Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Comparable Brain Relaxation and a Potential Antiemetic Advantage of Propofol-Based versus Volatile Anaesthesia in Brain Tumour Resection

Isha Ravichandran

iisharavichandran@gmail.com

King's College London https://orcid.org/0000-0002-6148-7372

Chriencia Odhach

University of Edinburgh

Nayef Soufan

Facharzt für Neurochirurgie

Systematic Review

Keywords: Craniotomy, Brain neoplasms, Propofol, Anesthetics, inhalation, Postoperative nausea and vomiting, Meta-analysis

Posted Date: November 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11816474/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: The authors declare no competing interests.

Comparable Brain Relaxation and a Potential Antiemetic Advantage of Propofol-Based versus Volatile Anaesthesia in Brain Tumour Resection

Running title: TIVA versus volatile anaesthesia for tumour craniotomy

Article type: Systematic Review/Meta-analysis

Authors: Isha Ravichandran, MBBS[1,2]; Chricencia Odhach, MSc[3]; Nayef Soufan, MSc, Facharzt für Neurochirurgie[2]

[1]Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom; [2]Department of Neurosurgery, Saudi German Hospital Dubai, Dubai, United Arab Emirates; [3]University of Edinburgh, Edinburgh, United Kingdom

Corresponding author: Isha Ravichandran, MBBS, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom. Email: iisharavichandran@gmail.com. ORCID 0000-0002-6148-7372

Word count: main text 4,270 words; abstract 295 words

Figures and tables: 6 figures; 3 tables

Registration: PROSPERO CRD420261399121

Details page

Compliance with instructions: The manuscript has been prepared for submission to Neurocritical Care.

Author contributions: Isha Ravichandran conceived and designed the review, performed the search and study selection, extracted and cleaned the data with Chricencia Odhach, prepared the tables and figures, and drafted the manuscript. Chricencia Odhach extracted and cleaned the data with Isha Ravichandran, performed the statistical analysis and interpreted the results. Nayef Soufan supervised the work and critically revised the manuscript for important intellectual content.

Authorship: The authorship requirements have been met, and all authors read and approved the final manuscript.

Prior publication: The manuscript has not been published and is not under consideration by another journal. Preliminary findings were presented as a poster at the Integrated Anesthesia and Comprehensive Care Conference (IACC 2026), Abu Dhabi, 27-28 June 2026, and as a virtual oral presentation at AVER Neuro in November 2026.

Ethical approval and informed consent: Not applicable. This systematic review analysed data from published studies only; no ethics committee approval or informed consent was required.

Conflicts of interest: Isha Ravichandran, Chricencia Odhach and Nayef Soufan declare that they have no conflicts of interest.

Reporting checklist: The review was reported with reference to PRISMA 2020. The completed PRISMA 2020 checklist is provided as a separate submission file.

Registration: PROSPERO CRD420261399121.

Source of support: No funding was received for this work.

Data availability: Extraction data and analysis code are available from the corresponding author on reasonable request.

Acknowledgements: None.

Artificial intelligence-assisted technology: Claude (Anthropic) was used to assist with language editing, structural refinement and document formatting.

Abstract

Background/Objective: Propofol-based total intravenous anaesthesia (TIVA) and volatile anaesthesia affect cerebral haemodynamics differently, but whether this changes surgical conditions in patients with an intracranial mass is unclear. We compared the two techniques in brain tumour craniotomy.

Methods: We systematically reviewed and pooled randomised controlled trials (RCTs) in adults undergoing craniotomy for brain tumour or supratentorial mass lesion (PROSPERO CRD420261399121). PubMed, Web of Science and Google Scholar were searched. The primary outcome was satisfactory intraoperative brain relaxation, harmonised across 3- and 4-point scales. Secondary outcomes were postoperative nausea and vomiting (PONV), time to extubation and emergence agitation. Risk of bias was assessed with RoB 2. Effects were pooled with restricted maximum likelihood random-effects models, with modified Hartung-Knapp intervals for every outcome as a sensitivity analysis.

Results: Sixteen studies were included (14 RCTs and two non-randomised cohorts), and 11 RCTs contributed to at least one meta-analysis. Brain relaxation was similar with both techniques (9 RCTs, 1,436 patients; risk ratio [RR] 1.04, 95% CI 0.99-1.09; modified Hartung-Knapp 0.98-1.10; I^2 0%; prediction interval 0.98-1.10). PONV was less frequent with TIVA (3 RCTs, 601 patients; RR 0.38, 95% CI 0.23-0.60; about 14 fewer per 100 patients), but the modified Hartung-Knapp interval crossed 1 (0.13-1.06). Time to extubation (3 RCTs, 226 patients; mean difference 0.15 min, 95% CI −0.58 to 0.87) and emergence agitation (2 RCTs, 521 patients; RR 1.68, 95% CI 0.88-3.20) showed no clear difference. All trials raised some concerns for risk of bias. Certainty was moderate for brain relaxation and low or very low for secondary outcomes.

Conclusions: In brain tumour craniotomy, TIVA and volatile maintenance provide comparable brain relaxation, with uncertain emergence differences. TIVA shows a consistent, clinically

relevant but low-certainty signal of reduced PONV. Both techniques remain acceptable; an adequately powered trial with PONV as its primary outcome is needed.

Keywords: Craniotomy; Brain neoplasms; Propofol; Anesthetics, inhalation; Postoperative nausea and vomiting; Meta-analysis

Introduction

Anaesthetic maintenance for brain tumour craniotomy has three goals: a slack, operable brain, stable cerebral perfusion, and rapid emergence that allows early neurological assessment. The two dominant techniques have different cerebral haemodynamic effects. Propofol-based TIVA reduces cerebral metabolic rate, cerebral blood flow and intracranial pressure, preserves cerebral autoregulation and is antiemetic. Volatile agents are cerebral vasodilators that can raise cerebral blood volume and intracranial pressure in a dose-dependent manner, but they are easily titrated, need no infusion equipment and, with desflurane or sevoflurane, allow predictable emergence.

In theory these differences matter most in patients with intracranial mass effect, where a small rise in cerebral blood volume may worsen surgical conditions, and where retching after surgery can raise intracranial and arterial pressure in the hours when these patients are monitored for haematoma and swelling. Despite three decades of randomised trials, neither technique has been shown to be superior. A meta-analysis of elective craniotomy found no difference in clinically important brain swelling, with lower intracranial pressure and higher cerebral perfusion pressure with propofol[1]. A Cochrane review of brain tumour surgery found little difference in emergence, on low-quality evidence[2]. A more recent meta-analysis reported less brain swelling with propofol across a broad craniotomy population[3], and a network meta-analysis ranked propofol highest for brain relaxation without clear differences between individual agents[4].

These reviews leave three problems unresolved. First, most pooled broad craniotomy populations, including aneurysm, vascular and functional surgery, in which mass effect is often absent. Second, brain relaxation, the outcome most relevant to the surgeon, is reported on 3-point and 4-point scales with different cut-points, which makes pooled estimates sensitive to how each scale is dichotomised. Third, most outcomes rest on few trials, and with so few trials

conventional random-effects confidence intervals can be too narrow, so that a nominally significant result may not survive a small-sample correction[5].

We therefore performed a systematic review and meta-analysis of randomised trials comparing propofol-based TIVA with volatile maintenance, restricted to craniotomy for brain tumour or supratentorial mass lesion. We harmonised brain relaxation to a single predefined dichotomy, handled multi-arm trials without double-counting, and tested every pooled estimate with a small-sample adjustment, so that robust findings could be separated from suggestive ones.

Methods

Protocol and registration

The review was registered with PROSPERO (CRD420261399121) and was reported with reference to PRISMA 2020[6]; the completed PRISMA 2020 checklist is provided as a separate submission file. Two analyses were decided after data extraction and are labelled post hoc: analysing Petersen 2003 as a separate mixed-arm subgroup, and the modified Hartung-Knapp sensitivity analysis. The review team listed at registration differs from the author list: one member listed at registration did not contribute to the conduct of the review and is not an author, and C.O. and N.S. joined after registration. An update to the registration record has been requested.

Eligibility criteria

We included RCTs that enrolled adults undergoing elective craniotomy for a brain tumour or supratentorial mass lesion, compared propofol-based TIVA (with or without an opioid infusion) with maintenance using sevoflurane, isoflurane or desflurane (with or without nitrous oxide or an opioid), and reported at least one outcome of interest. We excluded trials of awake craniotomy, aneurysm or vascular surgery, traumatic brain injury and transsphenoidal

surgery; trials in which the comparator combined a volatile agent with a barbiturate infusion; and trials in children. Where a trial had a third arm that was neither propofol-based TIVA nor volatile maintenance, only the two eligible arms were used. Non-randomised comparative studies meeting the same population and intervention criteria were identified but not pooled, and are summarised narratively.

Outcomes

The primary outcome was satisfactory intraoperative brain relaxation as assessed by the operating surgeon. Secondary outcomes were PONV, time to extubation (minutes) and emergence agitation, each as defined by the original trial.

Information sources and search

PubMed, Web of Science and Google Scholar were searched from inception to June 2026. The search combined terms for the population (craniotomy, brain tumour, brain neoplasm, supratentorial, intracranial mass) with terms for the interventions (propofol, total intravenous anaesthesia, sevoflurane, isoflurane, desflurane, volatile, inhalational). Reference lists of included trials and of earlier systematic reviews[1-4] were hand searched. Population and intervention terms were combined with the Boolean operator AND, and synonyms within each concept with OR. The full search strings are available from the corresponding author on request.

Study selection and data extraction

Records were screened in duplicate, first by title and abstract and then in full text, with disagreements resolved by consensus. Data were extracted independently by two reviewers into a piloted form and then reconciled. Extracted items were study design, country and period, funding, sample size, age and sex, tumour type, ASA class, duration of surgery, induction and maintenance regimens, volatile agent, opioid, use of depth-of-anaesthesia monitoring, outcome definitions and scales, and event counts or means with standard deviations for each arm. Trials

that reported a continuous outcome only as a median were not pooled for that outcome and are described narratively.

Harmonisation of brain relaxation

Trials reported brain relaxation on 3-point and 4-point surgeon-rated scales. Before analysis we defined a single dichotomy, using the definition applied by Liu and colleagues as the reference[3]: a relaxed brain or mild swelling was classified as satisfactory, and moderate or severe swelling, or swelling requiring intervention, as unsatisfactory. Each trial's categories were mapped to this dichotomy before pooling, and the mapping was cross-checked against the counts in Liu and colleagues' forest plot where the same trial appeared in both. Two trials needed a different cut. Petersen 2003 used a 3-level scale in which only 'no swelling' could be counted as satisfactory[7]. Magni 2005 reported only severe swelling needing decompression, so all other grades were counted as satisfactory[8]. Both were examined in sensitivity analyses.

Multi-arm trials

In trials with more than one volatile arm, the volatile arms were combined into one group compared with the shared TIVA group, to avoid double-counting TIVA participants. Bastola 2015 contributed combined sevoflurane and desflurane arms[9]. Citerio 2012 contributed combined sevoflurane-fentanyl and sevoflurane-remifentanil arms[10]. Petersen 2003 contributed combined isoflurane and sevoflurane arms[7]; because this mixed group could not be assigned to a single agent, it was analysed post hoc as a separate subgroup. In Todd 1993 the fentanyl-nitrous oxide arm was excluded, and in Talke 2002 the combined isoflurane-propofol arm was excluded[11,12].

Risk of bias

Risk of bias in randomised trials was assessed with the Cochrane RoB 2 tool across five domains: the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result[13]. Each domain and the

overall judgement were rated low risk, some concerns or high risk; domains for which the report gave too little information were recorded as no information, and judgements recorded as between low risk and some concerns were classified as some concerns. Non-randomised cohorts were assessed with ROBINS-I[14].

Statistical analysis

Dichotomous outcomes were pooled as risk ratios and continuous outcomes as mean differences, with 95% confidence intervals, using random-effects models with between-study variance (τ^2) estimated by restricted maximum likelihood. A risk ratio above 1 for brain relaxation, and below 1 for PONV or emergence agitation, favours TIVA; a negative mean difference in time to extubation favours TIVA. Heterogeneity was quantified with I^2 and τ^2 and tested with Cochran's Q[15]. Where three or more trials contributed, a 95% prediction interval was calculated. For PONV, the absolute effect was estimated by applying the pooled risk ratio and its confidence limits to the risk observed in the volatile arms.

Because every outcome was reported by few trials, we calculated Hartung-Knapp confidence intervals for every pooled outcome, together with the ad hoc variance correction (modified Hartung-Knapp), which prevents the adjusted variance estimate from falling below the conventional estimate, as a post hoc sensitivity analysis[5,16]. A result was interpreted as robust only if the conventional and modified Hartung-Knapp intervals agreed.

The primary outcome was analysed by volatile agent (sevoflurane or desflurane; isoflurane; mixed arm), with a test for subgroup differences. Sensitivity analyses for the primary outcome excluded, in turn, Petersen 2003 (strict cut and mixed arm), Magni 2005 (lenient cut), and Magni 2007, whose population included a broader range of intracranial surgery[17]; applied a strict grade I-only cut to Bastola 2015; and omitted each trial in turn. Robustness of the PONV result was examined by omitting each trial in turn. Publication bias was not assessed formally because fewer than ten trials contributed to each outcome. Analyses

were performed in R with the meta package[18], and the pooled estimates were reproduced independently from the extracted counts.

Certainty of evidence

Certainty of evidence was assessed for each outcome with GRADE, considering risk of bias, inconsistency, indirectness, imprecision and publication bias[19]. Evidence from randomised trials started at high certainty.

Results

Study selection

The database search identified 34 records. All 34 were screened and one was excluded. Of 33 reports sought, four could not be retrieved. Twenty-nine full texts were assessed and 13 were excluded: seven for an ineligible population or procedure (aneurysm surgery, traumatic brain injury, transsphenoidal or non-neurosurgical procedures), three because they were reviews or reported no extractable data, and three for an ineligible intervention or comparator (Fig. 1). Sixteen studies were included: 14 RCTs and two non-randomised cohorts. Eleven RCTs contributed to at least one meta-analysis.

Study characteristics

The nine trials contributing to the primary outcome were published between 1993 and 2023 and randomised between 68 and 411 patients each, 1,436 in total (Table 1)[7-11,17,20-22]. Six compared TIVA with sevoflurane or desflurane, two with isoflurane, and one (Petersen 2003) with a combined isoflurane and sevoflurane arm. Opioid co-administration varied between remifentanil and fentanyl. Two trials were multicentre (Citerio 2012, Lauta 2010).

Two further RCTs contributed only to time to extubation. Marković-Božić 2016 compared propofol-remifentanil with sevoflurane-remifentanil in 40 patients, with inflammatory cytokines as the primary outcome[23]. Necib 2014 (the PROMIFLUNIL trial)

compared bispectral index-guided propofol-remifentanil with sevoflurane-sufentanil in 66 analysed patients, with time to extubation as the primary outcome[24]. Three RCTs reported no outcome in a poolable form and were summarised narratively. Talke 2002 compared propofol with isoflurane and reported recovery only graphically, without significant differences[12]. Jansen 1999 compared jugular bulb oxygen saturation during propofol and isoflurane-nitrous oxide anaesthesia[25], and Bonhomme 2009 compared acid-base status and haemodynamic stability with propofol and sevoflurane[26]; neither reported patient-centred outcomes of this review.

Two trials reported time to extubation only as medians and were not pooled for that outcome. In Jiang 2023, extubation was later with TIVA than with desflurane (median 17 versus 13 min)[22]; in Lauta 2010 it was 10 versus 8 min with sevoflurane[20].

Two retrospective cohorts were summarised narratively. In 159 patients undergoing primary brain tumour excision, propofol-based anaesthesia was associated with shorter time to extubation than isoflurane (29.5 versus 39.6 min) and numerically less PONV (26% versus 30%)[27]. In 263 glioblastoma operations, TIVA was associated with shorter operative time and a shorter stay in the recovery room than sevoflurane[28]. Both cohorts were at serious risk of bias on ROBINS-I, mainly from confounding by period of practice and clinician choice of technique.

Risk of bias

All 14 trials had some concerns overall, and none was at high risk in any domain (Fig. 2). All had some concerns for deviations from intended interventions, because the anaesthetist cannot be blinded to the technique. The randomisation process was at low risk in five trials and raised some concerns in nine, mostly because allocation concealment was not described. Missing outcome data were at low risk in two trials, raised some concerns in nine and could not be judged in three. Measurement of the outcome was at low risk in four trials and raised

some concerns in ten; this matters for the primary outcome, because brain relaxation is rated by a surgeon who in most trials was not reported to be blinded. Only Jiang 2023, which was prospectively registered, was at low risk for selection of the reported result.

Primary outcome: brain relaxation

Nine RCTs with 1,436 patients (623 TIVA, 813 volatile) reported brain relaxation (Fig. 3). Satisfactory relaxation was similar with both techniques: 502 of 623 patients (81%) with TIVA and 609 of 813 (75%) with volatile anaesthesia (RR 1.04, 95% CI 0.99-1.09; I^2 0%, τ^2 0, p for heterogeneity 0.49). The modified Hartung-Knapp interval was 0.98-1.10, and the 95% prediction interval was 0.98-1.10, suggesting that large relative differences are unlikely in comparable settings.

In the sevoflurane or desflurane subgroup (six trials, 1,171 patients) the pooled RR was 1.03 (95% CI 0.98-1.08; I^2 0%), and in the two isoflurane trials (148 patients) 1.12 (0.86-1.45; I^2 0%). Petersen 2003 (117 patients), analysed separately because its volatile arm combined isoflurane and sevoflurane and its strict cut counted only 'no swelling' as satisfactory, showed a larger effect (RR 1.50, 1.12-2.02)[7]. The test for subgroup differences gave $p = 0.04$, driven by Petersen 2003: there was no clear evidence of a subgroup difference between trials using sevoflurane or desflurane and those using isoflurane alone ($p = 0.53$).

The result was stable in every sensitivity analysis. Excluding Petersen 2003 gave RR 1.03 (0.98-1.08); excluding Magni 2005 gave 1.04 (0.99-1.09); excluding both gave 1.03 (0.98-1.08); and excluding Magni 2007 gave 1.04 (0.99-1.09). Applying a strict grade I-only cut to Bastola 2015 gave 1.05 (1.00-1.11), with a modified Hartung-Knapp interval of 0.99-1.12. Omitting each trial in turn gave pooled estimates between 1.03 and 1.05, all with intervals including 1 or touching it.

Postoperative nausea and vomiting

Three RCTs with 601 patients reported PONV (Fig. 4)[10,11,22]. PONV occurred in 19 of 233 patients (8%) with TIVA and 82 of 368 (22%) with volatile anaesthesia (RR 0.38, 95% CI 0.23-0.60; I^2 0%, τ^2 0). Applied to the 22% risk in the volatile arms, this corresponds to about 14 fewer patients with PONV per 100 treated with TIVA (95% CI 9 to 17 fewer), a point estimate for the number needed to treat of about 7 under the conventional model. The direction was the same in all three trials: Jiang 2023 (6/55 versus 16/55), Citerio 2012 (12/138 versus 64/273) and Todd 1993 (1/40 versus 2/40). Citerio 2012 carried 66% of the weight. Omitting each trial in turn gave RRs between 0.37 and 0.39; omitting Citerio 2012 widened the interval to 0.17-0.87. With only three trials, however, the modified Hartung-Knapp interval crossed 1 (0.13-1.06) and the prediction interval was 0.02-8.04. The finding is therefore best read as a consistent signal favouring TIVA, not a definitive benefit.

Time to extubation

Three RCTs with 226 patients reported time to extubation as means with standard deviations (Fig. 5)[8,23,24]. The pooled estimate showed little difference (mean difference 0.15 min, 95% CI −0.58 to 0.87; I^2 0%), and the modified Hartung-Knapp interval (−1.45 to 1.74) was consistent with a small difference in either direction. Magni 2005 carried 85% of the weight. The two trials that reported only medians, both large, found slightly faster extubation with the volatile agent[20,22].

Emergence agitation

Two RCTs with 521 patients reported emergence agitation (Fig. 6)[10,22]. Agitation occurred in 19 of 193 patients (10%) with TIVA and 17 of 328 (5%) with volatile anaesthesia (RR 1.68, 95% CI 0.88-3.20; I^2 0%). The Hartung-Knapp interval was 0.26-10.84, and with only two trials the modified interval was uninformative (0.03-109.6). An important difference in either direction cannot be excluded. All pooled results are summarised in Table 2.

Certainty of evidence

Certainty was moderate for brain relaxation, rated down once for risk of bias; low for PONV and time to extubation, rated down for risk of bias and imprecision; and very low for emergence agitation, rated down for risk of bias and very serious imprecision (Table 3).

Discussion

Principal findings

In this meta-analysis of randomised trials restricted to brain tumour and supratentorial mass-lesion craniotomy, propofol-based TIVA and volatile anaesthesia produced comparable brain relaxation, with no detected statistical heterogeneity and a narrow prediction interval. Pooled extubation times showed little difference. TIVA was associated with less PONV; this was consistent across all three trials but not robust to small-sample adjustment. Evidence on emergence agitation was too sparse for conclusions.

Brain relaxation

The physiological case for TIVA in patients with mass effect is strong, and better surgical conditions with propofol would be a reasonable expectation. Our results suggest that, at the doses used in these trials, any advantage is small or absent. The pooled estimate was close to 1, the prediction interval excluded a difference of more than about 10% in either direction, and the pooled estimate remained stable across sensitivity analyses. Most of the weight came from trials using sevoflurane or desflurane at clinical concentrations, typically around 1 MAC or below, a range in which cerebral vasodilation is modest and cerebrovascular reactivity to carbon dioxide is preserved, so that moderate hyperventilation can offset any increase in cerebral blood volume.

The only clear difference came from Petersen 2003, which used a strict definition of satisfactory relaxation and a volatile arm combining isoflurane and sevoflurane. No clear

subgroup difference was identified between isoflurane and sevoflurane or desflurane, so the Petersen finding cannot confidently be attributed to the volatile agent. A more likely explanation is that a strict cut magnifies small differences in swelling that a surgeon would not consider clinically important. Petersen 2003 also measured subdural pressure directly and found lower pressure with propofol, which is consistent with physiology but did not translate into a difference in clinically rated relaxation in the other trials[7].

Our findings agree with Chui and colleagues, who found no clear evidence of a difference in clinically important brain swelling in elective craniotomy[1]. Liu and colleagues reported less brain swelling with propofol across a broader craniotomy population[3], and Intarakhao and colleagues ranked propofol highest for brain relaxation[4]. Several differences may explain the discrepancy. We restricted inclusion to tumour and mass-lesion surgery; we harmonised all scales to one dichotomy rather than analysing swelling on the scale reported or as a standardised mean difference; and we analysed the mixed-arm trial separately. In our data the apparent advantage of propofol depended on a single trial with a strict definition of relaxation.

Postoperative nausea and vomiting

In neurosurgical patients, PONV has implications beyond patient comfort. Retching and vomiting can raise intra-abdominal and intrathoracic pressures, impede cerebral venous drainage and cause transient increases in intracranial pressure (ICP); systemic arterial pressure may also rise. These physiological stresses are particularly concerning in the early hours after tumour resection, when intracranial compliance may be reduced by residual oedema and haemostasis at the resection bed is vulnerable[29]. Although reducing PONV could theoretically mitigate these risks, the included trials do not establish whether anaesthetic choice reduces postoperative ICP elevations, haematoma or neurological deterioration. Vomiting may also increase aspiration risk in patients with impaired consciousness or bulbar function, delay enteral medication such as anticonvulsants and steroids, and complicate early neurological

assessment. In the volatile arms of the trials reviewed here, PONV affected more than one patient in five.

Against that background, the size and consistency of the effect matter. Applied to the observed risk, the pooled estimate corresponds to about 14 fewer patients with PONV for every 100 anaesthetised with TIVA, or one patient spared PONV for about every seven treated. All three trials pointed the same way, with no detected statistical heterogeneity, across different decades, volatile agents and opioid regimens. The effect is also expected mechanistically: propofol has intrinsic antiemetic activity, and avoiding volatile agents is one of the most effective single measures for PONV prevention[30,31]. The relative reduction we found (about 60%) appears larger than in general surgical populations, which may reflect the high baseline risk after craniotomy.

We nevertheless rate the certainty as low, for reasons that are themselves informative. The estimate rests on three trials, one of which carries two-thirds of the weight; with the modified Hartung-Knapp correction the interval crossed 1; none of the trials was designed around PONV; and antiemetic prophylaxis was not standardised across them. In our view this combination, a large, consistent and biologically expected benefit on an outcome that matters to neurosurgical patients, resting on too few trials to be conclusive, is the most important evidence gap identified by this review, and the outcome on which the next trial should focus.

Emergence

Fast emergence is often cited as an advantage of volatile agents, particularly desflurane. The pooled mean difference in time to extubation was about nine seconds, but the pooled trials were small and used older regimens. The two large trials that reported medians, Lauta 2010 with sevoflurane and Jiang 2023 with desflurane, both found extubation a few minutes faster with the volatile agent[20,22]. Taken together, emergence is likely to be similar or slightly faster with modern volatile agents, by a margin of minutes that is unlikely to matter clinically but

may matter for theatre efficiency. The cohort data pointing the other way come from older isoflurane practice and carry a serious risk of confounding[27]. Emergence agitation was reported too rarely to support any conclusion.

Implications for practice

Both techniques are acceptable for elective brain tumour craniotomy with respect to surgical conditions, and the choice can rest on patient factors, team experience and local practice. The PONV findings support considering TIVA in patients at high risk of PONV, and in those in whom vomiting would be particularly hazardous, such as patients with large resection cavities, reduced consciousness or impaired airway protection. Where rapid extubation is the priority, sevoflurane or desflurane appears to provide comparable surgical conditions and may shorten emergence by a few minutes.

Designing the next trial

The differences, and the gaps, identified here point directly to how the next trial should be built. First, PONV should be the primary outcome. Taking the pooled risk in the volatile arms (22%) and a conservative target reduction to 13%, a relative reduction of 40% and smaller than our pooled estimate, a two-arm trial would need approximately 279 patients per arm for 80% power at a two-sided α of 0.05, or 620 patients in total allowing for 10% attrition; detecting a reduction to 15% would need approximately 1,072 patients, using a normal approximation for two independent proportions with equal allocation and the same attrition allowance. This is achievable in a multicentre neuroanaesthesia network and would help clarify whether the signal represents a clinically important benefit.

Second, the comparison must be protected from dilution and confounding. Antiemetic prophylaxis should be protocolised and stratified by a validated PONV risk score; PONV, vomiting episodes and rescue antiemetic use should be recorded at fixed windows (for example 0-2 h and 2-24 h) with a validated tool by assessors blinded to allocation; anaesthetic depth

should be guided by processed electroencephalography in both arms; and the opioid regimen should be the same in both arms, so that only the hypnotic differs.

Third, brain relaxation should be measured so that it can be pooled without assumptions: on a 4-point scale reported in full, scored at dural opening by a surgeon blinded to the technique, ideally with independent adjudication from intraoperative photographs and, where feasible, direct subdural pressure measurement. Fourth, the trial should include, or a dedicated trial should target, the patients in whom the physiological argument for TIVA is strongest: large supratentorial tumours with midline shift or marked peritumoural oedema, stratified by tumour volume. Fifth, emergence outcomes need common definitions, timed from the end of anaesthetic delivery to extubation and to obeying commands, with agitation scored on a validated sedation-agitation scale, and continuous outcomes should be reported as means with standard deviations as well as medians so that they can be pooled. Finally, trials should record outcomes that matter beyond the operating theatre, including postoperative haematoma, unplanned imaging, length of stay in recovery and hospital, patient-reported quality of recovery and cost, and should be registered prospectively with complete outcome definitions and share individual participant data.

Strengths and limitations

This review focused on a clinically coherent population, harmonised relaxation scales with a predefined rule cross-checked against published counts, handled multi-arm trials without double-counting, tested every pooled estimate with a small-sample correction, and explored the primary outcome in several sensitivity analyses demonstrating stability of the primary estimate. It has limitations. Harmonising 3-point and 4-point scales into one dichotomy may misclassify borderline ratings, and two trials needed a different cut. Anaesthetic protocols, opioid regimens and volatile agents varied over three decades, and depth-of-anaesthesia monitoring was reported in only some trials. All trials had some concerns for risk of bias,

mainly because clinicians were not blinded and outcome assessors were rarely reported to be blinded. Secondary outcomes rested on two or three trials each, and two large trials could not be pooled for extubation because they reported only medians. The search covered three sources and did not include Embase or CENTRAL, Google Scholar was used as the third source, and four reports could not be retrieved, so some trials may have been missed; the hand search of four earlier reviews partly mitigates this. A few trials enrolled mixed supratentorial mass-lesion populations rather than tumour-only cohorts, although excluding the broadest of these did not change the result.

Conclusions

In adults undergoing craniotomy for brain tumour or supratentorial mass lesion, propofol-based TIVA and volatile anaesthesia produce comparable brain relaxation, with moderate certainty, and little difference in pooled extubation times, although certainty for the latter remains low. The conventional pooled estimate suggests about 14 fewer patients with PONV per 100 treated with TIVA, a consistent and clinically relevant signal that rests on three trials and is not robust to small-sample adjustment. Both techniques remain clinically acceptable; TIVA is a reasonable choice when PONV risk is high, and an adequately powered trial with PONV as its primary outcome is now the priority.

References

1. Chui J, Mariappan R, Mehta J, Manninen P, Venkatraghavan L. Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis. Can J Anaesth. 2014;61:347-56.
2. Prabhakar H, Singh GP, Mahajan C, Kapoor I, Kalaivani M, Anand V. Intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery. Cochrane Database Syst Rev. 2016;9:CD010467.
3. Liu C-C, Chen I-W, Liu P-H, et al. Efficacy of propofol-based anesthesia against risk of brain swelling during craniotomy: a meta-analysis of randomized controlled studies. J Clin Anesth. 2024;92:111306.
4. Intarakhao P, Thiarawat P, Dhippayom T. Comparison of propofol and inhalational anaesthetics for brain relaxation in neurosurgery: a systematic review and network meta-analysis. Indian J Anaesth. 2025;69:770-8. doi:10.4103/ija.ija_189_25
5. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25.
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
7. Petersen KD, Landsfeldt U, Cold GE, et al. Intracranial pressure and cerebral hemodynamic in patients with cerebral tumors: a randomized prospective study of patients subjected to craniotomy in propofol-fentanyl, isoflurane-fentanyl, or sevoflurane-fentanyl anesthesia. Anesthesiology. 2003;98:329-36.
8. Magni G, Baisi F, La Rosa I, et al. No difference in emergence time and early cognitive function between sevoflurane-fentanyl and propofol-remifentanil in patients undergoing craniotomy for supratentorial intracranial surgery. J Neurosurg Anesthesiol. 2005;17:134-8.
9. Bastola P, Bhagat H, Wig J. Comparative evaluation of propofol, sevoflurane and desflurane for neuroanaesthesia: a prospective randomised study in patients undergoing elective supratentorial craniotomy. Indian J Anaesth. 2015;59:287-94.
10. Citerio G, Pesenti A, Latini R, et al. A multicentre, randomised, open-label, controlled trial evaluating equivalence of inhalational and intravenous anaesthesia during elective craniotomy. Eur J Anaesthesiol. 2012;29:371-9.
11. Todd MM, Warner DS, Sokoll MD, et al. A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy: propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology. 1993;78:1005-20.

12. Talke P, Caldwell JE, Brown R, et al. A comparison of three anesthetic techniques in patients undergoing craniotomy for supratentorial intracranial surgery. Anesth Analg. 2002;95:430-5.

13. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

14. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

15. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.

16. Röver C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. BMC Med Res Methodol. 2015;15:99.

17. Magni G, La Rosa I, Gimignani S, et al. Early postoperative complications after intracranial surgery: comparison between total intravenous and balanced anesthesia. J Neurosurg Anesthesiol. 2007;19:229-34.

18. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22:153-60.

19. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.

20. Lauta E, Abbinante C, Del Gaudio A, et al. Emergence times are similar with sevoflurane and total intravenous anesthesia: results of a multicenter RCT of patients scheduled for elective supratentorial craniotomy. J Neurosurg Anesthesiol. 2010;22:110-8.

21. Santra S, Das B. Subdural pressure and brain condition during propofol vs isoflurane-nitrous oxide anaesthesia in patients undergoing elective supratentorial tumour surgery. Indian J Anaesth. 2009;53:44-51.

22. Jiang Z, Wu Y, Liang F, et al. Brain relaxation using desflurane anesthesia and total intravenous anesthesia in patients undergoing craniotomy for supratentorial tumors: a randomized controlled study. BMC Anesthesiol. 2023;23:15. doi:10.1186/s12871-023-01970-z

23. Marković-Božić J, Karpe B, Potočnik I, et al. Effect of propofol and sevoflurane on the inflammatory response of patients undergoing craniotomy. BMC Anesthesiol. 2016;16:18. doi:10.1186/s12871-016-0182-5

24. Necib S, Tubach F, Peuch C, et al. Recovery from anesthesia after craniotomy for supratentorial tumors: comparison of propofol-remifentanil and sevoflurane-sufentanil (the PROMIFLUNIL trial). J Neurosurg Anesthesiol. 2014;26:37-44.

25. Jansen GFA, van Praagh BH, Kedaria MB, Odoom JA. Jugular bulb oxygen saturation during propofol and isoflurane/nitrous oxide anesthesia in patients undergoing brain tumor surgery. Anesth Analg. 1999;89:358-63.

26. Bonhomme V, Demoitie J, Schaub I, Hans P. Acid-base status and hemodynamic stability during propofol and sevoflurane-based anesthesia in patients undergoing uncomplicated intracranial surgery. J Neurosurg Anesthesiol. 2009;21:112-9.

27. Miura Y, Kamiya K, Kanazawa K, et al. Superior recovery profiles of propofol-based regimen as compared to isoflurane-based regimen in patients undergoing craniotomy for primary brain tumor excision: a retrospective study. J Anesth. 2012;26:721-7.

28. Kumaria A, Hughes M, Fenner H, et al. Total intravenous anaesthesia with propofol and remifentanil is associated with reduction in operative time in surgery for glioblastoma when compared with inhalational anaesthesia with sevoflurane. J Clin Neurosci. 2024;120:191-5.

29. Uribe AA, Stoicea N, Echeverria-Villalobos M, et al. Postoperative nausea and vomiting after craniotomy: an evidence-based review of general considerations, risk factors, and management. J Neurosurg Anesthesiol. 2021;33:212-20. doi:10.1097/ANA.0000000000000667.

30. Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350:2441-51.

31. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2020;131:411-48.

Figure legends

Fig. 1 PRISMA 2020 flow diagram of study identification, screening and inclusion.

Fig. 2 Risk of bias in the 14 included randomised trials (RoB 2). Top: judgement for each trial and domain. Bottom: proportion of trials in each category by domain. Judgements recorded as between low risk and some concerns are shown as some concerns.

Fig. 3 Satisfactory brain relaxation, TIVA versus volatile anaesthesia, by volatile agent. Risk ratios with 95% confidence intervals from random-effects (REML) models; values above 1 favour TIVA. The bar under the overall estimate is the 95% prediction interval. Petersen 2003 contributes a combined isoflurane and sevoflurane arm and is shown as its own group.

Fig. 4 Postoperative nausea and vomiting, TIVA versus volatile anaesthesia. Risk ratios with 95% confidence intervals from a random-effects (REML) model; values below 1 favour TIVA. Modified Hartung-Knapp interval for the pooled estimate 0.13-1.06.

Fig. 5 Time to extubation, TIVA versus volatile anaesthesia. Mean differences in minutes with 95% confidence intervals from a random-effects (REML) model; negative values favour TIVA. Modified Hartung-Knapp interval for the pooled estimate −1.45 to 1.74. Trials reporting medians only (Lauta 2010, Jiang 2023) are not shown.

Fig. 6 Emergence agitation, TIVA versus volatile anaesthesia. Risk ratios with 95% confidence intervals from a random-effects (REML) model; values below 1 favour TIVA. Hartung-Knapp interval 0.26-10.84.

Table 1. Characteristics of trials contributing to the primary outcome

Trial	Volatile comparator	Patients, TIVA / volatile	Outcomes contributed
Todd 1993 [11]	Isoflurane	40 / 40	Brain relaxation, PONV
Petersen 2003 [7]	Isoflurane and sevoflurane arms combined (analysed as mixed arm)	41 / 76	Brain relaxation
Magni 2005 [8]	Sevoflurane	60 / 60	Brain relaxation, time to extubation
Magni 2007 [17]	Sevoflurane	80 / 82	Brain relaxation
Santra 2009 [21]	Isoflurane	34 / 34	Brain relaxation
Lauta 2010 [20]	Sevoflurane	150 / 143	Brain relaxation
Citerio 2012 [10]	Sevoflurane (two sevoflurane arms combined)	138 / 273	Brain relaxation, PONV, emergence agitation
Bastola 2015 [9]	Sevoflurane and desflurane arms combined	25 / 50	Brain relaxation
Jiang 2023 [22]	Desflurane	55 / 55	Brain relaxation, PONV, emergence agitation

PONV, postoperative nausea and vomiting; TIVA, total intravenous anaesthesia. Two further RCTs contributed only to time to extubation (Marković-Božić 2016; Necib 2014), and three reported no poolable outcome (Talke 2002; Jansen 1999; Bonhomme 2009).

Table 2. Summary of pooled results

Outcome	Trials (patients)	Pooled effect (95% CI)	Modified HK 95% CI	I^2	Interpretation
Brain relaxation (primary)	9 (1,436)	RR 1.04 (0.99-1.09)	0.98-1.10	0%	Comparable relaxation; moderate certainty
PONV	3 (601)	RR 0.38 (0.23-0.60)	0.13-1.06	0%	Potential benefit with TIVA; sensitive to small-sample adjustment
Time to extubation	3 (226)	MD 0.15 min (−0.58 to 0.87)	−1.45 to 1.74	0%	Little difference in pooled estimates; low certainty
Emergence agitation	2 (521)	RR 1.68 (0.88-3.20)	0.03-109.6	0%	Inconclusive; substantial imprecision

CI, confidence interval; HK, Hartung-Knapp; MD, mean difference; PONV, postoperative nausea and vomiting; RR, risk ratio; TIVA, total intravenous anaesthesia. Prediction intervals: brain relaxation 0.98-1.10; PONV 0.02-8.04. RR above 1 for brain relaxation, below 1 for PONV and agitation, and a negative MD favour TIVA.

Table 3. Certainty of evidence (GRADE)

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
Brain relaxation	Serious	Not serious	Not serious	Not serious	Moderate
PONV	Serious	Not serious	Not serious	Serious	Low
Time to extubation	Serious	Not serious	Not serious	Serious	Low
Emergence agitation	Serious	Not serious	Not serious	Very serious	Very low

GRADE, Grading of Recommendations Assessment, Development and Evaluation; PONV, postoperative nausea and vomiting. Evidence from randomised trials starts at high certainty.

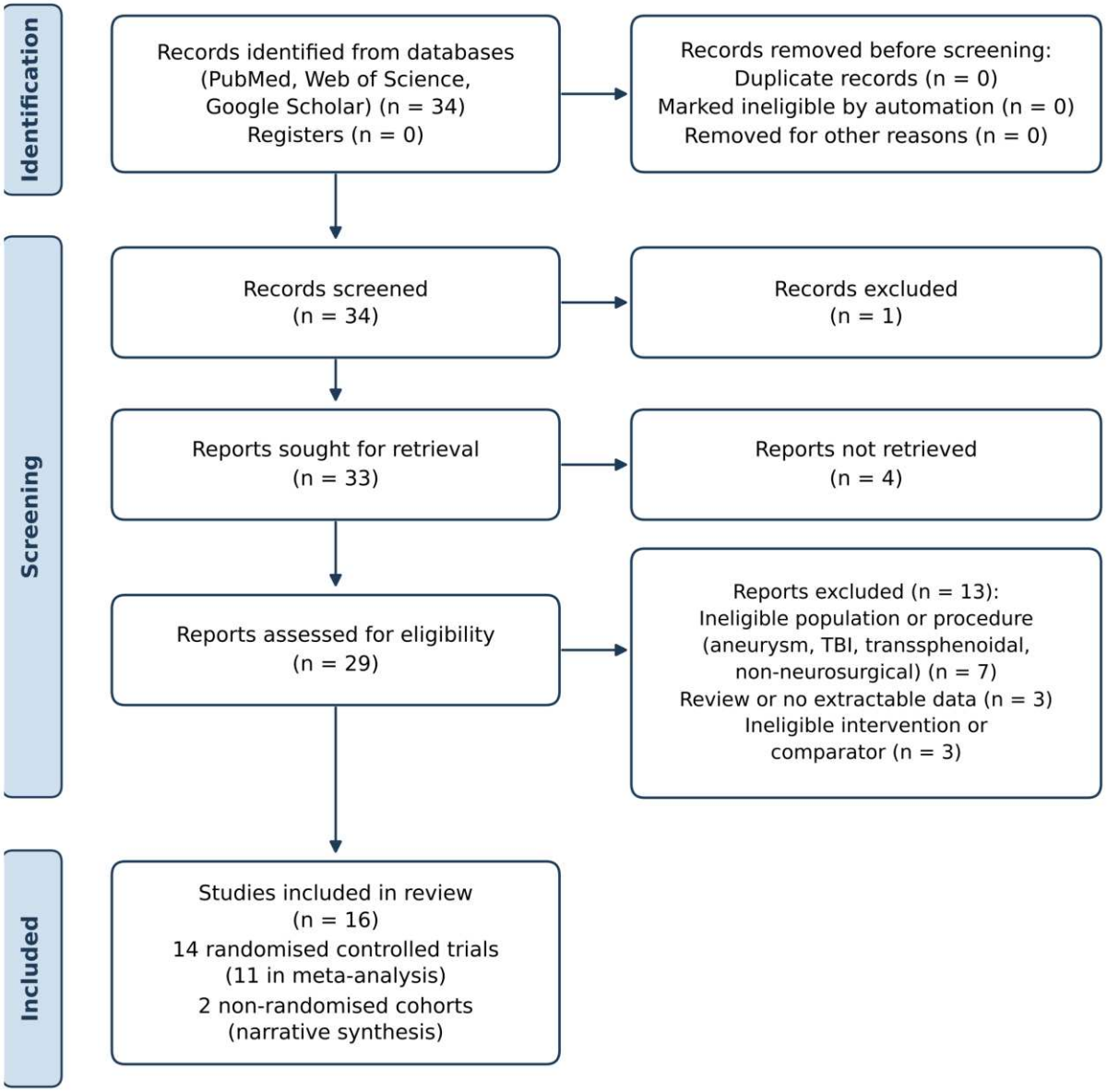


Fig. 1 PRISMA 2020 flow diagram of study identification, screening and inclusion.

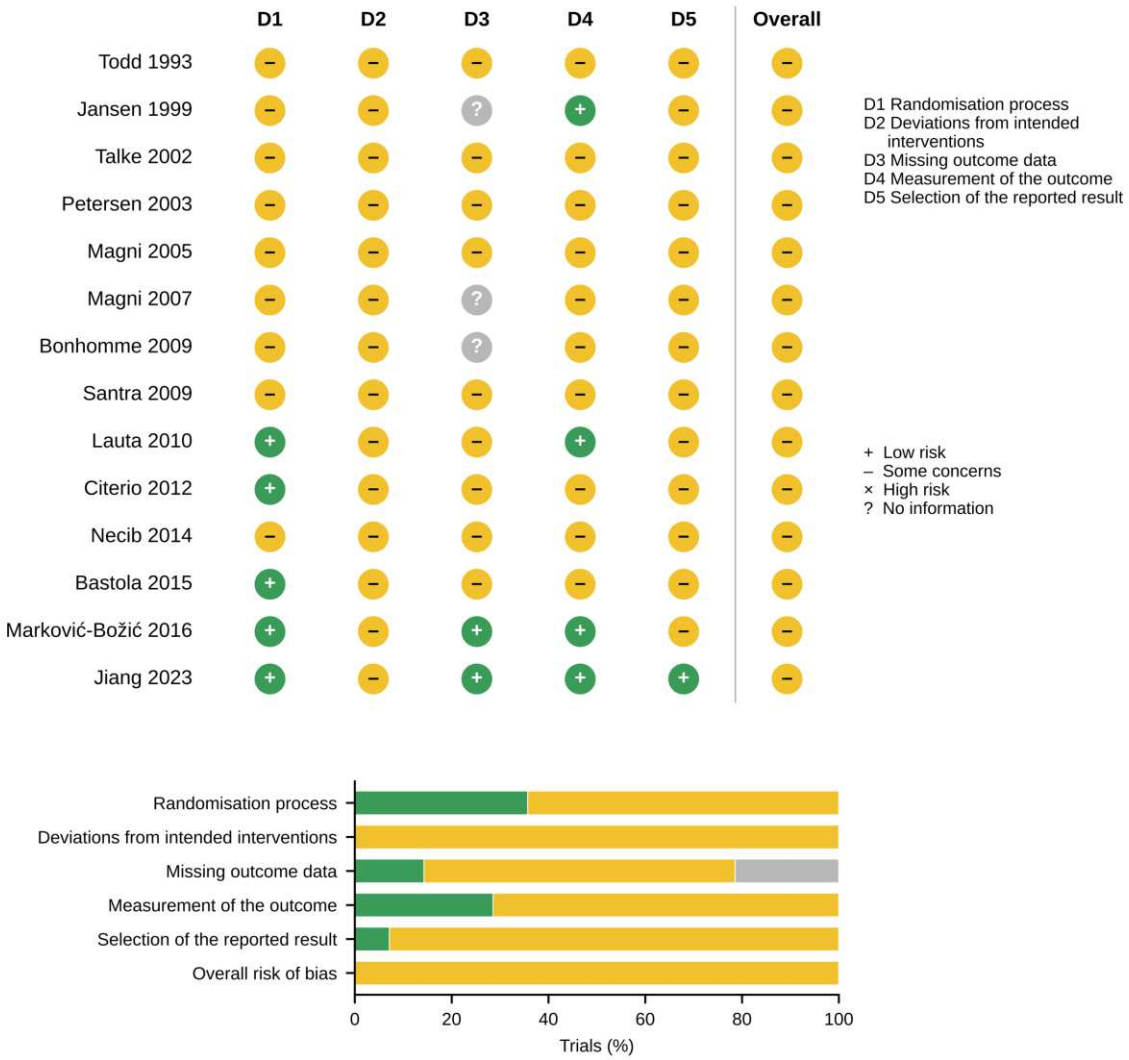


Fig. 2 Risk of bias in the 14 included randomised trials (RoB 2). Top: judgement for each trial and domain. Bottom: proportion of trials in each category by domain. Judgements recorded as between low risk and some concerns are shown as some concerns.

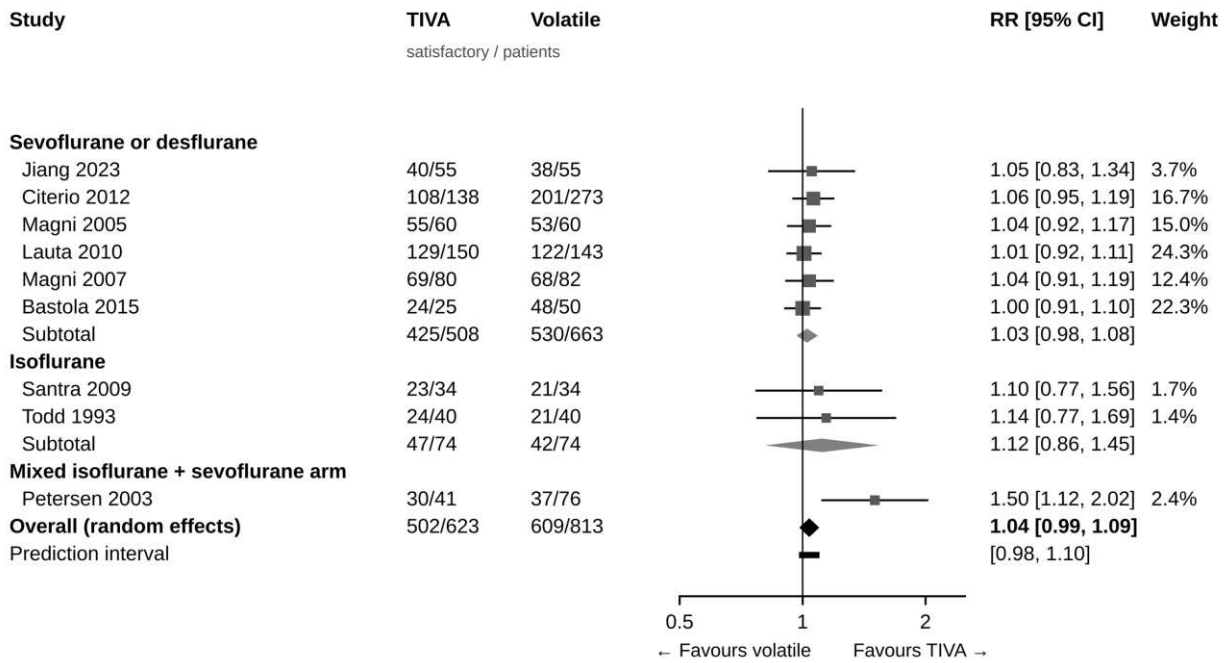


Fig. 3 Satisfactory brain relaxation, TIVA versus volatile anaesthesia, by volatile agent. Risk ratios with 95% confidence intervals from random-effects (REML) models; values above 1 favour TIVA. The bar under the overall estimate is the 95% prediction interval. Petersen 2003 contributes a combined isoflurane and sevoflurane arm and is shown as its own group.

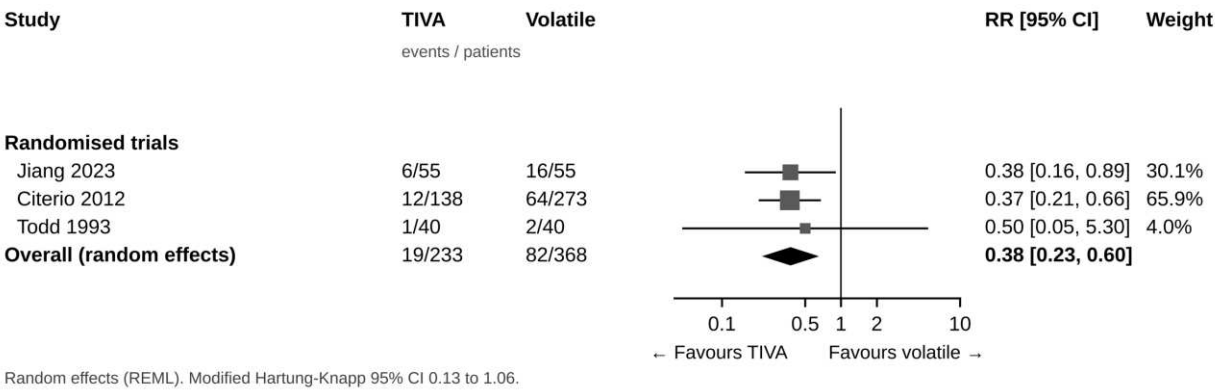


Fig. 4 Postoperative nausea and vomiting, TIVA versus volatile anaesthesia. Risk ratios with 95% confidence intervals from a random-effects (REML) model; values below 1 favour TIVA. Modified Hartung-Knapp interval for the pooled estimate 0.13-1.06.

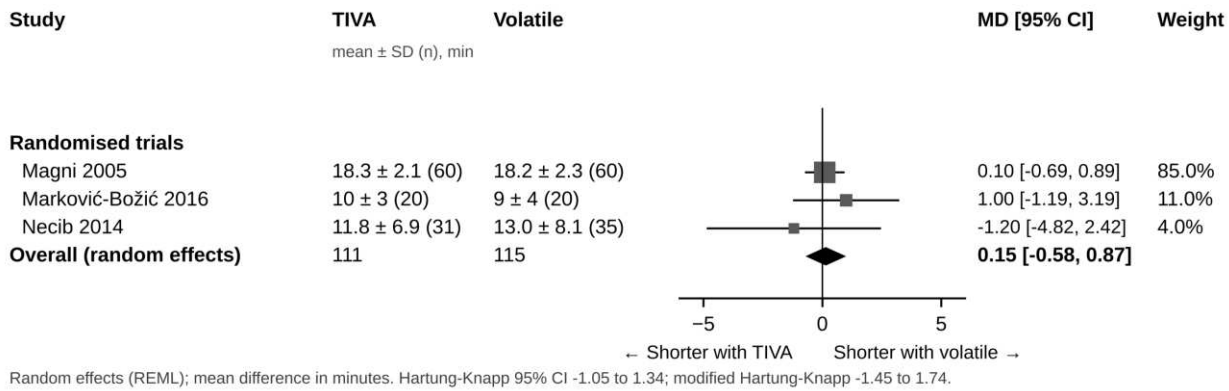


Fig. 5 Time to extubation, TIVA versus volatile anaesthesia. Mean differences in minutes with 95% confidence intervals from a random-effects (REML) model; negative values favour TIVA. Modified Hartung-Knapp interval for the pooled estimate −1.45 to 1.74. Trials reporting medians only (Lauta 2010, Jiang 2023) are not shown.

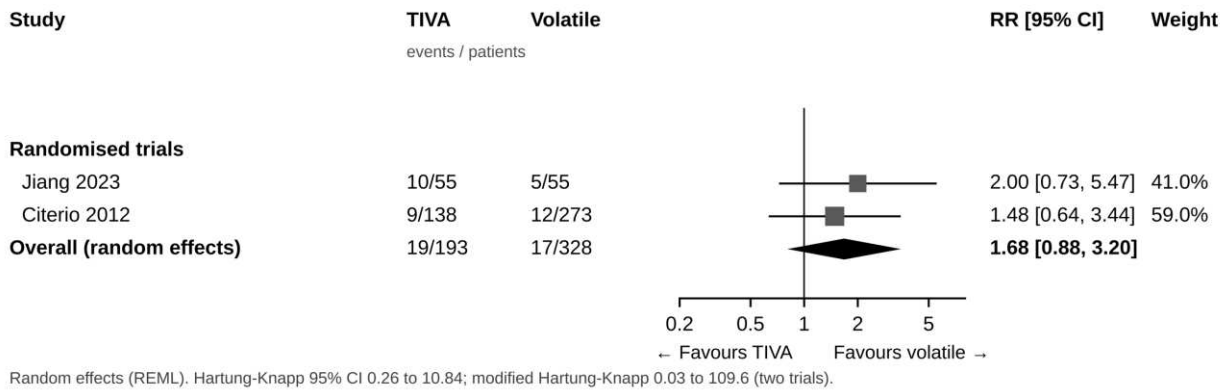


Fig. 6 Emergence agitation, TIVA versus volatile anaesthesia. Risk ratios with 95% confidence intervals from a random-effects (REML) model; values below 1 favour TIVA. Hartung-Knapp interval 0.26-10.84.