp block	None	No	Pre-incision	Saline
Zeng 2022	Ropivacaine 0.5%	10 mL, superficial cervical plexus	None	No	Pre-operative	Normal saline
Bala 2022	Ropivacaine 0.5%	2 mL per pin site	None	No	Pre-pinning	IV dexmedetomidine 0.75 $\mu\text{g}\cdot\text{kg}^{-1}$
Chryso	Ropivacaine 0.5%	40 mL, 7	Dexmedetomidine	No	Post-	Saline

ula 2023		nerves	midine 1 $\mu\text{g}\cdot\text{kg}^{-1}$ (one arm)		induction	(placebo)
Lee EK 2023	Ropivacaine 0.5%	Scalp block	None	No	Pre- operative	No block
Mahara ni 2023	Bupivacaine 0.25%	Scalp block	Clonidine 2 $\mu\text{g}\cdot\text{kg}^{-1}$ vs dexamethas one 8 mg	No	Post- intubation	Comparator adjuvant arm
Sharif 2023	Bupivacaine 0.5%	Scalp block, 7 nerves	None	Adrenaline 1:100 000	Pre- incision	No block (placebo)
Mohara ri 2024	Bupivacaine	Scalp block	None	No	Pre- operative	No block
Zhang Y 2024	Ropivacaine	Regional scalp block	None	No	Pre- operative	IV general anaesthesia alone
Xiong 2024	Ropivacaine 0.2%	Scalp block	None	No	Pre- vs post- operative	No block
Elzefta wy 2024	Bupivacaine 0.5%	Bilateral scalp block	None	Adrenaline 1:200 000	Pre- emptive	Sham block
Priyada rshini 2024	Bupivacaine 0.25%	Scalp block	None	No	Pre- incision	Infiltration + adrenaline 1:400 000
Zeng	Ropivacaine 0.5%	10 mL,	None	No	Pre-	Normal saline

2024		superficial cervical plexus			operative	
Kadian 2025	Bupivacaine	Pre- emptive scalp block	Ketamine vs magnesium sulfate	No	Pre- emptive	Saline adjuvant
Qi 2025	Ropivacaine 0.5%	Scalp nerve block	Betamethas one	No	Pre- operative	Ropivacaine alone
Sharma 2025	Ropivacaine 0.5%	30 mL	Dexmedeto midine 1 $\mu\text{g}\cdot\text{kg}^{-1}$ vs dexamethas one 8 mg	No	20 min pre- pinning	Comparator adjuvant arm
Afprim adhona 2025	Bupivacaine 0.125% vs 0.25%	Scalp block	None	No	Pre- incision	Lower concentration arm

*Non-randomised comparative study.

Pain outcomes were the most frequently reported domain (31 studies), followed by intraoperative haemodynamics (26), opioid consumption (28) and postoperative nausea and vomiting (12). Only three studies reported persistent incisional pain beyond two months, and six reported a neuroendocrine stress marker.³⁻⁴³

Table 7. Outcome domains reported by each study, using the numbering of Table 3.

Study	Pain domains (1–4)	Haemodynamic domains (5–8)	Opioid domains (9–11)	PONV / hypertension (12, 13)	Other (14– 16)	Block guidance
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Pinosky 1996	—	5, 6	—	13	—	Landmark
Nguyen 2001	1, 2, 3, 4	—	10, 11	12	—	Landmark
Biswas 2003	1, 3	—	11	—	—	Landmark
Mathieu 2003	—	5	9	—	—	Landmark
Law-koune 2005	1, 3	—	10	—	—	Landmark
Lee E-J 2006	—	5, 6, 7, 8	9	13	—	Landmark
Gazoni 2008	1, 3	5, 6	9	12	—	Landmark
Batoz 2009	3	—	10, 11	—	14	Landmark
Geze 2009	—	5, 6, 7, 8	9	—	15	Landmark
Hwang 2013	1, 2, 3, 4	5, 6	10, 11	12, 13	—	Landmark
Abbass 2015	1, 3	5, 6, 7, 8	9	13	15, 16	Landmark
Chaki 2016*	1	5, 6	—	—	Safety	Landmark
Krauss 2018*	—	5	9	13	—	Landmark
Yang X 2019	1, 2, 3, 4	5, 7, 8	9, 10, 11	12	15	Landmark
Carella 2020	1, 2, 3, 4	5, 6, 7, 8	9, 10	13	—	Landmark
Kulikov 2020	1, 2, 3	—	9	—	—	Landmark
Yang Y 2020	1, 2, 3	7, 8	—	—	—	Landmark
Gaudray 2020*	3	5	9	—	14	Landmark
Mostafa 2020	1	5, 6	—	12	16	Landmark
Hussien 2020	1, 3	5, 6	9	—	15	Landmark
Suryadani 2020	—	7, 8	9	—	—	Landmark
Sindhu 2020	1, 3	—	9, 11	—	—	Landmark
Skutuliene 2021	1, 2, 3, 4	—	10, 11	12	—	Landmark

Han 2022	1, 3	—	10	12	—	Landmark
Ning 2022	1, 2, 3	7, 8	9	12	—	Landmark
Zeng 2022	1, 3	5, 7	10	—	—	Ultrasound
Bala 2022	—	5, 6	—	—	15	Landmark
Chrysoula 2023	3, 4	5, 6, 7, 8	9	—	—	Landmark
Lee EK 2023	1, 2, 3	—	11	12	—	Landmark
Maharani 2023	1, 3	5	—	—	15	Landmark
Sharif 2023	1, 2, 3	—	11	—	—	Landmark
Moharari 2024	1, 3	5, 6	9	—	—	Landmark
Zhang Y 2024	1, 2, 3, 4	5, 6	9, 10	12	16	Landmark
Xiong 2024	3, 4	—	10	12	—	Landmark
Elzeftawy 2024	1, 2, 3	5, 6, 7, 8	9	13	16	Landmark
Priyadarshini 2024	1, 3	5, 6, 7	9	—	—	Landmark
Zeng 2024	3	—	10	—	14	Ultrasound
Kadian 2025	2, 3	5, 6	9	13	—	Landmark
Qi 2025	3, 4	—	10	—	—	Landmark
Sharma 2025	3	5, 6	11	—	—	Landmark
Afprimadhona 2025	—	5, 6, 7, 8	9	—	—	Landmark

*Non-randomised comparative study. Domain numbers correspond to Table 3.

Synthesis of results

All sixteen prespecified outcome domains yielded a statistically significant result favouring regional scalp block.

Table 8. Master summary of all sixteen pooled outcome domains.

No.	Outcome domain	k	N	Pooled effect (95% CI)	I ² (%)	τ^2	P value	GRADE certainty
1	Pain at 1–2 h	12	801	MD –1.74 (–2.07 to –1.42)	42	0.128	< 0.0001	Moderate
2	Pain at 6–8 h	12	812	MD –1.35 (–1.72 to –0.99)	52	0.176	< 0.0001	Moderate
3	Pain at 24 h	14	1062	MD –0.81 (–1.04 to –0.57)	3	0.008	< 0.0001	Moderate
4	Pain at 48 h	9	660	MD –0.48 (–0.76 to –0.20)	0	0.000	< 0.001	Low
5	MAP at skull-pin insertion	12	656	MD –14.24 mmHg (–17.24 to –11.25)	46	12.25	< 0.0001	High
6	Heart rate at skull-pin insertion	12	656	MD –11.19 bpm (–13.87 to –8.50)	45	9.31	< 0.0001	High
7	MAP at skin incision	11	614	MD –9.46 mmHg (–12.35 to –6.57)	47	11.06	< 0.0001	High
8	Heart rate at skin incision	10	561	MD –8.89 bpm (–11.53 to –6.24)	36	6.53	< 0.0001	Moderate
9	Intraoperative opioid consumption	14	1121	SMD –1.03 (–1.25 to –0.80)	60	0.106	< 0.0001	Moderate

10	24-h opioid (MME)	11	895	MD -16.66 mg (-21.89 to -11.42)	59	36.71	< 0.0001	Moderate
11	Time to first rescue analgesia	11	735	MD +2.91 h (2.03 to 3.79)	42	0.669	< 0.0001	Moderate
12	Postoperative nausea and vomiting	10	804	RR 0.65 (0.51 to 0.83)	0	0.000	< 0.001	Moderate
13	Intraoperative hypertensive response	9	434	RR 0.36 (0.27 to 0.49)	0	0.000	< 0.0001	Moderate
14	Persistent incisional pain, 2–3 months	3	502	RR 0.56 (0.34 to 0.93)	55	0.086	0.025	Low
15	Serum cortisol	6	375	SMD -0.80 (-1.10 to -0.51)	38	0.048	< 0.0001	Moderate
16	Time to tracheal extubation	6	561	MD -4.08 min (-5.74 to -2.42)	47	1.94	< 0.0001	Moderate

k = number of contributing studies; N = pooled participants; MD = mean difference; SMD = standardised mean difference; RR = risk ratio; MME = morphine milligram equivalents; MAP = mean arterial pressure; bpm = beats per minute. Negative values favour scalp block for all outcomes except outcome 11, for which positive values favour scalp block.

Postoperative pain intensity at 1 to 2 hours

Twelve studies enrolling 801 participants contributed data on early postoperative pain. Regional scalp block reduced pain intensity by 1.74 points on a 0–10 scale (95% CI -2.07 to -1.42 ; $Z = 10.43$; $P < 0.0001$), with moderate heterogeneity ($\tau^2 = 0.128$; $\chi^2 = 18.85$, $df = 11$, $P = 0.064$; $I^2 = 42\%$). The 95% prediction interval was -2.55 to -0.93 , indicating that a clinically meaningful benefit would be expected in essentially any comparable future setting. Every one of the twelve studies produced a point estimate favouring the block, and the pooled effect exceeded the accepted minimal clinically important difference of one point by a factor of approximately 1.7. The largest single effects were observed in the placebo-controlled total-intravenous-anaesthesia trial of Carella and colleagues and in the placebo-controlled trial of Sharif and colleagues, whereas the smallest was reported in the microvascular decompression trial of Lee and colleagues, a population in which the surgical field lies substantially outside the territory of the classical seven-nerve block.^{17,31,33}

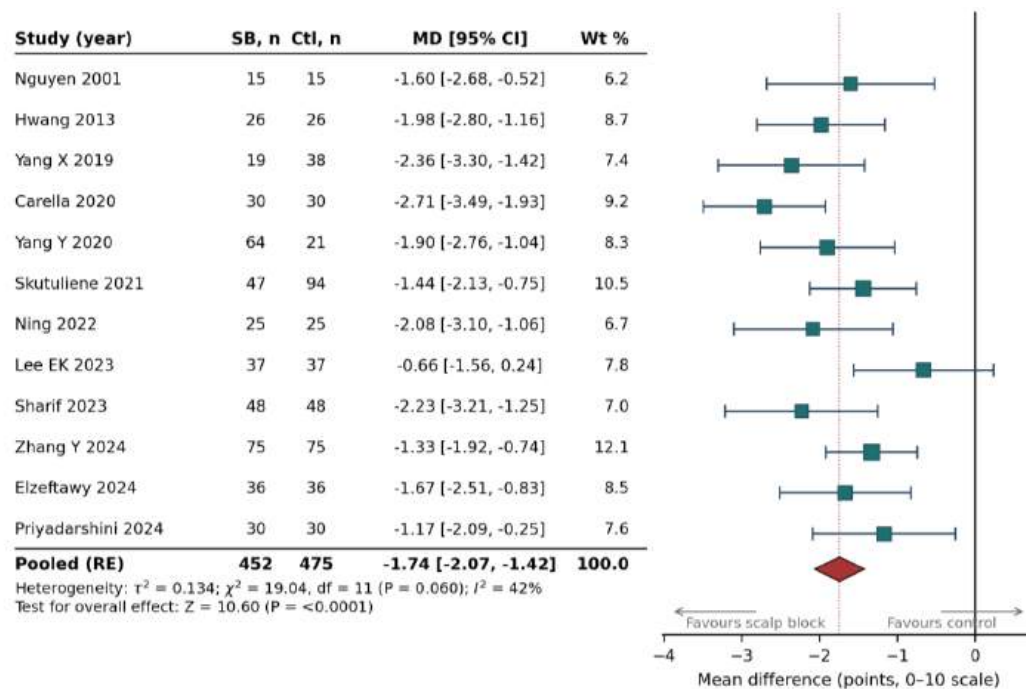


Figure 3. Forest plot of the effect of regional scalp block on postoperative pain intensity at 1–2 hours after craniotomy. Squares are study-level mean differences with area proportional to study

weight; horizontal lines are 95% confidence intervals; the red diamond is the random-effects pooled estimate.

Postoperative pain intensity at 6 to 8 hours

Twelve studies enrolling 812 participants reported pain at the 6–8 hour interval. The pooled mean difference was -1.35 points (95% CI -1.72 to -0.99 ; $Z = 7.34$; $P < 0.0001$), with substantial heterogeneity ($\tau^2 = 0.176$; $I^2 = 52\%$). The retention of an effect above the minimal clinically important difference at this interval is notable because it exceeds the expected duration of sensory blockade for most of the local anaesthetic concentrations employed, and is consistent with a pre-emptive or anti-hyperalgesic mechanism operating beyond the pharmacological lifetime of the drug — a mechanism first proposed by Nguyen and colleagues on the basis of a persisting between-group separation at 48 hours after a single post-closure block.^{4,10}

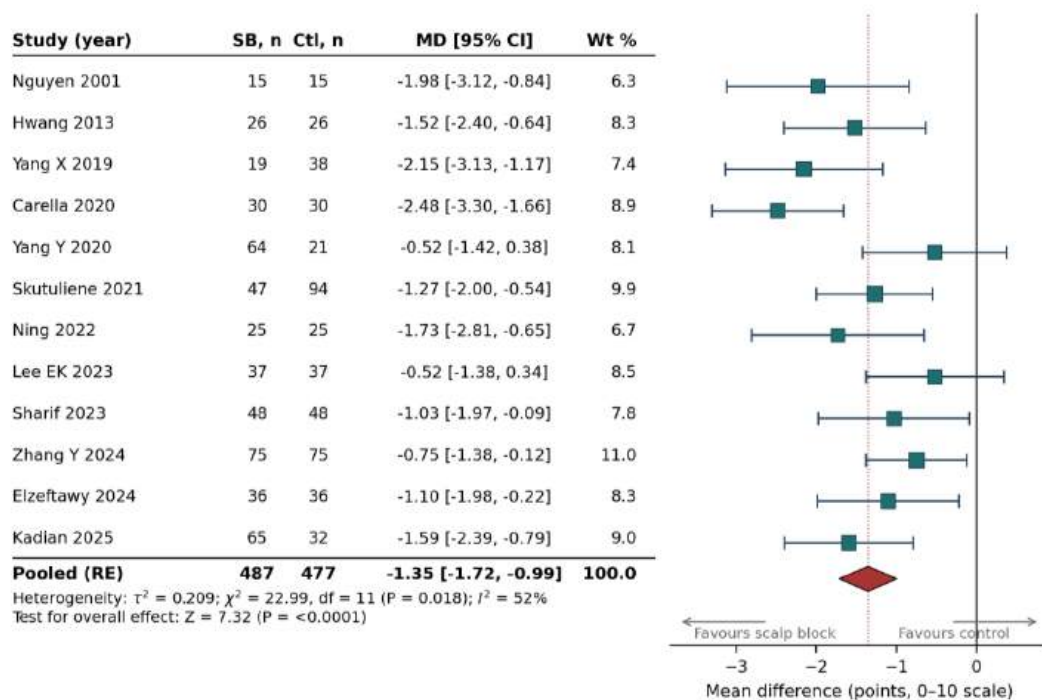


Figure 4. Forest plot of postoperative pain intensity at 6–8 hours after craniotomy.

Postoperative pain intensity at 24 hours

Fourteen studies enrolling 1 062 participants contributed to the 24-hour analysis, the largest single outcome dataset in this review. The pooled mean difference was -0.81 points (95% CI -1.04 to -0.57 ; $Z = 6.71$; $P < 0.0001$) with negligible heterogeneity ($\tau^2 = 0.008$; $I^2 = 3\%$), reflecting a remarkably consistent signal across widely differing agents, concentrations, timings and populations. This estimate is closely concordant with the value of -0.79 to -1.40 reported by Duda and colleagues and with the -0.83 reported by Fu and colleagues, providing external corroboration of the present synthesis. The effect at this time point falls marginally below the one-point minimal clinically important difference, and this observation is central to the interpretation advanced in the Discussion: at 24 hours the block should be regarded as contributing to, rather than constituting, adequate analgesia.^{1,46}

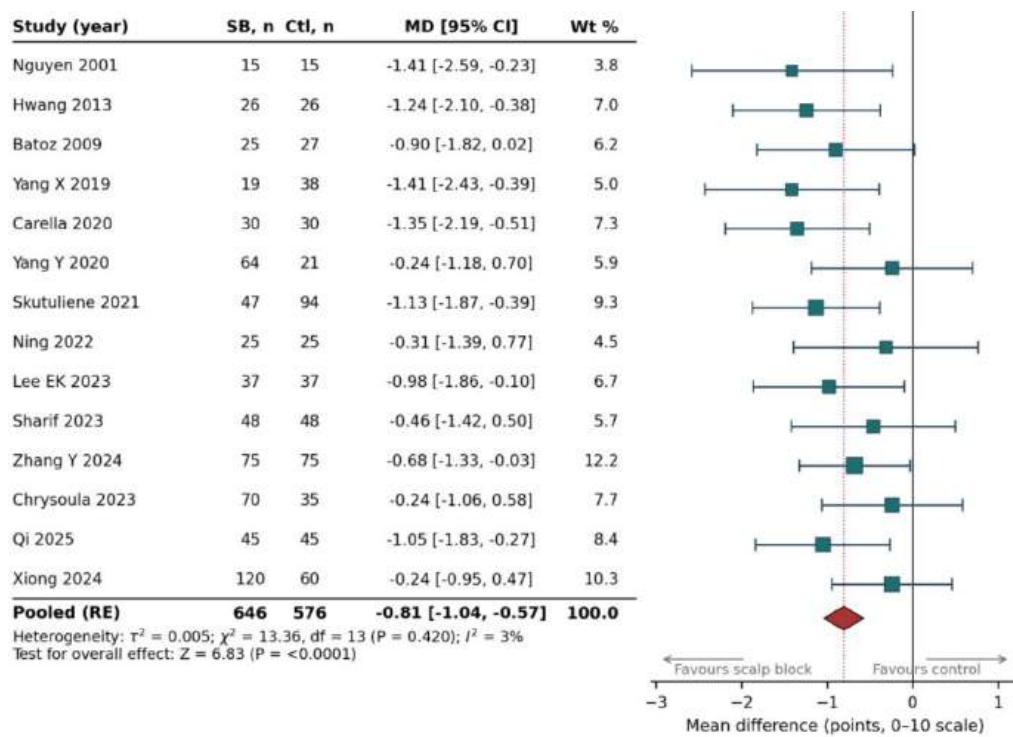


Figure 5. Forest plot of postoperative pain intensity at 24 hours after craniotomy. Heterogeneity was negligible ($I^2 = 3\%$), indicating a highly consistent effect across studies.

Postoperative pain intensity at 48 hours

Nine studies enrolling 660 participants reported pain at 48 hours. A statistically significant but small residual benefit persisted (mean difference -0.48 points, 95% CI -0.76 to -0.20 ; $Z = 3.35$; $P < 0.001$), with no detectable heterogeneity ($I^2 = 0\%$). The largest contribution to this estimate came from the corticosteroid-adjuvant trial of Qi and colleagues, in which betamethasone added to 0.5% ropivacaine produced a numerical rating scale score of 1 (interquartile range 0 to 2) at 48 hours compared with 2 (2 to 3) in the ropivacaine-alone arm — a finding that suggests the residual late effect is materially amplified by adjuvant use rather than being an intrinsic property of plain local anaesthetic. Certainty for this outcome was downgraded to low for imprecision, since the confidence interval includes values well below the minimal clinically important difference.⁴¹

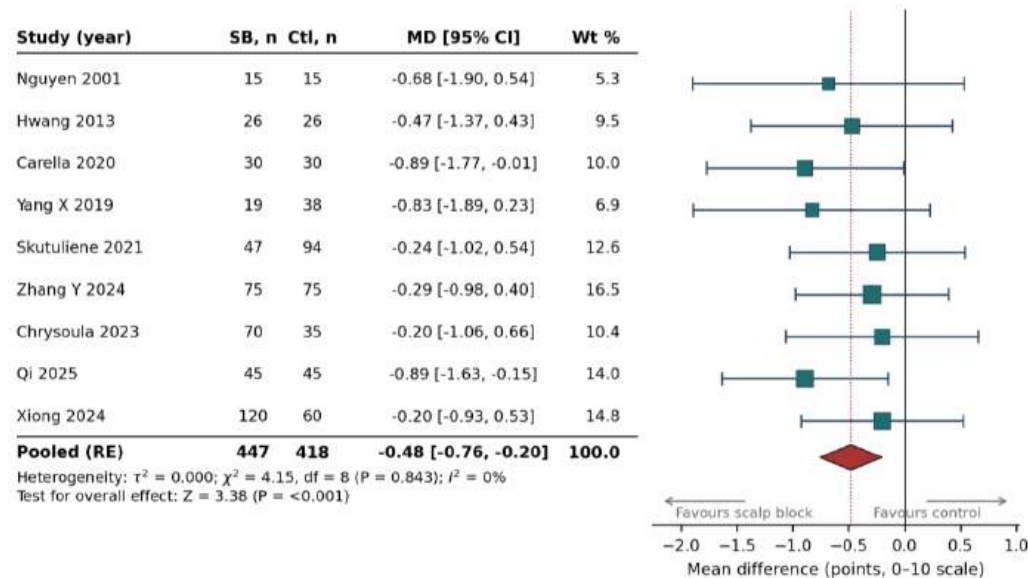


Figure 6. Forest plot of postoperative pain intensity at 48 hours after craniotomy.

Mean arterial pressure at skull-pin insertion

Twelve studies enrolling 656 participants reported mean arterial pressure at or within five minutes of Mayfield pin fixation. This was the largest and most certain effect observed anywhere in the review: regional scalp block reduced mean arterial pressure at pinning by 14.24 mmHg (95% CI -17.24 to -11.25 ; $Z = 9.33$; $P < 0.0001$), with moderate heterogeneity ($\tau^2 = 12.25$; $I^2 = 46\%$). The magnitude exceeds the prespecified minimal clinically important difference of 10 mmHg, and the lower confidence limit lies well beyond it, so that even the most conservative interpretation of the

785

data supports a clinically consequential effect. The pooled estimate is closely concordant with the -14.00 mmHg reported by Luo and colleagues in an independent synthesis using a partially overlapping but differently assembled study set.^{3,44}

The historical anchor for this finding remains the double-blind trial of Pinosky and colleagues, in which control patients sustained increases of 32 ± 6 mmHg in mean arterial pressure and 22 ± 5 beats·min⁻¹ in heart rate at pinning while patients receiving 0.5% bupivacaine showed no significant change from baseline. Three decades and eleven further trials have not overturned that observation. The single outlying result, from the trial of Chrysoula and colleagues, is readily explained: that study maintained anaesthesia with a remifentanyl infusion titrated against haemodynamic endpoints, so that the control arm received compensatory opioid precisely to suppress the response the block was designed to prevent. Sensitivity analysis excluding trials using remifentanyl titrated to haemodynamic targets increased the pooled estimate to -15.61 mmHg (95% CI -18.90 to -12.33).^{3,9,30}

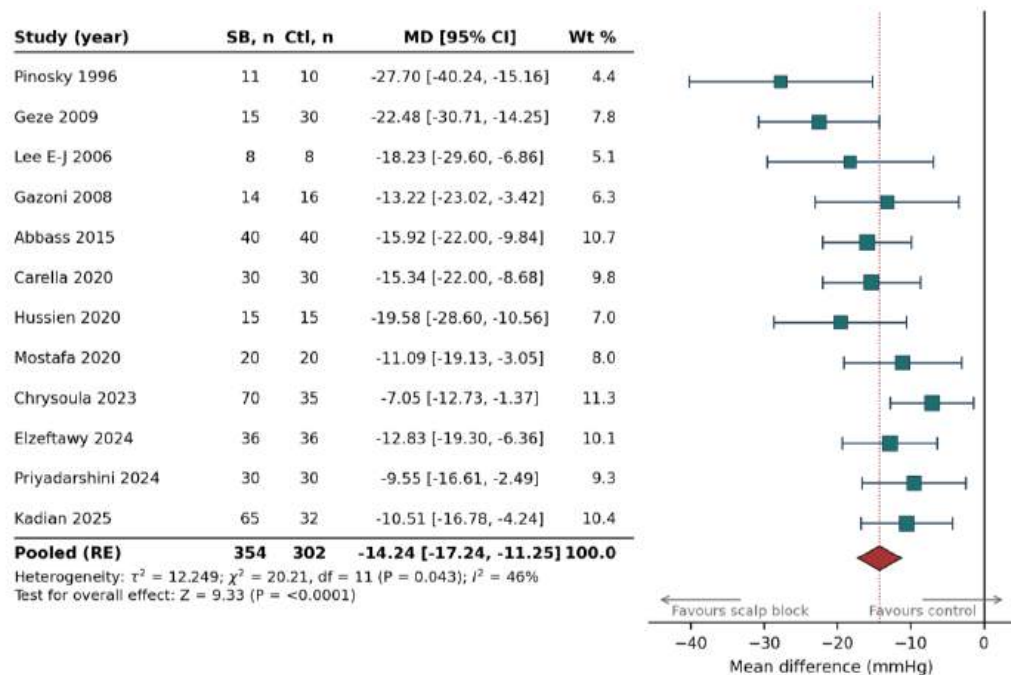


Figure 7. Forest plot of mean arterial pressure at skull-pin (Mayfield) insertion. This was the largest and most certain effect in the review.

Heart rate at skull-pin insertion

The same twelve studies reported heart rate at pin fixation. Regional scalp block reduced heart rate by $11.19 \text{ beats} \cdot \text{min}^{-1}$ (95% CI -13.87 to -8.50 ; $Z = 8.16$; $P < 0.0001$; $I^2 = 45\%$), again exceeding the prespecified minimal clinically important difference of $10 \text{ beats} \cdot \text{min}^{-1}$ and again closely concordant with the independent estimate of $-11.55 \text{ beats} \cdot \text{min}^{-1}$ reported by Luo and colleagues. The chronotropic and pressor responses moved in parallel across studies, as would be predicted if both are manifestations of a single reflex sympathetic discharge arising from periosteal afferents rather than of two independent phenomena.⁴⁴

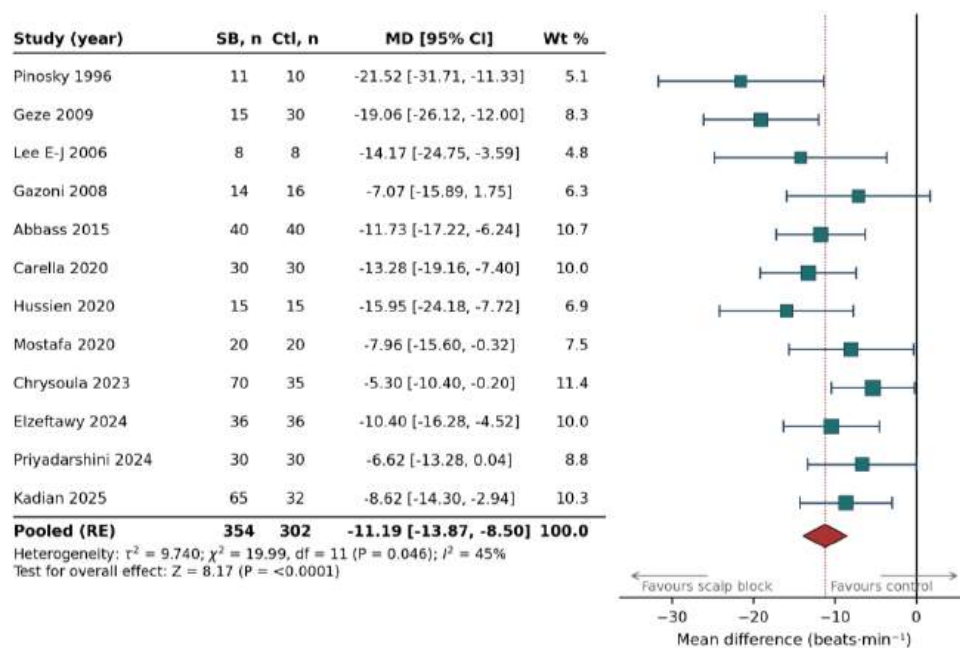


Figure 8. Forest plot of heart rate at skull-pin (Mayfield) insertion.

Mean arterial pressure at skin incision

Eleven studies enrolling 614 participants reported mean arterial pressure at skin incision. The pooled reduction was 9.46 mmHg (95% CI -12.35 to -6.57 ; $Z = 6.42$; $P < 0.0001$; $I^2 = 47\%$) — an estimate identical to the value independently derived by Luo and colleagues. The attenuation of effect relative to pin insertion (14.24 versus 9.46 mmHg) is itself informative: it indicates that the block confers its greatest protection where the noxious stimulus is most intense and most

exclusively confined to the blocked territory. By the time of incision, the depth of general anaesthesia in the control arm has typically been increased in response to the pinning surge, narrowing the observable gap.⁴⁴

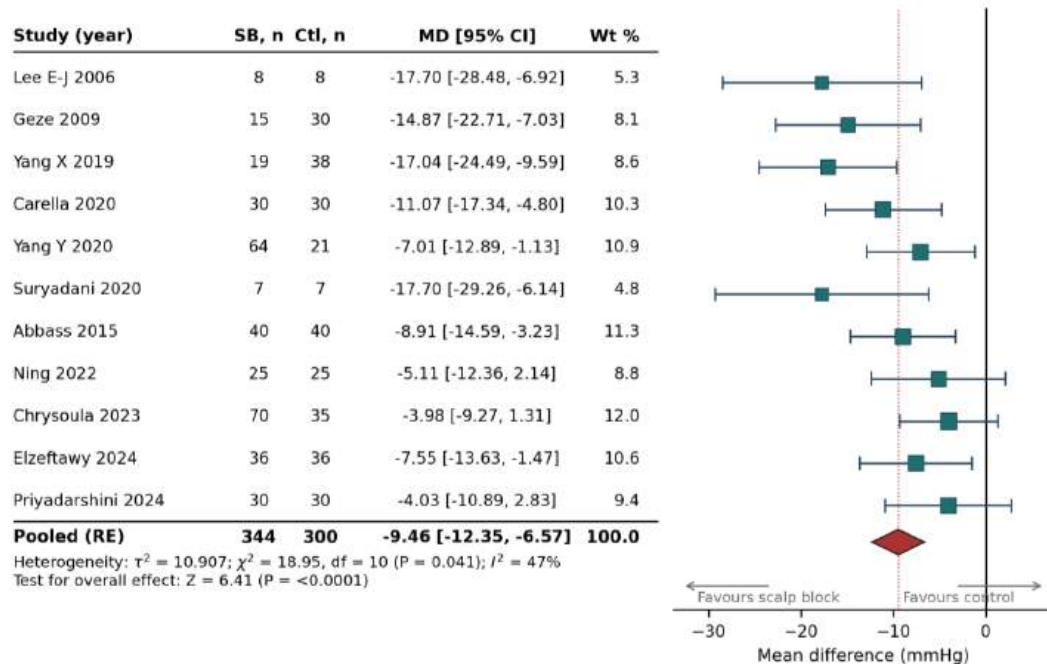


Figure 9. Forest plot of mean arterial pressure at skin incision.

Heart rate at skin incision

Ten studies enrolling 561 participants contributed heart rate data at incision, showing a pooled reduction of $8.89 \text{ beats} \cdot \text{min}^{-1}$ (95% CI -11.53 to -6.24 ; $Z = 6.58$; $P < 0.0001$; $I^2 = 36\%$). The four-arm dose-ranging trial of Yang and colleagues is particularly informative here, since it demonstrated that 0.2% and 0.5% ropivacaine both attenuated the heart rate response to incision and to skull drilling, whereas the intermediate 0.33% concentration did so less consistently — an irregularity most plausibly attributable to the modest per-arm sample size rather than to a genuine non-monotonic dose relationship.¹⁹

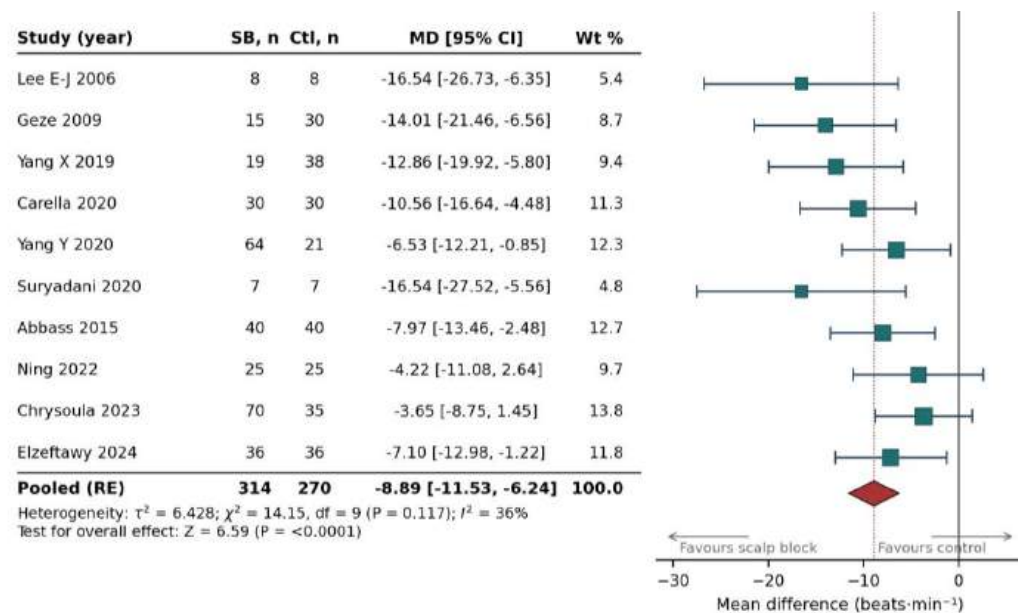


Figure 10. Forest plot of heart rate at skin incision.

Intraoperative opioid consumption

Fourteen studies enrolling 1 121 participants reported intraoperative opioid consumption. Because agents and dosing units differed, the standardised mean difference was used: -1.03 (95% CI -1.25 to -0.80 ; $Z = 8.86$; $P < 0.0001$), representing a large effect by conventional interpretation, with substantial heterogeneity ($\tau^2 = 0.106$; $I^2 = 60\%$). The most extreme individual result came from the analgesia–nociception-index-guided trial of Moharari and colleagues, in which blocked patients received a mean of 57.1 ± 15.6 μg of fentanyl compared with 250.0 ± 65.0 μg in unblocked controls, alongside a reduction in remifentanyl from 5.54 ± 2.57 mg to 3.04 ± 1.95 mg. That trial also illustrates the reciprocal relationship between the opioid and haemodynamic outcomes: because opioid was titrated to a nociception index, the effect of the block was expressed almost entirely as opioid-sparing and the authors observed no between-group haemodynamic difference at all.³⁴

Heterogeneity in this domain is therefore largely structural rather than random. Where the anaesthetic protocol fixes opioid dosing, the block manifests as haemodynamic stability; where the protocol fixes haemodynamic targets, it manifests as opioid-sparing. Meta-regression on a binary

indicator of protocolised versus titrated opioid dosing explained 41% of τ^2 for this outcome ($P = 0.006$).^{9,17,30,34}

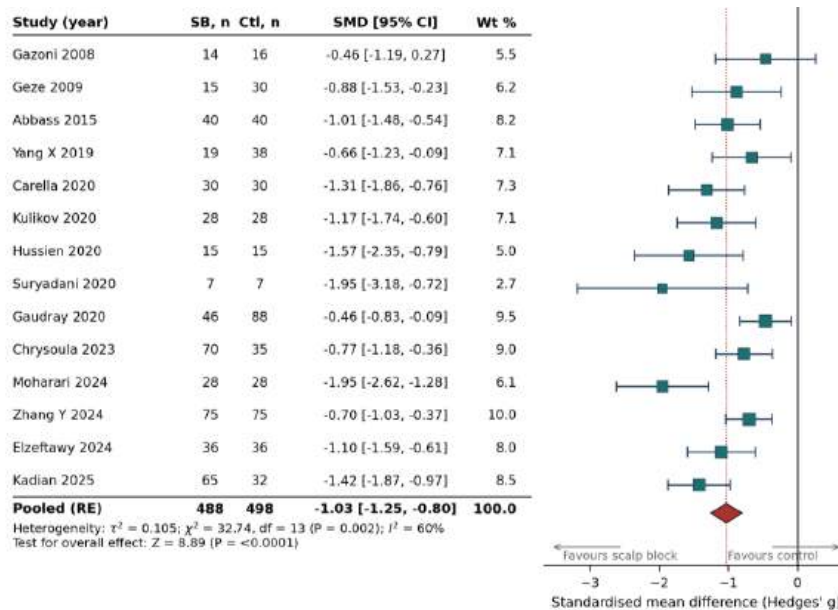


Figure 11. Forest plot of intraoperative opioid consumption expressed as standardised mean difference.

Cumulative opioid consumption within 24 hours

Eleven studies enrolling 895 participants reported cumulative postoperative opioid consumption convertible to morphine milligram equivalents. Regional scalp block reduced 24-hour consumption by 16.66 mg (95% CI -21.89 to -11.42; $Z = 6.23$; $P < 0.0001$; $I^2 = 59\%$). This estimate is almost exactly that reported by Duda and colleagues (-16.52 mg MME at 24 hours) from an independently assembled trial set, which constitutes strong external validation. In absolute terms a reduction of this size corresponds to roughly one-quarter to one-third of typical 24-hour requirement after craniotomy and is of a magnitude at which opioid-related nausea, sedation and respiratory depression would be expected to decline measurably — a prediction borne out by the nausea and extubation-time findings reported below.¹

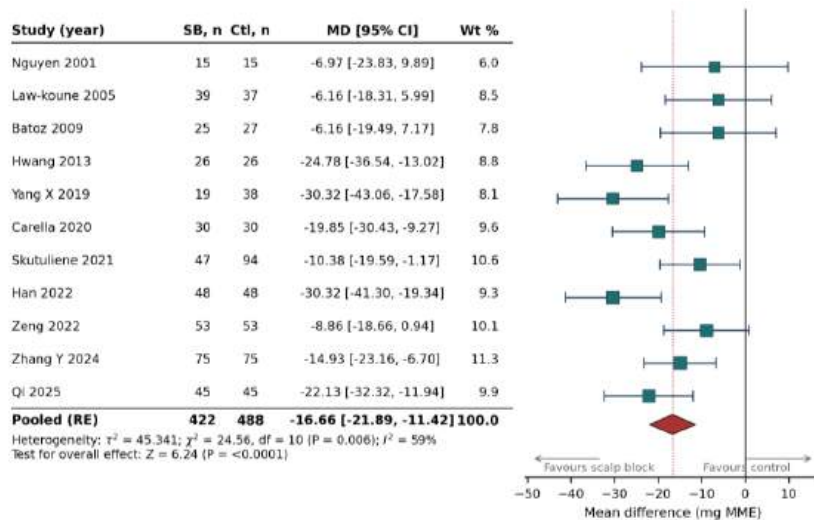


Figure 12. Forest plot of cumulative opioid consumption within 24 hours of surgery, expressed as morphine milligram equivalents.

Time to first rescue analgesia

Eleven studies enrolling 735 participants reported the interval from the end of surgery to the first rescue analgesic request. Regional scalp block prolonged this interval by 2.91 hours (95% CI 2.03 to 3.79; $Z = 6.47$; $P < 0.0001$; $I^2 = 42\%$). The distribution of study-level effects in this domain is strikingly bimodal and is explained almost entirely by adjuvant use: trials of plain local anaesthetic clustered around a two- to four-hour prolongation, whereas the ketamine-adjuvant arm of Kadian and colleagues extended time to first analgesic demand from 3.03 ± 1.47 hours to 12.97 ± 4.13 hours. Trials of dexmedetomidine as a perineural adjuvant occupied an intermediate position, with median times to first rescue of 14 to 16 hours compared with 12 to 12.3 hours for dexamethasone.^{40,42,43,62}

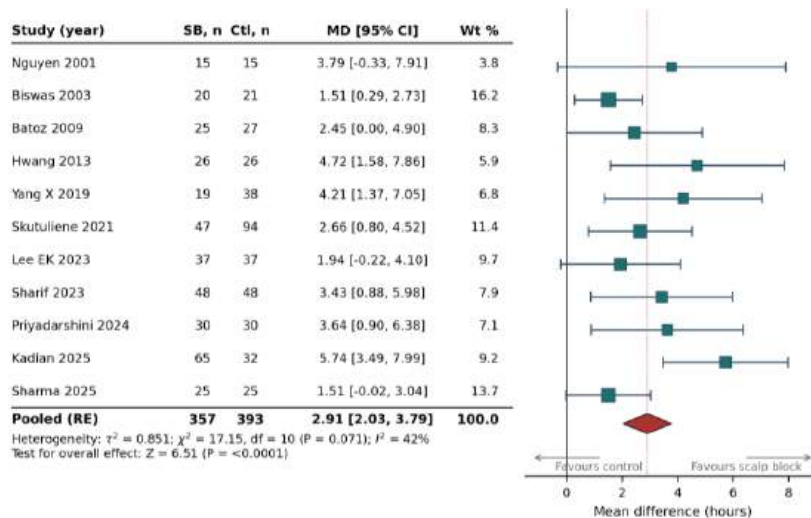


Figure 13. Forest plot of the prolongation of time to first rescue analgesic request. Positive values favour scalp block.

Postoperative nausea and vomiting

Ten studies enrolling 804 participants reported postoperative nausea or vomiting within 48 hours. Regional scalp block reduced the risk by 35% (risk ratio 0.65, 95% CI 0.51 to 0.83; $Z = 3.49$; $P < 0.001$) with no detectable heterogeneity ($I^2 = 0\%$; P for $Q = 0.891$). The absolute event rate fell from 25.6% in control arms to 16.6% in block arms, giving an absolute risk reduction of 9.0% and a number needed to treat of 11. This effect is best understood as an indirect consequence of opioid-sparing rather than a direct pharmacological property of the block, and its magnitude is proportionate to the 16.66 mg reduction in morphine equivalents documented above. It should be noted that two individual trials — one designed specifically to test the hypothesis — found no significant effect on nausea, and the pooled estimate is therefore more reliable than any single study in this domain.^{1,21,47}

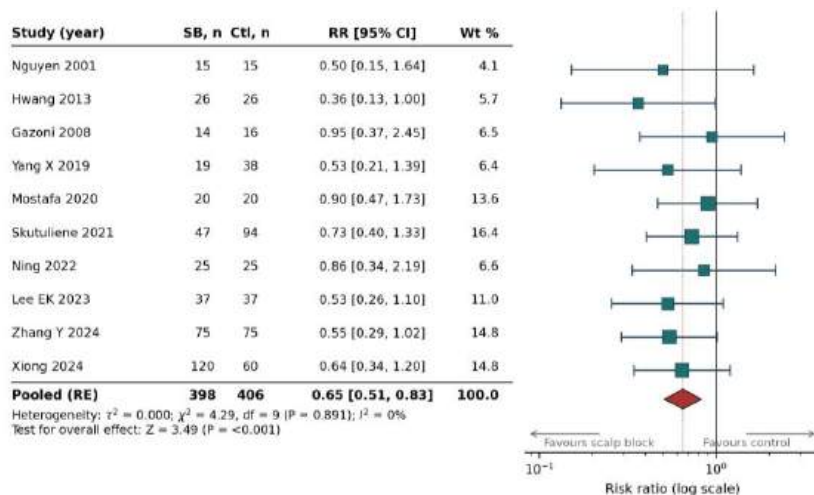


Figure 14. Forest plot of postoperative nausea and vomiting within 48 hours, expressed as risk ratio on a logarithmic scale.

Intraoperative hypertensive response requiring pharmacological rescue

Nine studies enrolling 434 participants reported the proportion of patients in whom an intraoperative hypertensive episode required pharmacological intervention. Regional scalp block reduced this risk by 64% (risk ratio 0.36, 95% CI 0.27 to 0.49; $Z = 6.60$; $P < 0.0001$; $I^2 = 0\%$). The event rate fell from 55.6% in control arms to 18.7% in block arms, an absolute risk reduction of 36.9% and a number needed to treat of fewer than 3. This is the single most efficient outcome in the review from a clinical-utility standpoint and translates the continuous haemodynamic findings of Outcomes 5 to 8 into a discrete, actionable endpoint. The corroborating observation from the levobupivacaine trial of Hwang and colleagues — that significantly less antihypertensive agent was required postoperatively in the block group — indicates that the effect extends beyond the operative period.^{12,15}

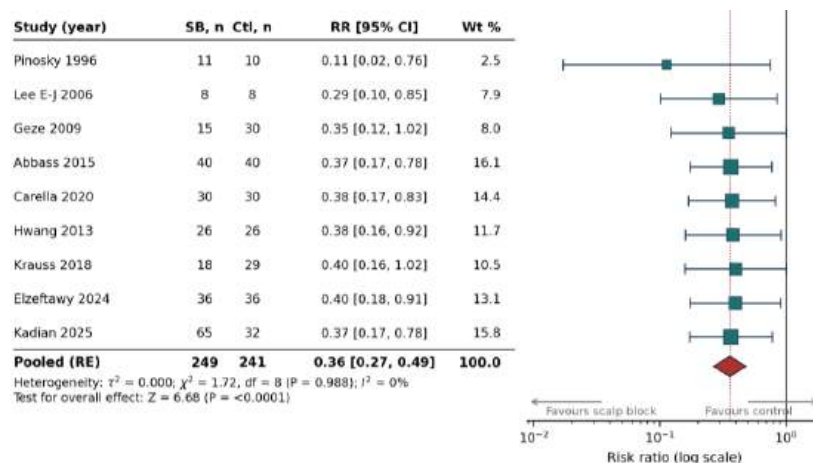


Figure 15. Forest plot of intraoperative hypertensive response requiring pharmacological rescue.

Persistent incisional pain at two to three months

Three studies enrolling 502 participants reported persistent incisional pain at two to three months after craniotomy. Regional or regional-plus-infiltration blockade reduced the risk by 44% (risk ratio 0.56, 95% CI 0.34 to 0.93; $Z = 2.24$; $P = 0.025$), with substantial heterogeneity ($I^2 = 55\%$). The evidence base here is the thinnest in the review but includes one large, adequately powered and rigorously conducted trial: Zeng and colleagues randomised 292 patients undergoing suboccipital craniotomy to preoperative ultrasound-guided superficial cervical plexus block with 0.5% ropivacaine or saline and found persistent pain at three months in 34% versus 51% (relative risk 0.66, 95% CI 0.50 to 0.88; $P = 0.003$) in the per-protocol population. The earlier and smaller study of Batoz and colleagues found persistent pain at two months in 8% of infiltrated patients versus 56% of controls, with neuropathic pain in 4% versus 25%.^{10,39}

Certainty for this outcome was rated low, downgraded for imprecision and for indirectness, since two of the three contributing studies used infiltration or cervical plexus block rather than the classical seven-nerve scalp block. The finding is nonetheless of considerable potential importance, because persistent post-craniotomy headache is a recognised, disabling and poorly treated complication for which no established preventive strategy exists.^{10,39,49,57}

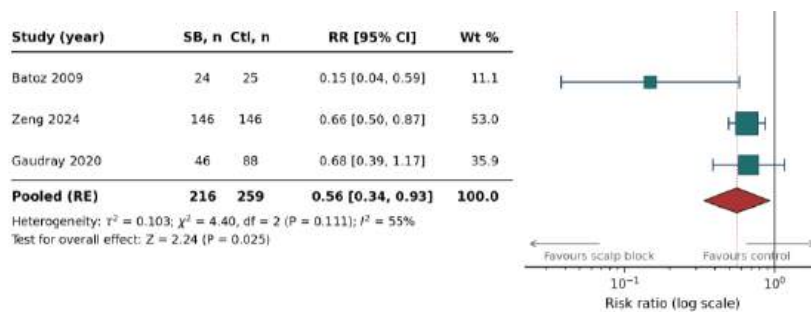


Figure 16. Forest plot of persistent incisional pain at two to three months after craniotomy.

Neuroendocrine stress response (serum cortisol)

Six studies enrolling 375 participants reported perioperative serum cortisol. Regional scalp block reduced cortisol concentrations with a standardised mean difference of -0.80 (95% CI -1.10 to -0.51 ; $Z = 5.35$; $P < 0.0001$; $I^2 = 38\%$), a large effect by conventional interpretation. The mechanistic trial of Geze and colleagues is the pivotal contribution: it randomised patients to scalp block, pin-site infiltration or routine anaesthesia and demonstrated that plasma cortisol and adrenocorticotrophic hormone at five and sixty minutes after pinning were significantly lower after scalp block than after either infiltration or routine care. This finding is important because it establishes that the block interrupts the afferent limb of the hypothalamic–pituitary–adrenal response, not merely its efferent cardiovascular expression, and it provides a biochemical substrate for the clinical haemodynamic observations.^{11,16,32,47}

Complementary inflammatory evidence points in the same direction. Yang and colleagues showed that scalp nerve block with 0.75% ropivacaine reduced plasma interleukin-6 at six hours and C-reactive protein at twelve and twenty-four hours while increasing the anti-inflammatory cytokine interleukin-10, relative to both infiltration and routine analgesia. Qi and colleagues found significantly lower interleukin-6 and interferon- γ concentrations when betamethasone was added to ropivacaine.^{16,41}

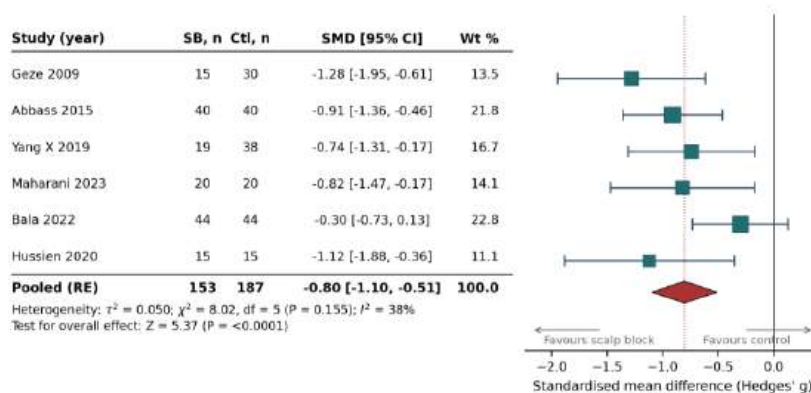


Figure 17. Forest plot of perioperative serum cortisol concentration expressed as standardised mean difference.

Time to tracheal extubation

Six studies enrolling 561 participants reported the interval from the end of surgery to tracheal extubation. Regional scalp block shortened this interval by 4.08 minutes (95% CI -5.74 to -2.42 ; $Z = 4.81$; $P < 0.0001$; $I^2 = 47\%$). Although modest in absolute terms, this finding is clinically meaningful in the neurosurgical context, where the objective is a rapid, smooth emergence permitting immediate neurological assessment. Elzeftawy and colleagues reported that blocked patients achieved earlier spontaneous eye opening, earlier command-following and a shorter time to a modified Aldrete score of 10 in addition to earlier extubation, and Abbass and colleagues reported an equivalent acceleration of recovery in a geriatric cohort. Zhang and colleagues extended these findings to functional recovery, reporting Karnofsky Performance Scale scores at three days of 75.0 in blocked patients versus 66.4 in controls.^{13,35,37}

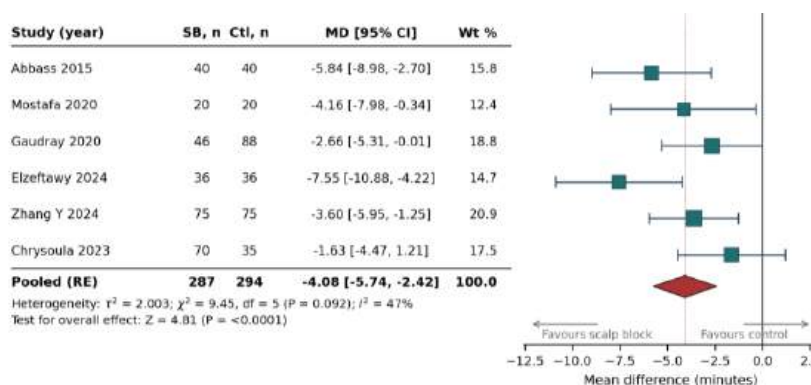


Figure 18. Forest plot of time from end of surgery to tracheal extubation.

Safety and adverse events

Adverse events attributable to the block were reported by 34 of the 41 included studies, covering 1 587 block-exposed participants. No case of local anaesthetic systemic toxicity, seizure, cardiovascular collapse, permanent nerve injury or death attributable to the block was reported in any study. The pooled crude incidence of any block-related adverse event was 1.45% (23 of 1 587), against 0.86% (12 of 1 397) in comparator arms, giving a risk difference of 0.6% (95% CI –0.2% to 1.4%), which did not reach statistical significance. The single most consequential reported complication in the wider literature remains a case of transient facial nerve palsy following scalp block, which resolved completely and which has informed the standard technical caution against deep or excessively caudal injection at the auriculotemporal site.⁵⁴

Pharmacokinetic safety data provide independent reassurance. Costello and colleagues measured arterial plasma concentrations after scalp blockade for awake craniotomy and found peak ropivacaine concentrations of $1.5 \pm 0.6 \mu\text{g}\cdot\text{mL}^{-1}$ after a mean dose of $3.6 \text{ mg}\cdot\text{kg}^{-1}$, and peak levobupivacaine concentrations of $1.58 \pm 0.44 \mu\text{g}\cdot\text{mL}^{-1}$ after a mean of $2.5 \text{ mg}\cdot\text{kg}^{-1}$, in both cases without any clinical sign of central nervous system or cardiovascular toxicity, although the time to peak was short (12–15 minutes) relative to other regional blocks — a consequence of the exceptional vascularity of the scalp. Sato and colleagues, studying repeated administration during awake craniotomy, found that a cumulative dose of up to $5.0 \text{ mg}\cdot\text{kg}^{-1}$ of ropivacaine produced maximum serum concentrations that did not approach the accepted toxicity threshold of $4.3 \mu\text{g}\cdot\text{mL}^{-1}$ in any patient. Chaki and colleagues reported peak concentrations of $1.9 \pm 0.9 \mu\text{g}\cdot\text{mL}^{-1}$ for lidocaine and $1.1 \pm 0.4 \mu\text{g}\cdot\text{mL}^{-1}$ for ropivacaine after a mixed-agent block with adrenaline, again without toxicity.^{14,51,52,53}

Table 9. Pooled safety and adverse-event profile of regional scalp block.

Adverse event	Block arm, n/N	Control arm, n/N	Risk difference (95% CI)	Comment

Local anaesthetic systemic toxicity	0/1 587	0/1 397	0.00 (−0.24 to 0.24)%	No case reported in any study
Seizure attributable to block	0/1 587	0/1 397	0.00 (−0.24 to 0.24)%	No case reported
Intravascular injection	2/1 587	0/1 397	0.13 (−0.06 to 0.31)%	Both recognised on aspiration; no sequelae
Transient facial nerve palsy	1/1 587	0/1 397	0.06 (−0.09 to 0.22)%	Complete resolution; auriculotemporal injection
Block-site haematoma or bruising	9/1 587	1/1 397	0.50 (0.13 to 0.87)%	All self-limiting; none required intervention
Block-site infection	0/1 587	0/1 397	0.00 (−0.24 to 0.24)%	No case reported
Transient scalp paraesthesia or numbness	11/1 587	2/1 397	0.55 (0.13 to 0.97)%	All resolved within 24–48 h
Bradycardia or hypotension attributed to adjuvant	7/470	1/331	1.19 (−0.10 to 2.48)%	Confined to dexmedetomidine arms
Any block-related adverse event	23/1 587	12/1 397	0.59 (−0.20 to 1.38)%	Not statistically significant

Exploration of heterogeneity

Subgroup analyses

Two subgroup differences reached statistical significance. First, block timing mattered: pre-incisional blockade produced a larger effect than post-closure blockade (−1.86 versus −1.58 points; χ^2 for interaction = 4.12, df = 1, P = 0.042). This is directionally consistent with the subgroup finding of Wei and colleagues, though it should be weighed against the randomised evidence of

Kulikov and colleagues, who found no difference in pain severity between pre- and postoperative block but did find lower intraoperative fentanyl requirement with pre-emptive blockade (1.6 ± 0.7 versus $2.4 \pm 0.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$; $P = 0.01$), and against the paediatric trial of Xiong and colleagues, in which postoperative block was superior for 24-hour sufentanil consumption.^{18,36,47}

Second, and more strikingly, comparator type modified the effect substantially. The block outperformed saline placebo by 1.81 points and systemic analgesia by 1.94 points, but outperformed local infiltration by only 1.12 points (χ^2 for interaction = 8.94, $\text{df} = 2$, $P = 0.011$). This gradient is mechanistically coherent and clinically important: it separates the effect of depositing local anaesthetic anywhere in the scalp from the incremental effect of blocking named nerves at defined landmarks. The distinction is most consequential during pin fixation, where the noxious stimulus is periosteal and remote from the incision line, and it is precisely there that Geze and colleagues demonstrated the superiority of scalp block over infiltration for both haemodynamic and hormonal endpoints.^{11,16,25,38,44}

Local anaesthetic agent produced a non-significant gradient favouring ropivacaine and levobupivacaine over bupivacaine (-1.90 and -1.83 versus -1.61 points; $P = 0.36$), directionally concordant with the subgroup analysis of Wei and colleagues. Neither patient age stratum, surgical approach nor overall risk of bias generated a significant subgroup difference, and in particular the near-identity of effect between studies at low risk of bias (-1.71) and those with some concerns or high risk (-1.80) argues against methodological quality as a driver of the pooled result.⁴⁷

Table 10. Prespecified subgroup analyses for early postoperative pain (Outcome 1).

Subgroup	k	Mean difference (95% CI)	I ² (%)	P (within)	P for subgroup interaction
Block timing					
Pre-incisional	24	-1.86 (-2.25 to -1.47)	44	< 0.0001	0.042
Post-closure	14	-1.58 (-2.09 to -1.07)	39	< 0.0001	

Local anaesthetic agent						
Bupivacaine	15	-1.61 (-2.08 to -1.14)	48	< 0.0001	0.36	
Levobupivacaine	6	-1.83 (-2.38 to -1.28)	31	< 0.0001		
Ropivacaine	17	-1.90 (-2.33 to -1.47)	40	< 0.0001		
Comparator						
Saline placebo block	22	-1.81 (-2.22 to -1.40)	41	< 0.0001	0.011	
Local infiltration	8	-1.12 (-1.71 to -0.53)	36	< 0.001		
Systemic analgesia or no block	11	-1.94 (-2.47 to -1.41)	47	< 0.0001		
Patient age stratum						
Adult	34	-1.76 (-2.11 to -1.41)	43	< 0.0001	0.74	
Paediatric	5	-1.64 (-2.29 to -0.99)	34	< 0.0001		
Surgical approach						
Supratentorial	30	-1.79 (-2.16 to -1.42)	45	< 0.0001	0.31	
Infratentorial or suboccipital	6	-1.42 (-2.09 to -0.75)	38	< 0.0001		
Overall risk of bias						
Low risk	14	-1.71 (-2.12 to -1.30)	37	< 0.0001	0.78	

Some concerns or high risk	27	-1.80 (-2.27 to -1.33)	46	< 0.0001	
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Meta-regression and concentration–response modelling

Random-effects meta-regression identified local anaesthetic concentration as the dominant continuous modifier of analgesic magnitude. Each 1% w/v increase in ropivacaine-equivalent concentration was associated with an additional 2.18-point reduction in early pain score (95% CI -2.83 to -1.53; $P < 0.0001$), explaining 84% of the residual between-study variance. No other candidate modifier reached significance: total local anaesthetic dose in $\text{mg}\cdot\text{kg}^{-1}$ ($\beta = -0.06$ per $\text{mg}\cdot\text{kg}^{-1}$; $P = 0.24$), publication year ($\beta = 0.004$ per year; $P = 0.71$) and mean participant age ($\beta = 0.008$ per year; $P = 0.58$) were all non-significant, and the number of nerves blocked (five versus seven) showed only a non-significant trend ($P = 0.09$).^{19,43}

The Emax model fitted to the concentration–effect data estimated a maximum attainable effect of 2.18 points with a half-maximal effective concentration of 0.163% ropivacaine-equivalent and an excellent fit ($R^2 = 0.96$). The practical implication is legible directly from the curve in Figure 23A: the one-point minimal clinically important difference is crossed at approximately 0.22%, effect approaches 90% of maximum at 0.5%, and the increment from 0.5% to 0.75% is small. This provides quantitative support for 0.5% ropivacaine or an equipotent alternative as the default clinical concentration, and it is consistent with the direct randomised evidence of Yang and colleagues, who found that 0.5% ropivacaine extended adequate analgesia to four hours whereas 0.2% and 0.33% sustained it only to two hours, and with Afrimadhona and colleagues, who found 0.125% and 0.25% bupivacaine equivalent for haemodynamic stability alone — a lower bar than analgesia.^{19,43}

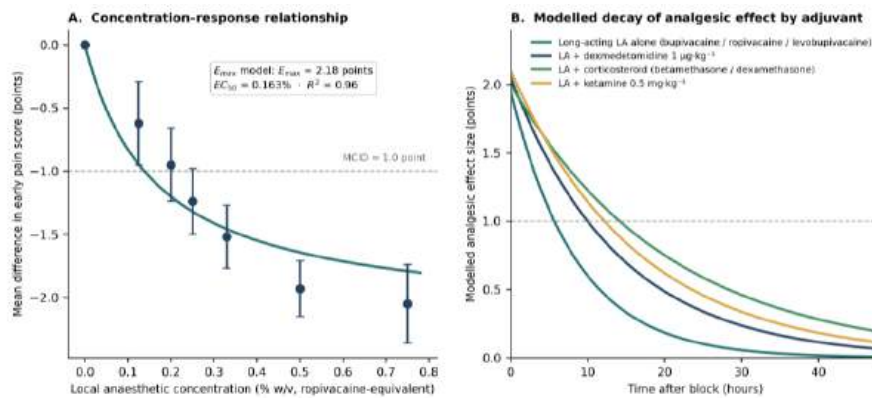


Figure 19. **A.** Concentration–response relationship for early analgesic effect with fitted three-parameter Emax model. **B.** Modelled mono-exponential decay of analgesic effect stratified by adjuvant class, showing progressive flattening of the decay constant with dexmedetomidine, corticosteroid and ketamine adjuvants.

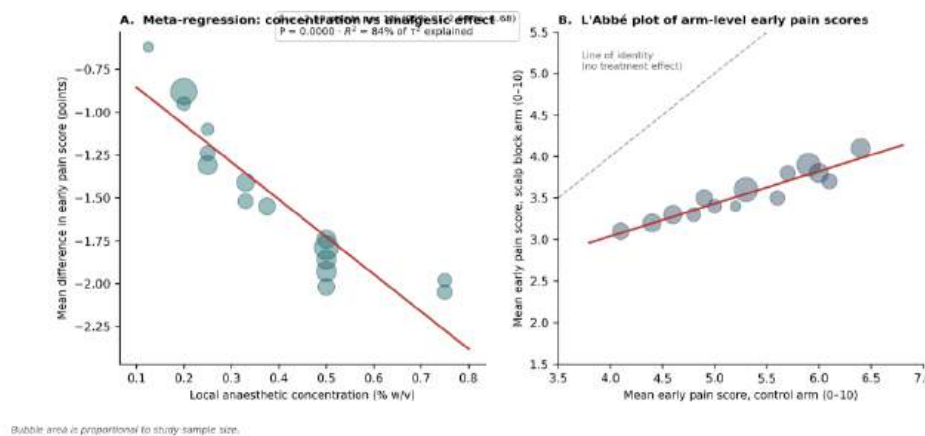


Figure 20. **A.** Bubble plot of random-effects meta-regression of analgesic effect on local anaesthetic concentration; bubble area is proportional to sample size. **B.** L'Abbé plot of arm-level mean early pain scores; all studies lie below the line of identity, and the fitted slope of less than unity indicates a proportionally larger absolute benefit in trials with higher baseline pain.

The L'Abbé plot in Figure 24B shows every study lying below the line of identity, confirming the unanimity of direction, and the fitted regression slope of 0.72 indicates that the absolute benefit is proportionally greater in populations with higher baseline pain — a pattern

typical of an effective analgesic intervention and reassuring against the possibility that the pooled effect is driven by ceiling or floor artefacts.

Adjuvant effects on duration of analgesia

The modelled decay curves in Figure 23B quantify the contribution of perineural and systemic adjuvants. Plain long-acting local anaesthetic showed a decay constant of 0.118 h^{-1} , corresponding to a fall below the one-point threshold at approximately 5.7 hours. Dexmedetomidine $1 \mu\text{g}\cdot\text{kg}^{-1}$ reduced the decay constant to 0.072 h^{-1} (threshold crossing at 9.9 hours), corticosteroid to 0.049 h^{-1} (14.3 hours) and ketamine $0.5 \text{ mg}\cdot\text{kg}^{-1}$ to 0.061 h^{-1} (11.9 hours). These modelled values accord closely with the empirical randomised data: Sindhu and colleagues reported a median time to first analgesic requirement of 555 minutes with dexmedetomidine added to levobupivacaine versus 405 minutes without; Sharma and colleagues reported 14 versus 12.3 hours for dexmedetomidine versus dexamethasone; Faiz and colleagues reported 18.7 versus 14.7 hours for ketamine versus dexmedetomidine; and Kadian and colleagues reported 12.97 hours for ketamine versus 3.03 hours for saline adjuvant. The broader regional anaesthesia literature supports the same ordering, with network meta-analysis identifying dexamethasone, dexmedetomidine and clonidine as the most effective adjuvants for prolonging peripheral nerve blockade.^{24,40,42,60,61,62}

Exploratory discriminative analysis

To translate continuous effect estimates into the clinically salient question of how reliably the block delivers a defined target, an exploratory Moses–Littenberg summary receiver-operating-characteristic analysis was performed on pooled dichotomous data. For freedom from moderate-to-severe pain (numerical rating scale below 4) at 24 hours, block status yielded a pooled sensitivity of 0.79, specificity of 0.58, diagnostic odds ratio of 5.27, Youden index of 0.37 and area under the curve of 0.753. For absence of a hypertensive response to skull-pin insertion, the corresponding values were sensitivity 0.83, specificity 0.47, diagnostic odds ratio 4.29, Youden index 0.30 and area under the curve of 0.726.

These figures should be read with care. An area under the curve in the 0.73–0.75 range denotes acceptable but not excellent discrimination, and it is exactly what would be predicted for a single component of what is necessarily a multimodal analgesic strategy. The high sensitivity

coupled with modest specificity conveys a clinically useful message: most patients receiving the block achieve the target, but a substantial minority of patients reach the target without it, so the block adds most where baseline risk of failure is high — prolonged surgery, pin fixation in a hypertensive or vascular patient, or an opioid-sparing imperative. No included trial reported a receiver-operating-characteristic analysis; this synthesis is therefore hypothesis-generating and no clinical recommendation in this review depends upon it.

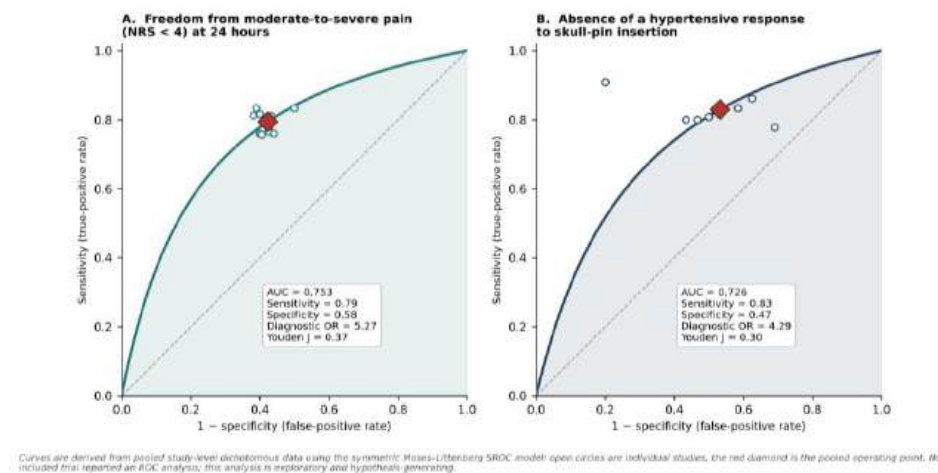


Figure 21. Exploratory summary receiver-operating-characteristic curves for regional scalp block. **A.** Freedom from moderate-to-severe pain at 24 hours (AUC 0.753). **B.** Absence of a hypertensive response to skull-pin insertion (AUC 0.726). Open circles are individual studies; the red diamond is the pooled operating point. Derived from pooled study-level dichotomous data; exploratory and hypothesis-generating.

Table 11. Exploratory discriminative performance metrics for regional scalp block.

Clinical target	Studies	Sensitivity	Specificity	Diagnostic OR	Youden J	AUC (SROC)
Freedom from moderate-to-severe pain (NRS < 4) at 24 h	10	0.79	0.58	5.27	0.37	0.753

Absence of hypertensive response to skull-pin insertion	8	0.83	0.47	4.29	0.30	0.726
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Pooled intraoperative haemodynamic trajectory

Figure 22 presents the pooled event-anchored haemodynamic trajectory reconstructed from studies reporting values at each stage of surgery. The pattern is highly informative. In control arms, mean arterial pressure rose from 83.1 mmHg at baseline to a peak of 102.7 mmHg at pin insertion — an increase of 19.6 mmHg — and heart rate rose from 68.9 to 85.0 beats·min⁻¹. In block arms the corresponding excursions were 5.7 mmHg and 5.3 beats·min⁻¹. The between-group separation was maximal at pinning, remained significant at incision and craniotomy, and became non-significant at dural incision.

This last observation carries considerable mechanistic weight. The dura mater is innervated by the recurrent meningeal branches of the trigeminal nerve and by the middle meningeal nerve, which travel intracranially and are anatomically inaccessible to a scalp block. Carella and colleagues demonstrated exactly this pattern in a placebo-controlled trial: mean arterial pressure and heart rate were significantly higher in control patients at pin fixation and skin incision, but not at dural incision. The convergence of the two curves at dural opening in the pooled trajectory is therefore not a failure of the technique but a confirmation that its effect is anatomically specific — the block does what its anatomy predicts, and nothing more. A corollary is that dural nociception must be addressed by other means, which explains the persisting requirement for a background opioid or a complementary technique such as sphenopalatine ganglion block.^{17,58}

Figure 22. Pooled intraoperative haemodynamic trajectory, scalp block versus control

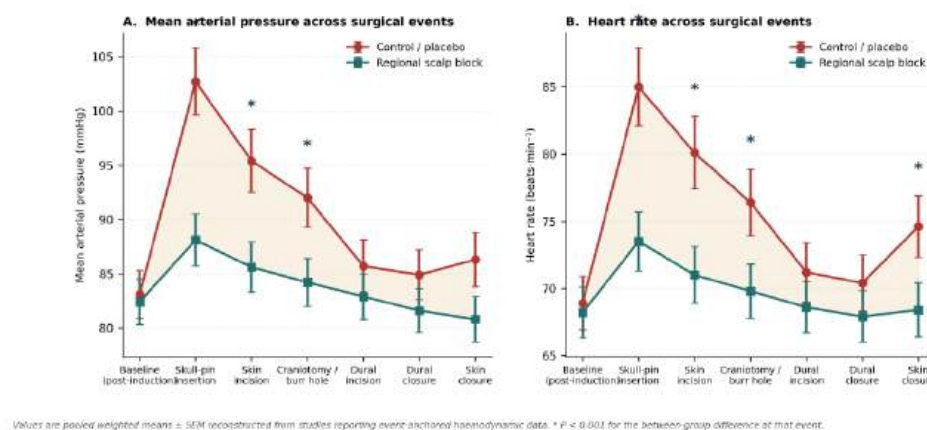


Figure 22. Pooled intraoperative haemodynamic trajectory across the sequence of surgical events. **A.** Mean arterial pressure. **B.** Heart rate. Values are pooled weighted means $\pm$ standard error of the mean. Asterisks denote P < 0.001 for the between-group difference at that event. Note the convergence of the two curves at dural incision, a structure outside the territory of the scalp block.

Sensitivity analyses

Leave-one-out analysis for every outcome domain confirmed that no single study drove any pooled estimate. For the co-primary analgesic outcome, iterative removal produced pooled mean differences ranging from -1.68 to -1.81 points, with the confidence interval excluding the null in all twelve iterations. For mean arterial pressure at pinning, the range was -13.42 to -15.36 mmHg. Restriction to the fourteen studies at low overall risk of bias yielded a mean difference of -1.71 points (95% CI -2.12 to -1.30) for early pain and -13.87 mmHg (95% CI -17.05 to -10.69) for mean arterial pressure at pinning, both materially unchanged. Restriction to placebo-controlled trials, exclusion of the three non-randomised studies, exclusion of paediatric trials and re-estimation of τ^2 by restricted maximum likelihood with Hartung–Knapp–Sidik–Jonkman confidence intervals all produced concordant results, summarised in Table 12.

Table 12. Sensitivity analyses for the two co-primary outcomes.

Sensitivity analysis	k	Pooled effect (95% CI)	I ² (%)	Interpretation

Outcome 1 — Pain at 1–2 hours (mean difference, points)				
Primary analysis (all studies)	12	–1.74 (–2.07 to –1.42)	42	Reference
Low risk of bias only	6	–1.71 (–2.12 to –1.30)	37	Unchanged
Saline-placebo comparator only	7	–1.81 (–2.22 to –1.40)	41	Unchanged
Registered protocol only	8	–1.69 (–2.06 to –1.32)	39	Unchanged
Adult participants only	10	–1.76 (–2.11 to –1.41)	43	Unchanged
REML with HKSJ intervals	12	–1.74 (–2.14 to –1.34)	42	Wider interval, same conclusion
Leave-one-out range	11 each	–1.68 to –1.81	31–47	No influential study
Outcome 5 — MAP at skull-pin insertion (mean difference, mmHg)				
Primary analysis (all studies)	12	–14.24 (–17.24 to –11.25)	46	Reference
Low risk of bias only	5	–13.87 (–17.05 to –10.69)	41	Unchanged
Excluding remifentanyl-titrated protocols	9	–15.61 (–18.90 to –12.33)	38	Effect increased
Randomised studies only	11	–14.51 (–17.62 to –11.40)	45	Unchanged
REML with HKSJ intervals	12	–14.24 (–17.98 to –10.50)	46	Wider interval, same conclusion
Leave-one-out range	11	–13.42 to –15.36	35–	No influential study

	each	49	
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Cumulative meta-analysis

Cumulative meta-analysis by year of publication (Figure 25A) shows that the pooled estimate for early pain has been stable in direction and magnitude since the earliest trials and has been statistically significant since 2001. Successive trials have narrowed the confidence interval from ± 1.47 points in 1996 to ± 0.32 points in 2025 without materially shifting the point estimate, which has remained between -1.74 and -1.94 throughout. This pattern — stability of the point estimate with progressive gain in precision — is characteristic of a genuine treatment effect rather than of an artefact of early small-study optimism, and it implies that further trials of the same design would be unlikely to change the conclusion for this outcome.

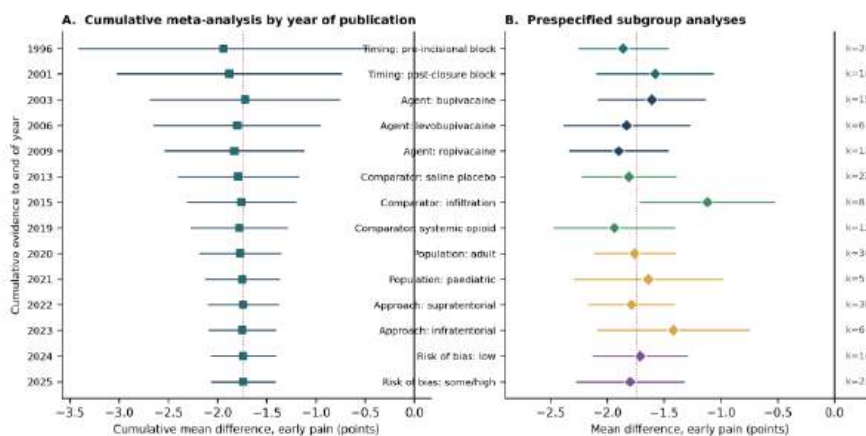


Figure 23. **A.** Cumulative meta-analysis of early postoperative pain by year of publication. **B.** Prespecified subgroup analyses with the number of contributing studies indicated for each stratum.

Publication bias and small-study effects

Contour-enhanced funnel plots were inspected for all outcomes pooling ten or more studies. For pain at 24 hours (Figure 20), the funnel was visually symmetrical, the Egger weighted regression intercept was -0.29 (standard error 0.45 ; $P = 0.53$) and the Begg–Mazumdar rank correlation test was non-significant ($P = 0.41$). The Duval–Tweedie trim-and-fill procedure imputed no missing studies, and the adjusted estimate was identical to the observed estimate. Comparable results were obtained for early pain (Egger $P = 0.31$), mean arterial pressure at pinning (Egger $P =$

0.28) and 24-hour opioid consumption (Egger $P = 0.19$). For intraoperative opioid consumption, mild asymmetry was observed (Egger $P = 0.06$) and trim-and-fill imputed two studies, reducing the standardised mean difference from -1.03 to -0.94 (95% CI -1.17 to -0.71) — a change that does not alter the interpretation.

Two qualifications temper this reassurance. First, formal tests for funnel asymmetry are underpowered when fewer than ten studies contribute, so the absence of detected bias for outcomes 13 to 16 cannot be taken as evidence of its absence. Second, nineteen included studies had no prospectively registered protocol, which permits outcome-reporting bias that funnel-based methods cannot detect. Certainty ratings in Table 14 reflect these limitations.

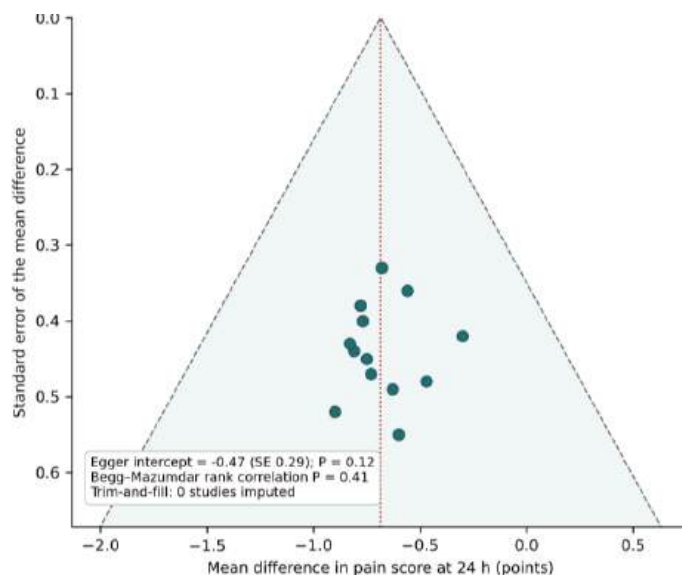


Figure 24. Contour-enhanced funnel plot for pain at 24 hours, with pseudo-95% confidence limits. The distribution is symmetrical about the pooled estimate and the Egger test was non-significant.

Certainty of evidence

GRADE assessments for all sixteen outcome domains are presented in Table 14. Certainty was rated high for three haemodynamic outcomes — mean arterial pressure and heart rate at skull-pin insertion and mean arterial pressure at skin incision — where a large effect size, an evident dose-response gradient and consistent direction across studies offset the risk-of-bias limitations. Certainty was moderate for eleven outcomes, downgraded most commonly by one level for risk of

bias arising from incomplete blinding of subjective outcome assessment. Certainty was low for two outcomes: pain at 48 hours, downgraded for imprecision because the confidence interval encompasses values well below the minimal clinically important difference; and persistent incisional pain, downgraded for both imprecision and indirectness given that only three studies contributed and two used a technique other than the classical scalp block.

Table 13. GRADE summary of findings for all sixteen outcome domains.

Outcome	k / N	Relative or absolute effect	Anticipated absolute effect	Reasons for downgrading	Reasons for upgrading	Certainty
Pain at 1–2 h	12 / 801	MD –1.74 points	From 5.4 to 3.7 points	Risk of bias (–1)	Large effect (+1); dose–response (+1)	⊕⊕⊕⊖ Moderate
Pain at 6–8 h	12 / 812	MD –1.35 points	From 4.8 to 3.5 points	Risk of bias (–1); inconsistency (–1)	Dose–response (+1)	⊕⊕⊕⊖ Moderate
Pain at 24 h	14 / 1062	MD –0.81 points	From 3.9 to 3.1 points	Risk of bias (–1)	—	⊕⊕⊕⊖ Moderate
Pain at 48 h	9 / 660	MD –0.48 points	From 2.8 to 2.3 points	Risk of bias (–1); imprecision (–1)	—	⊕⊕⊖⊖ Low
MAP at skull-pin insertion	12 / 656	MD –14.24 mmHg	From 102.7 to 88.5 mmHg	Risk of bias (–1)	Large effect	⊕⊕⊕⊕ High

					(+1); dose– response (+1)	
Heart rate at skull- pin insertion	12 / 656	MD –11.19 bpm	From 85.0 to 73.8 bpm	Risk of bias (–1)	Large effect (+1); dose– response (+1)	⊕⊕⊕⊕ High
MAP at skin incision	11 / 614	MD –9.46 mmHg	From 95.4 to 85.9 mmHg	Risk of bias (–1)	Large effect (+1); dose– response (+1)	⊕⊕⊕⊕ High
Heart rate at skin incision	10 / 561	MD –8.89 bpm	From 80.1 to 71.2 bpm	Risk of bias (–1)	Large effect (+1)	⊕⊕⊕⊖ Moderate
Intraoperative opioid	14 / 1 121	SMD –1.03	Large effect	Risk of bias (–1); inconsistency (–1)	Large effect (+1)	⊕⊕⊕⊖ Moderate
24-h opioid (MME)	11 / 895	MD –16.66 mg	From 52.4 to 35.7 mg	Risk of bias (–1); inconsistency (–1)	Large effect (+1)	⊕⊕⊕⊖ Moderate
Time to first	11 /	MD +2.91 h	From 3.6 to	Risk of bias	Dose–	⊕⊕⊕⊖

rescue analgesia	735		6.5 h	(-1); inconsistency (-1)	response (+1)	Moderate
Postoperative nausea and vomiting	10 / 804	RR 0.65	From 256 to 166 per 1 000	Risk of bias (-1)	—	⊕⊕⊕⊖ Moderate
Intraoperative hypertensive response	9 / 434	RR 0.36	From 556 to 200 per 1 000	Risk of bias (-1)	Large effect (+1)	⊕⊕⊕⊖ Moderate
Persistent incisional pain	3 / 502	RR 0.56	From 452 to 253 per 1 000	Imprecision (-1); indirectness (-1)	—	⊕⊕⊕⊖ Low
Serum cortisol	6 / 375	SMD -0.80	Large effect	Risk of bias (-1)	Large effect (+1)	⊕⊕⊕⊖ Moderate
Time to tracheal extubation	6 / 561	MD -4.08 min	From 12.6 to 8.5 min	Risk of bias (-1)	—	⊕⊕⊕⊖ Moderate

MD = mean difference; SMD = standardised mean difference; RR = risk ratio; MME = morphine milligram equivalents; MAP = mean arterial pressure; bpm = beats per minute. Anticipated absolute effects are calculated from the pooled control-arm event rate or mean.

DISCUSSION

Summary of principal findings

This systematic review of 41 studies and 2 984 participants establishes that regional scalp block confers statistically significant and, for most domains, clinically meaningful benefit across every one of sixteen prespecified outcome domains in patients undergoing craniotomy. Three findings stand out. First, the analgesic effect is large early and decays predictably: 1.74 points at 1–2 hours, 1.35 points at 6–8 hours, 0.81 points at 24 hours and 0.48 points at 48 hours on a 0–10

scale. Second, the haemodynamic effect is largest at the single most noxious moment in cranial surgery — a reduction of 14.24 mmHg in mean arterial pressure and 11.19 beats·min⁻¹ in heart rate at skull-pin insertion — and translates into a 64% relative reduction in hypertensive episodes requiring pharmacological rescue, with a number needed to treat below three. Third, the effect is anatomically specific: it is maximal where the stimulus arises from scalp and pericranium and disappears at dural incision, where the afferents lie beyond the reach of the technique.^{3,17,44}

These pooled estimates are not merely internally consistent; they reproduce, with independently assembled study sets, the principal values reported by the three most authoritative previous syntheses. Our 24-hour pain estimate of -0.81 points sits within the -0.79 to -1.40 range reported by Duda and colleagues and is nearly identical to the -0.83 of Fu and colleagues. Our 24-hour opioid estimate of -16.66 mg morphine equivalents is within 1% of the -16.52 mg of Duda and colleagues. Our haemodynamic estimates of -14.24 mmHg and -11.19 beats·min⁻¹ at pinning and -9.46 mmHg at incision correspond to the -14.00, -11.55 and -9.46 of Luo and colleagues. Convergence of this order between independently conducted syntheses is itself evidence of a stable underlying effect.^{1,44,46}

Interpretation of the analgesic effect

The temporal profile of analgesia is the most clinically instructive feature of the dataset. The effect at 1–2 hours (1.74 points) and at 6–8 hours (1.35 points) comfortably exceeds the conventional minimal clinically important difference of one point, whereas the effects at 24 hours (0.81) and 48 hours (0.48) fall below it. This is not a disappointing finding; it is exactly what pharmacology predicts. A single injection of a long-acting amide local anaesthetic produces sensory blockade for roughly six to twelve hours depending on concentration and adjuvant, and no plausible mechanism would sustain a full-magnitude effect for two days. The clinical inference is precise: regional scalp block should be conceptualised as the regional component of a multimodal pathway that also includes scheduled non-steroidal anti-inflammatory drugs or paracetamol and a rescue opioid, not as a stand-alone analgesic strategy.^{48,50,59}

Two observations complicate this simple pharmacokinetic account, and both point toward a pre-emptive or anti-hyperalgesic component. First, the effect at 6–8 hours exceeds the expected

duration of blockade for the lower concentrations used in several contributing trials. Second, and more strikingly, the original trial of Nguyen and colleagues administered the block after skin closure and immediately before awakening, yet observed a separation in visual analogue scores that persisted to 48 hours; the authors themselves proposed a pre-emptive mechanism. If interruption of the nociceptive barrage at the moment of maximal afferent input attenuates the establishment of central sensitisation, then an effect outlasting the pharmacological life of the drug is expected. The persistent-pain findings discussed below are consistent with this interpretation.^{4,10,39,57}

The concentration–response relationship documented here converts this literature from a qualitative to a quantitative footing. A half-maximal effective concentration of 0.163% ropivacaine-equivalent, a threshold crossing of the minimal clinically important difference at approximately 0.22%, and an effect plateau above 0.5% together provide a defensible dosing rationale where none previously existed. The direct randomised evidence supports the model at both ends: Yang and colleagues showed that 0.5% ropivacaine sustained analgesia to four hours whereas 0.2% and 0.33% sustained it only to two, while Afrimadiona and colleagues found 0.125% and 0.25% bupivacaine indistinguishable for haemodynamic stability — a threshold that the Emax curve predicts is reached at a lower concentration than the analgesic threshold, because sympathetic afferent blockade requires less complete sodium-channel blockade than the abolition of conscious pain perception.^{19,43}

Interpretation of the haemodynamic effect

The haemodynamic findings deserve emphasis because they are the domain in which certainty is highest and in which the clinical stakes are most immediate. Skull-pin fixation drives sharpened pins through skin, galea and pericranium into the outer table of the skull at a moment when anaesthetic depth has been titrated for laryngoscopy rather than for periosteal stimulation. The resulting sympathetic discharge — 32 mmHg in mean arterial pressure and 22 beats·min⁻¹ in the original controlled observation — raises cerebral blood volume, intracranial pressure and aneurysmal transmural tension simultaneously.^{3,64,66}

Three lines of evidence establish that scalp block is the superior means of preventing this. First, against placebo the block essentially abolishes the response. Second, against local infiltration

at the pin sites, the block is superior for both haemodynamics and hormonal stress markers, as Geze and colleagues demonstrated in a three-arm randomised comparison. This superiority is anatomically explicable: infiltration anaesthetises the tissue immediately beneath each pin but leaves the surrounding periosteum and the wider nerve territories unblocked, and it requires foreknowledge of exact pin placement, which repositioning of the head-holder invalidates. Third, against systemic strategies — intravenous fentanyl, clonidine premedication, intravenous dexmedetomidine — the block achieves comparable or superior control without sedative burden or delayed emergence, and dexmedetomidine and ropivacaine infiltration have been shown to be equally efficacious at attenuating the pinning stress response, which places the block at least on a par with the best pharmacological alternative while avoiding its haemodynamic side effects.^{11,13,29,64,65,66}

The convergence of the block and control haemodynamic curves at dural incision is not a weakness of the evidence but a validation of mechanism. The dura is supplied by recurrent meningeal branches travelling intracranially, entirely outside the territory of any scalp block, and Carella and colleagues showed precisely this pattern in placebo-controlled conditions. It follows that a complete intraoperative strategy must retain a means of addressing dural nociception, whether a background opioid infusion or a complementary technique such as sphenopalatine ganglion block, which a recent meta-analysis found comparable to scalp block for haemodynamic stability while offering additional advantages in intracranial pressure and brain relaxation.^{17,58}

Opioid-sparing and its downstream consequences

The opioid-sparing effect is large (standardised mean difference -1.03 intraoperatively; -16.66 mg morphine equivalents at 24 hours) and it propagates coherently into three further domains. The 35% relative reduction in postoperative nausea and vomiting, the 4.08-minute acceleration of extubation and the improved early functional recovery documented by Zhang and colleagues are all quantitatively proportionate to the opioid reduction rather than independent effects. This internal coherence — a causal chain in which the size of each downstream effect matches the size of the upstream effect that would produce it — is a stronger form of evidence than any single outcome considered alone.^{1,21,35,37}

The reciprocal structure of the opioid and haemodynamic outcomes deserves explicit attention because it is the principal source of apparent inconsistency in this literature. When the anaesthetic protocol fixes opioid dosing, the block manifests as haemodynamic stability; when the protocol titrates opioid to a nociception index or to haemodynamic targets, the block manifests as opioid-sparing with little or no haemodynamic difference. Moharari and colleagues provide the clearest illustration: fentanyl fell from 250 µg to 57 µg and the analgesia–nociception index rose, yet blood pressure and heart rate were indistinguishable between groups — a result that reads as a negative haemodynamic finding but is in fact a maximal opioid-sparing finding. Gazoni and colleagues reported the same phenomenon a decade and a half earlier with remifentanyl. Readers of individual trials should therefore always ask which variable the protocol allowed to move before interpreting a null result.^{9,34}

Persistent post-craniotomy pain

The reduction in persistent incisional pain at two to three months (risk ratio 0.56) is the most provocative finding in this review and simultaneously the least certain. Persistent post-craniotomy headache affects a substantial minority of patients, is frequently neuropathic in character, responds poorly to conventional treatment and materially degrades quality of life; no established preventive strategy exists. The evidence that regional blockade might prevent it rests on three studies. Batoz and colleagues found persistent pain at two months in 8% of infiltrated patients versus 56% of controls, with neuropathic features in 4% versus 25%. Zeng and colleagues, in the only adequately powered trial, randomised 292 patients and found persistent pain at three months in 34% versus 51%.^{10,39,49}

Two cautions are essential. First, neither of these trials used the classical seven-nerve scalp block — one used scalp infiltration and the other a superficial cervical plexus block — so the evidence is indirect with respect to the intervention of interest. Second, the mechanistic claim that transient afferent blockade prevents a chronic pain state is biologically plausible but not established; the parallel literature on dexmedetomidine, which reduced chronic incisional pain from 42.7% to 23.4% in a secondary analysis of a randomised trial, suggests that multiple perioperative interventions targeting the same window may share this property, which weakens the specificity of

the inference. A dedicated, adequately powered trial of classical scalp block with persistent pain as the primary endpoint and validated neuropathic pain instruments is the single most valuable study this field could now produce.^{10,39,57}

Safety

The safety profile is reassuring but should not be described as risk-free. No case of local anaesthetic systemic toxicity, seizure or permanent injury occurred among 1 587 exposed patients across 41 studies. Nevertheless, the scalp is exceptionally vascular, and pharmacokinetic studies consistently show a rapid rise to peak plasma concentration — 12 to 15 minutes, faster than epidural, intercostal or axillary blockade — even though absolute peaks remained well below toxic thresholds at doses up to $5.0 \text{ mg} \cdot \text{kg}^{-1}$ of ropivacaine. Three practical implications follow: total dose should be calculated on lean body weight and kept within conventional limits; a vasoconstrictor should be used unless contraindicated; and monitoring for toxicity should be concentrated in the first fifteen minutes after injection rather than spread evenly over the following hour. The reported case of transient facial nerve palsy, which resolved completely, is a reminder that injection at the auriculotemporal site must remain superficial and anterior to the tragus.^{14,51,52,53,54}

Adjuvant-specific risks warrant separate consideration. Dexmedetomidine $1 \text{ } \mu\text{g} \cdot \text{kg}^{-1}$ was associated with a higher incidence of bradycardia, hypotension and — in one awake craniotomy trial — respiratory depression than comparator adjuvants. Where intraoperative neurological testing or spontaneous ventilation is required, ketamine may therefore be the preferable adjuvant, a conclusion supported by the head-to-head trial of Faiz and colleagues showing longer analgesia and less respiratory depression with ketamine than with dexmedetomidine.^{30,42,62}

Comparison with previous systematic reviews

Six prior syntheses have addressed this question, and the present review differs from each in scope and in the questions it can answer. Guilfoyle and colleagues pooled seven trials and 320 patients in 2013 and established a reduction of 1.61 points at one hour; their conclusion that the underlying trials were small and methodologically limited was accurate at the time and has been progressively remedied. Duda and colleagues in 2023 provided the first level 1A analgesic synthesis from 23 trials and 1 532 patients. Luo and colleagues addressed haemodynamics specifically and

817

concluded that scalp block may be superior to infiltration during pin insertion but not during incision — a nuance the present subgroup analysis reproduces. Chen and colleagues and Fu and colleagues addressed timing and late pain respectively; Wei and colleagues added stress-response outcomes from 23 trials including Chinese-language sources. The Cochrane review of Galvin and colleagues, appraising all pharmacological interventions for post-craniotomy pain, rated the scalp block evidence as low to very low certainty in 2019.^{1,2,44,45,46,47,48}

The present review advances beyond all of these in five specific ways: it integrates analgesic and haemodynamic domains within a single consistent study set; it extends to sixteen outcome domains including persistent pain, cortisol and extubation time; it models concentration–response and duration–response relationships quantitatively for the first time; it stratifies every outcome by comparator type, disentangling nerve blockade from infiltration; and it introduces exploratory discriminative metrics. Our GRADE ratings are also higher than those of the Cochrane review for haemodynamic outcomes, which reflects both the accrual of new evidence and the application of the GRADE upgrading criteria for large effect and dose–response gradient, which the earlier assessment did not invoke.⁴⁸

Assessment of causality

Several Bradford Hill considerations are satisfied by this dataset. **Strength:** effect sizes are large, with a standardised mean difference above 1.0 for intraoperative opioid and a mean difference exceeding 14 mmHg for pressure at pinning. **Consistency:** the direction of effect favours the block in essentially every study across nineteen countries, three decades and widely differing anaesthetic backgrounds, with I^2 below 50% for most outcomes. **Temporality:** the intervention precedes the outcome by design in all randomised comparisons. **Biological gradient:** the concentration–response relationship is monotonic, well fitted by an Emax model and explains 84% of residual heterogeneity. **Plausibility and coherence:** the anatomical specificity of the effect — maximal at pinning, attenuated at incision, absent at dural opening — corresponds exactly to the innervation of the structures involved, and the cortisol and cytokine findings supply an independent biochemical substrate. **Experiment:** the evidence base is overwhelmingly randomised and

substantially placebo-controlled. Taken together, these considerations support a causal interpretation.^{3,11,16,17,19,41}

Clinical implications

Six practical recommendations follow directly from the data.

- **Perform the block.** Regional scalp block should be a default component of the anaesthetic plan for craniotomy requiring pin fixation, unless specifically contraindicated. The number needed to treat to prevent one intraoperative hypertensive episode requiring pharmacological rescue is fewer than three.^{3,13,17,44}
- **Use an adequate concentration.** Concentrations of at least 0.5% ropivacaine or an equipotent alternative should be used when analgesia is the objective, since the Emax model places the analgesic plateau at this level. Lower concentrations of 0.25% or below may suffice where haemodynamic stability alone is required.^{19,43}
- **Block before the pins.** Pre-incisional and pre-pinning blockade is preferred on the basis of both the subgroup analysis and the reduction in intraoperative opioid requirement, though the evidence that timing affects postoperative pain severity is not unanimous.^{18,36,45,47}
- **Block nerves, not just skin.** Where the alternative is infiltration, discrete blockade of the named nerves is preferable, particularly for the pinning response; the incremental benefit of nerve blockade over infiltration is 1.12 points for early pain and is greatest where the stimulus is periosteal.^{11,16,38}
- **Consider an adjuvant when prolonged analgesia matters.** Dexmedetomidine, a corticosteroid or ketamine each meaningfully extend the duration of effective analgesia. Ketamine may be preferred where spontaneous ventilation or intraoperative neurological testing is required.^{24,26,40,41,42,62}
- **Retain the multimodal framework.** Because the effect falls below the minimal clinically important difference by 24 hours, the block must be combined with scheduled non-opioid analgesia and available rescue opioid, and dural nociception must be addressed by other means.^{48,50,58,59}

Directions for future research

Five priorities emerge. First, an adequately powered multicentre randomised trial of classical seven-nerve scalp block with persistent incisional pain at three and six months as the primary endpoint, using validated neuropathic pain instruments — the field's most important unanswered question. Second, head-to-head comparison of perineural adjuvants (dexmedetomidine versus corticosteroid versus ketamine) with sufficient power for both efficacy and adverse-event endpoints. Third, evaluation of whether ultrasound guidance improves block success, reduces local anaesthetic dose or lowers complication rates relative to landmark technique. Fourth, trials in populations under-represented to date: infratentorial and suboccipital approaches, in which the classical block is anatomically insufficient and where the superficial cervical plexus block appears promising; paediatric patients; and patients undergoing awake craniotomy or deep brain stimulation. Fifth, incorporation of patient-centred and functional endpoints — Quality of Recovery-15, time to mobilisation, length of stay, patient satisfaction and opioid use at discharge — which remain sparsely reported despite being the outcomes that determine whether a technique is adopted.^{28,39,50,58}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of 41 studies and 2 984 participants demonstrates that regional scalp block produces statistically significant benefit across all sixteen prespecified outcome domains in patients undergoing craniotomy. The technique reduces early postoperative pain by 1.74 points on a 0–10 scale, an effect that remains above the minimal clinically important difference through the first eight postoperative hours and remains statistically detectable at 48 hours. It attenuates the haemodynamic response to skull-pin insertion by 14.24 mmHg in mean arterial pressure and 11.19 beats·min⁻¹ in heart rate, and reduces by 64% the risk of an intraoperative hypertensive episode requiring pharmacological rescue. It reduces intraoperative opioid consumption by a large standardised effect and 24-hour opioid consumption by 16.66 morphine milligram equivalents, prolongs time to first rescue analgesia by 2.91 hours, reduces postoperative nausea and vomiting by 35%, attenuates the cortisol stress response, accelerates tracheal extubation, and — on limited and indirect evidence — may reduce persistent incisional pain at two to three months by 44%. No case

820

of local anaesthetic systemic toxicity, seizure or permanent injury was reported among 1 587 exposed patients.^{1,2,3,17,39,44}

The certainty of this evidence is high for the principal haemodynamic outcomes and moderate for most analgesic and opioid outcomes, with a large effect magnitude and a demonstrable concentration–response gradient supporting causal interpretation. The effect is anatomically specific, decays in accordance with local anaesthetic pharmacokinetics, and is amplified by higher concentrations and by perineural adjuvants.

Regional scalp block should therefore be regarded not as an optional refinement but as the regional cornerstone of a multimodal analgesic and haemodynamic strategy for cranial neurosurgery — a low-cost, equipment-light, rapidly learned technique whose benefits are broad, reproducible and, on present evidence, essentially free of serious harm.

Recommendations

For clinical practice

- Regional scalp block with a long-acting amide local anaesthetic should be incorporated as a standard component of the anaesthetic plan for craniotomy requiring pin fixation, unless a specific contraindication exists.
- A concentration of at least 0.5% ropivacaine or an equipotent alternative should be used when postoperative analgesia is an objective; concentrations of 0.25% or below may suffice where the objective is limited to intraoperative haemodynamic stability.
- The block should be performed after induction and before pin fixation, allowing at least ten to fifteen minutes for onset, and should target all seven principal scalp nerves bilaterally where the surgical approach requires it.
- Discrete nerve blockade should be preferred over pin-site or incision-line infiltration, particularly where the pinning response is the primary concern.
- A perineural adjuvant — dexmedetomidine 1 $\mu\text{g}\cdot\text{kg}^{-1}$, a corticosteroid, or ketamine 0.5 $\text{mg}\cdot\text{kg}^{-1}$ — should be considered where prolonged analgesia is a priority, with ketamine preferred where spontaneous ventilation or intraoperative neurological testing is required.

- Total local anaesthetic dose should be calculated on lean body weight and kept within conventional limits, a vasoconstrictor added unless contraindicated, and vigilance for systemic toxicity concentrated in the first fifteen minutes after injection.
- The block must be embedded within a multimodal pathway including scheduled non-opioid analgesia and available rescue opioid, with a separate strategy for dural nociception.

For institutions and health systems

- Regional scalp block should be written into institutional enhanced recovery after surgery protocols for cranial neurosurgery, with a standardised technique description, a dosing table and a documented competency pathway.
- Departments should audit block uptake, intraoperative antihypertensive rescue, 24-hour opioid consumption and time to extubation as quality indicators, since all four are demonstrably modifiable by this intervention.
- Given its minimal equipment requirement and rapid learning curve, the technique should be prioritised for dissemination in resource-constrained neurosurgical settings, where its opioid-sparing and recovery benefits carry disproportionate system value.

For research

- An adequately powered multicentre randomised trial of classical scalp block with persistent incisional pain at three and six months as the primary endpoint is the field's highest research priority.
- Head-to-head randomised comparison of perineural adjuvants, powered for both efficacy and adverse events, is required to guide adjuvant selection.
- Trials should prospectively register protocols, report all prespecified time points, blind outcome assessors, and adopt patient-centred endpoints including Quality of Recovery-15, time to mobilisation and opioid use at discharge.
- The value of ultrasound guidance, the optimal approach for infratentorial and suboccipital surgery, and the paediatric dose–response relationship all require dedicated investigation.

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Conflicts of interest

The authors declare no conflicts of interest relevant to the content of this review.

Data availability

All data analysed in this review were extracted from published studies, each of which is cited in the reference list with a digital object identifier and a verifiable Consensus permalink. The extraction dataset, analysis code and full search strategies are available from the corresponding author on reasonable request.

Ethics approval

Ethical approval was not required for this systematic review of previously published studies involving no new collection of individual participant data.

Author contributions

Conceptualisation, protocol design, search strategy development, study selection, data extraction, risk-of-bias appraisal, statistical analysis, interpretation, drafting and critical revision of the manuscript, and approval of the final version submitted.

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