ORIGINAL ARTICLE

Intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery: A Cochrane systematic review

Hemanshu Prabhakar, Gyaninder P. Singh, Charu Mahajan, Indu Kapoor, Mani Kalaivani[1], Vidhu Anand[2]

Abstract

Background: Early and rapid emergence from anaesthesia is desirable for most neurosurgical patients. With the availability of newer intravenous and inhalational anaesthetic agents, all of which have inherent advantages and disadvantages, we remain uncertain as to which technique may result in more rapid early recovery from anaesthesia. The objective of this review was to assess the effects of intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery. **Methods:** We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 6) in The Cochrane Library, MEDLINE via Ovid SP (1966 to June 2014) and EMBASE via Ovid SP (1980 to June 2014). We also searched specific websites, such as www.indmed.nic.in, www.cochrane-sadcct.org and www.clinicaltrials.gov (October 2014). We included randomised controlled trials (RCTs) that compared the use of intravenous anaesthetic agents such as propofol and thiopentone with inhalational anaesthetic agents such as isoflurane and sevoflurane for maintenance of general anaesthesia during brain tumour surgery. Primary outcomes were emergence from anaesthesia (assessed by time to follow verbal commands, in minutes) and adverse events during emergence, such as haemodynamic changes, agitation, desaturation, muscle weakness, nausea and vomiting, shivering and pain. Secondary outcomes were time to eye opening, recovery from anaesthesia using the Aldrete or modified Aldrete score (i.e., time to attain score ≥9, in minutes), opioid consumption, brain relaxation (as assessed by the surgeon on a 4- or 5-point scale) and complications of anaesthetic techniques, such as intraoperative haemodynamic instability in terms of hypotension or hypertension (mmHg), increased or decreased heart rate (beats/min) and brain swelling. We used standardised methods in conducting the systematic review, as described by the Cochrane Handbook for Systematic Reviews of Interventions. We used a fixed-effect model when we found no evidence of significant heterogeneity between studies, and a random-effects model when heterogeneity was likely. **Results:** We included 15 RCTs with 1833 participants. We determined that none of the RCTs were of high methodological quality. For our primary outcomes, pooled results from two trials suggest that time to emergence from anaesthesia, that is, time needed to follow verbal commands, was longer with isoflurane than with propofol (mean difference [MD] –3.29 min, 95%

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confidence interval [CI] –5.41—1.18, low-quality evidence), and time to emergence from anaesthesia was not different with sevoflurane compared with propofol (MD 0.28 min slower with sevoflurane, 95% CI – 0.56–1.12, four studies, low-quality evidence). Pooled analyses for adverse events suggest lower risk of nausea and vomiting with propofol than with sevoflurane (risk ratio [RR] 0.68, 95% CI 0.51–0.91, low-quality evidence) or isoflurane (RR 0.45, 95% CI 0.26–0.78) and greater risk of haemodynamic changes with propofol than with sevoflurane (RR 1.85, 95% CI 1.07–3.17), but no differences in the risk of shivering or pain. Pooled analyses for brain relaxation suggest lower risk of tense brain with propofol than with isoflurane (RR 0.88, 95% CI 0.67–1.17, low-quality evidence), but no difference when propofol is compared with sevoflurane. **Conclusions:** The finding of our review is that the intravenous technique is comparable with the inhalational technique of using sevoflurane to provide early emergence from anaesthesia. Adverse events with both techniques are also comparable. However, we derived evidence of low quality from a limited number of studies. The use of isoflurane delays emergence from anaesthesia. These results should be interpreted with caution. RCTs based on uniform and standard methods are needed.

Key words: Brain relaxation, inhalational anaesthetic, intravenous anaesthetic

INTRODUCTION

Brain tumour surgery usually is carried out with the patient under general anaesthesia. Over past years, both intravenous and inhalational anaesthetic agents have been used, but the superiority of one over the other is a topic of ongoing debate.[1-4] The goal of anaesthesia during any neurosurgical procedure is to achieve smooth induction of anaesthesia, stable intraoperative haemodynamics such as heart rate and blood pressure while maintaining appropriate cerebral oxygen supply, good operative conditions and smooth and rapid emergence from anaesthesia. The latter permits early neurological examination.[2,5,6] Early and rapid emergence from anaesthesia is desirable in most neurosurgical patients for early screening of potential complications, such as haematoma, cerebrovascular ischaemia, cerebral herniation, neurological deficits and tension pneumocephalus.[2] Early awakening is important as the residual effect of anaesthesia may give the false impression of a neurological deficit or may prevent early diagnosis of an impending intracranial problem.[2]

Several studies have shown that maintenance of anaesthesia with propofol, an intravenous anaesthetic agent, results in shorter emergence time following surgical procedures.[7,8] Propofol has many of the properties of an ideal agent for neurosurgical patients, with beneficial cerebral haemodynamic effects reducing cerebral blood flow (CBF), favourable pharmacokinetics and a high-quality recovery profile despite prolonged duration of infusion.[5] Propofol produces a dose-dependent reduction in both brain oxygen requirements and CBF.[9] It maintains cerebrovascular reactivity to carbon dioxide,[10] preserves autoregulation of arterial blood pressure[11] and reduces intracranial pressure.[12] All of these are desirable effects during anaesthesia for neurosurgical procedures. However, the availability of newer, less-soluble inhalational anaesthetic agents, such as sevoflurane and desflurane, has added a new dimension to recovery by allowing more rapid emergence and earlier discharge.[13]

Propofol is highly lipophilic and rapidly crosses the blood–brain barrier, resulting in rapid onset of action. Emergence from sedation is also rapid because of fast redistribution into peripheral tissues and metabolic clearance.[14] Anaesthesia for craniotomy must be conducted with emphasis on haemodynamic stability, sufficient cerebral perfusion pressure and avoidance of agents and procedures that increase intracranial pressure.[15] In patients with brain tumour who undergo craniotomy, propofol anaesthesia is associated with lower intracranial pressure and less cerebral swelling than are seen with volatile anaesthesia.[16] The potentially neuroprotective effects of this drug could be mediated by its antioxidant properties, which can play a role in apoptosis, ischaemia-reperfusion injury and inflammation-induced neuronal damage.[16]

Rapid emergence from anaesthesia is always desirable in neurosurgical patients. This allows early neurological assessment and prompts recognition of potential post-operative complications, such as haematoma formation and development of new neurological deficits. Rapid diagnosis and treatment of complications in these patients confer the advantage of reducing both morbidity and mortality, thereby shortening the duration of intensive care unit and hospital stay. This may improve clinical outcomes and may reduce the cost of care. Advantages of intravenous anaesthesia with propofol over inhaled anaesthesia have been intensively discussed as the topic of numerous studies with opposing results.[13] With the availability of newer intravenous and inhalational anaesthetic agents that have inherent advantages and disadvantages, we remain uncertain as to which technique may result in more rapid early recovery from anaesthesia. In this systematic review, we seek to explore the uncertainty arising from conflicting results reported by studies on this topic. The objective of this review was to assess the effects of intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that compared the use of intravenous anaesthetic agents such as propofol, thiopentone sodium or etomidate versus inhalational anaesthetic agents such as halothane, isoflurane, sevoflurane, enflurane or desflurane for maintenance of general anaesthesia during brain tumour surgery.

Types of participants

We included patients from all age groups except neonates (infants <28 days old) who received inhalational or intravenous anaesthesia during craniotomy for brain tumour.

Types of interventions

In our experimental group, we compared participants receiving intravenous anaesthetic agents (propofol, etomidate, thiopentone sodium) versus controls. Our control group included participants receiving inhalational anaesthetic agents such as halothane, isoflurane, enflurane, sevoflurane and desflurane. We excluded studies in which researchers used both inhalational and intravenous anaesthetic agents for maintenance of anaesthesia in the same participant during surgery.

Types of outcome measures

Primary outcomes

1. Emergence from anaesthesia (assessed by time to follow verbal commands), in minutes
2. Adverse events during emergence, such as haemodynamic changes, agitation, desaturation, muscle weakness, nausea and vomiting, shivering and pain.

Secondary outcomes

1. Time to eye opening, in minutes
2. Recovery from anaesthesia based on the Aldrete or Modified Aldrete score (i.e., time to attain score ≥9, in minutes)
3. Opioid consumption, in micrograms
4. Brain relaxation (as assessed by the surgeon on a 3- or 4-point scale). For 4-point scores, we dichotomised the outcome and considered scores of 1 and 2 as good and scores of 3 and 4 as Bad. For 3-point scales, we considered soft/adequate/no swelling and moderate swelling as good and tight/pronounced swelling as bad
5. Complications of anaesthetic techniques, such as intraoperative haemodynamic instability in terms of hypotension or hypertension (mmHg), increased or decreased heart rate (beats/min) and brain swelling.

Outcomes prioritised for GRADE assessment were:

1. Emergence from anaesthesia
2. Adverse events during emergence - haemodynamic changes
3. Adverse events during emergence - nausea and vomiting
4. Adverse events during emergence - shivering
5. Adverse events during emergence - pain
6. Recovery from anaesthesia; and
7. Brain relaxation.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 6) in The Cochrane Library [Appendix 1 for detailed search strategy], MEDLINE via Ovid SP [1966 to June 2014; Appendix 2] and EMBASE via Ovid SP [1980 to June 2014; Appendix 3].

We combined the MEDLINE search strategy with the Cochrane highly sensitive search filter for identifying RCTs.[17] We adapted the MEDLINE search strategy for searching other databases.

We applied no language restrictions. We reran the searches in all databases in March 2016, and when we update the review, we will deal with the two studies of interest found through this search.

Searching other resources

We searched for relevant ongoing trials on specific websites (October 2014):

1. www.indmed.nic.in
2. www.cochrane-sadcct.org
3. www.clinicaltrials.gov.

Data collection and analysis

Selection of studies

Using results of the above searches, we screened all titles and abstracts for eligibility. Two review authors (Hemanshu Prabhakar and Vidhu Anand) independently performed this screening. We obtained and assessed for relevance the full articles and abstracts of all potentially eligible RCTs identified through the pre-planned checklist. Each review author documented the reason for exclusion of each trial. We resolved disagreements between the two review authors by discussion with a third review author (Gyaninder P Singh), who decided on inclusion or exclusion of the studies in dispute. We compiled a list of all eligible trials. When additional information was required, Hemanshu Prabhakar contacted the first named author of relevant trials.

Data extraction and management

Two review authors (Charu Mahajan and Indu Kapoor) independently extracted data and assessed trial quality

using a standardised form. We resolved disagreements by discussion with a third review author (Hemanshu Prabhakar). We performed assessment as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.[18]

Assessment of risk of bias in included studies

We judged the quality of studies on the basis of the following quality domains:

1. Random sequence generation
2. Allocation concealment
3. Blinding and outcome assessment
4. Incomplete outcome data
5. Selective reporting
6. Any other bias.

We considered a trial as having low risk of bias if we assessed all domains as adequate. We considered a trial as having high risk of bias if we assessed one or more domains as inadequate or unclear.

We included a 'Risk of bias' table as part of the characteristics of included studies and a 'Risk of bias summary' figure, which detailed all judgements made for all studies included in the review [Figures 1 and 2].

Measures of treatment effect

We undertook the analysis using RevMan 5.3 software. We used risk ratios (RRs) to measure treatment effects for proportions (dichotomous outcomes) among primary and secondary outcomes. We converted continuous data to mean differences (MDs) using the inverse variance method and calculated an overall MD. We used a fixed-effect model when we found no evidence of significant heterogeneity between studies, and a random-effects model when heterogeneity was likely.[19] As an estimate of the statistical significance of a difference between experimental and control interventions, we calculated the RR and the MD between groups, along with 95% confidence intervals (CIs). We assumed a statistically significant difference between intervention and control groups when the 95% CI did not include the value of no differential effect.

Unit of analysis issues

We included in this review only RCTs with a parallel-group design.

Dealing with missing data

We performed quantitative analysis on an intention-to-treat basis and contacted trial authors to obtain any missing data. We analysed missing data by imputation using a best case and worst case scenario method. When data were insufficient, we considered the potential impact of the missing data when interpreting study results.

Assessment of heterogeneity

We did not perform meta-analysis when we suspected important clinical heterogeneity on examination of the included trials. We used the Q statistic to test statistical heterogeneity between trials and considered a $P \leq 0.05$ as indicating significant heterogeneity; we used the I^2 statistic to assess the magnitude of heterogeneity.[20] We considered I^2 >50% to indicate problematic heterogeneity between trials and carefully considered the value of any pooled analyses. We used a random-effects model for analysis with I^2 >30%.

Assessment of reporting biases

We planned to assess publication bias and small-study effects in a qualitative manner using a funnel plot. We planned to test for funnel plot asymmetry if we included more than ten studies in the meta-analysis. However, we did not include ten studies in the meta-analysis for any outcomes and could not create a funnel plot.

Data synthesis

We quantitatively reviewed and combined included data by intervention, outcome and population using Cochrane statistical software (RevMan 5.3). We synthesised data only in the absence of important clinical or statistical heterogeneity, and we expressed pooled estimates of the MD for continuous variables and the RR for proportions, as described above.

Subgroup analysis and investigation of heterogeneity

When appropriate, with obvious clinical or statistical (I^2 >50%) heterogeneity, we planned to consider subgroup analysis based on gender, location of the tumour, size of the tumour, types of opioids used, types of muscle relaxants used, use of local anaesthetic or use of nitrous oxide when data indicated heterogeneity on that basis.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the consistency of effect size measures in trials with low risk of bias versus those with high risk of bias,

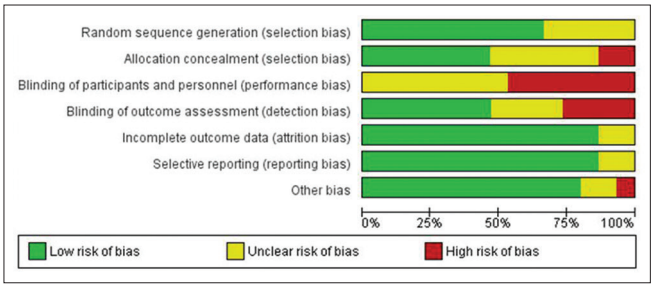

Figure 1: Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies

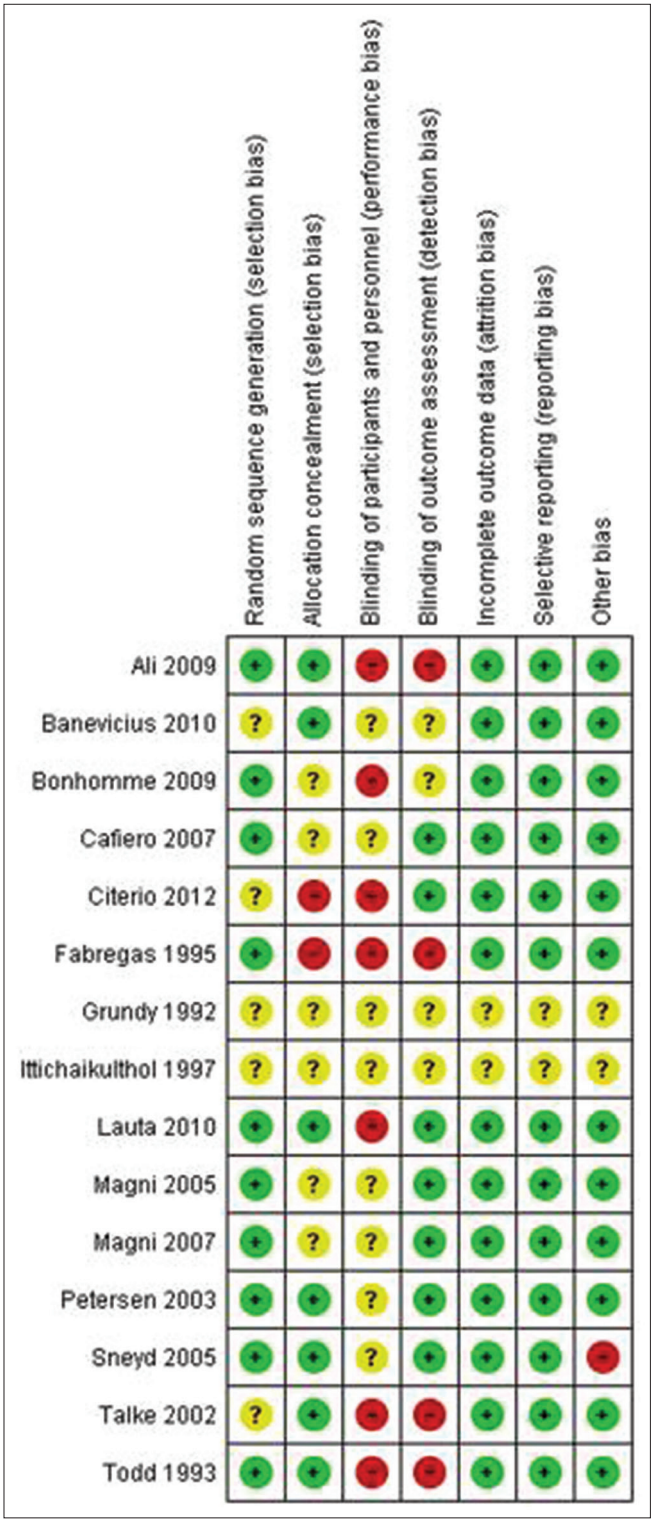

Figure 2: Risk of bias summary: Review authors' judgements about each risk of bias item for each included studies

and to use the imputation method described above to investigate the impact of missing data. We could not perform sensitivity analysis as all studies were nearly similar in terms of risk of bias. We found no studies of high methodological quality.

Summary of findings

In our review, we used the principles of the GRADE approach[21] to assess the quality of the body of evidence associated with specific outcomes (emergence from anaesthesia, adverse events (haemodynamic changes, nausea and vomiting, shivering, pain), recovery from anaesthesia and brain relaxation), and we constructed summary of findings (SoF) [Table 1] using GRADE software. When using the GRADE approach, one appraises the quality of a body of evidence on the basis of the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of a body of evidence considers within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias. For assessments of the overall quality of evidence for each outcome that included pooled data from RCTs only, we downgraded evidence from 'high quality' by one level for serious (and by two levels for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect or potential publication bias.

RESULTS

Description of studies

Included studies

We included 15 studies in our review [Figure 3].[2-4,6,15,22-31] All included studies were of parallel design. Propofol was the intravenous anaesthetic agent used in all studies except one, in which thiopentone sodium was used.[28] Isoflurane was the inhalational anaesthetic agent used in five studies,[4,6,27-29] sevoflurane was used in eight studies[2,3,23-26,30,31] and both sevoflurane and isoflurane were used in two studies.[15,22] We retrieved no studies in which enflurane, halothane and desflurane were used in the control group.

Of our primary outcomes, (1) emergence from anaesthesia was reported in nine studies[2-4,6,22,25,27,30,31] and (2) adverse events were reported in eight studies.[2-4,6,25,26,30,31] Among our secondary outcomes, (1) time to eye opening was reported in three studies;[27,29,31] (2) recovery from anaesthesia in five studies;[2,4,6,25,26] (3) opioid consumption in nine studies;[2,4,6,15,24-27,31] (4) brain relaxation in six studies[2,4,15,26,30,31] and (5) complications of anaesthetic techniques in four studies.[3,24,26,27]

Data from some studies were not reported in a manner suitable for pooling, including presentation of results in graphical form[6] or as medians with a range.[4,6] Others reported infusion rates for intravenous agents, but not total doses.[6,15,25]

Table 1: Propofol versus sevoflurane for rapid emergence from anaesthesia in patients undergoing brain tumour surgery

Patient or population: Patients with rapid emergence from anaesthesia after undergoing brain tumour surgery
Settings: Brain tumour surgery, anaesthetic techniques, emergence
Intervention: Propofol versus sevoflurane

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (grade)	Comments
	Assumed risk Control	Corresponding risk Propofol versus sevoflurane				
Emergence from anaesthesia, minutes	Mean emergence from anaesthesia in control groups in minutes	Mean emergence from anaesthesia in intervention groups was 0.28 min longer (0.56 lower to 1.12 higher)		384 (4 studies)	⊕⊕⊖⊖ Low[a,b]	This was assessed by time needed to follow verbal commands (min)
Adverse event-haemodynamic changes, number of events	Study population 120/1000 Moderate 122/1000	221/1000 (128-380) 226/1000 (131-387)	RR 1.85 (1.07-3.17)	282 (2 studies)	⊕⊕⊖⊖ Low[b,c]	These were noted at the time of emergence from anaesthesia
Adverse event-nausea and vomiting, number of events	Study population 192/1000 Moderate 138/1000	130/1000 (98-174) 94/1000 (70-126)	RR 0.68 (0.51-0.91)	952 (6 studies)	⊕⊕⊖⊖ Low[a,b]	These were noted at the time of emergence from anaesthesia
Adverse event-shivering, number of events	Study population 80/1000 Moderate 54/1000	107/1000 (71-160) 72/1000 (48-107)	RR 1.33 (0.88-1.99)	902 (5 studies)	⊕⊕⊖⊖ Low[a,b]	These were noted at the time of emergence from anaesthesia
Adverse event-pain, visual analogue scale	Study population 230/1000 Moderate 220/1000	207/1000 (163-262) 198/1000 (156-251)	RR 0.9 (0.71-1.14)	908 (5 studies)	⊕⊕⊖⊖ Low[a,b]	These were noted at the time of emergence from anaesthesia
Brain relaxation, scales or grades	Study population 197/1000 Moderate 228/1000	174/1000 (132-231) 201/1000 (153-267)	RR 0.88 (0.67-1.17)	867 (5 studies)	⊕⊕⊖⊖ Low[a,b]	Assessed by surgeon on a 4- or 5-point scale. Lower values indicate relaxed brain; higher values indicate tense brain

Grade working group grades of evidence-High quality: Further research is very unlikely to change our confidence in the estimate of effect, Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, Very low quality: We are very uncertain about the estimate. *The basis for the assumed risk (e.g., median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). [a]Downgraded one level owing to serious concerns about allocation, blinding and potential sources of other bias noted in the included studies, [b]Wide confidence intervals crossing the line of "no effect" were noted; we downgraded one level for imprecision, [c]Downgraded one level owing to serious concerns about allocation and performance bias noted in the included studies. CI: Confidence interval, RR: Risk ratio

Excluded studies

We excluded three studies. These studies were not RCTs as they included no control groups.[32-34] We suspected possible duplication of data in two studies.[32,33]

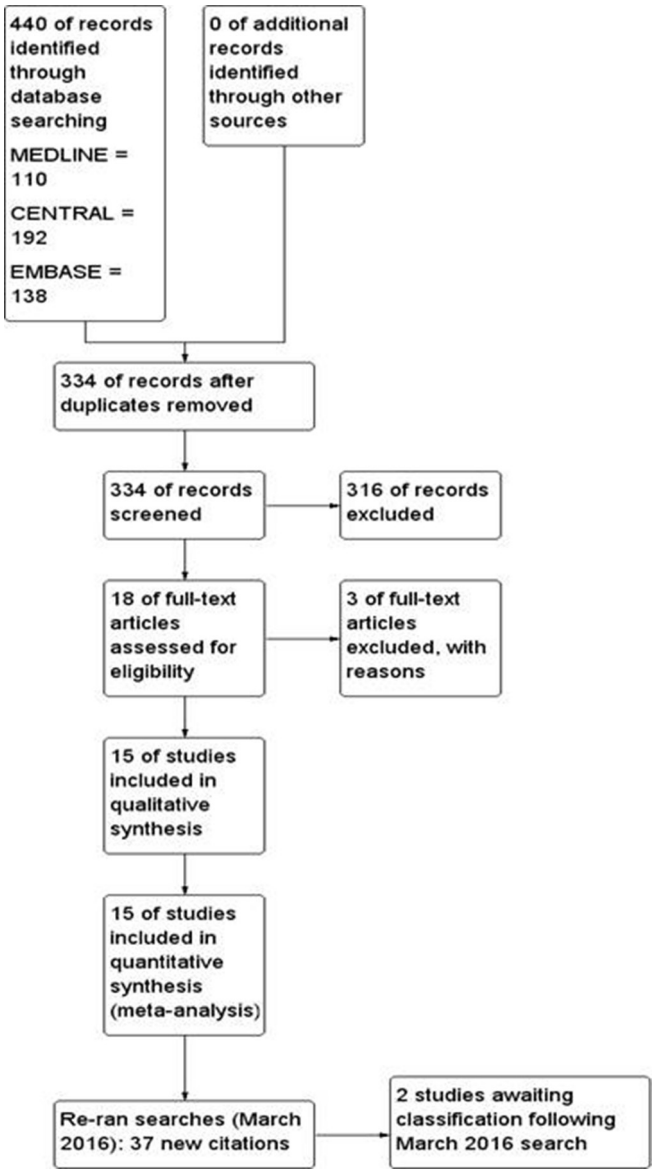

Figure 3: Study flow diagram

Ongoing studies

We found no ongoing studies.

Studies awaiting classification

Two studies are awaiting classification.[35,36]

Risk of bias in included studies

We assessed the risk of bias of included studies using the 'Risk of bias' tool developed by The Cochrane Collaboration.[18] This risk of bias tool invites judgements on five items for each trial (selection bias, performance bias, detection bias, attrition bias and reporting bias). All review authors independently assessed risk of bias for each study and resolved disagreements by discussion. We have shown in Figures 1 and 2 the characteristics of included studies used for our assessment of risk of bias. We found no studies of high methodological quality.

Allocation (selection bias)

Of the 15 included studies, only seven[2,4,6,15,22,23,31] reported allocation concealment. The remaining studies did not describe or did not perform allocation concealment.

Blinding (performance bias and detection bias)

Among the 15 included studies, we observed performance bias in six studies,[2,4,6,24,26,27] but the other studies did not report it. We noted detection bias in four studies[4,6,22,27] and found uncertain risk in four studies,[23,24,28,29] as they did not describe or perform blinding of outcome assessment.

Incomplete outcome data (attrition bias)

Thirteen studies reported data on all participants.[2-4,6,15,22-27,30] However, this information remained unclear in two studies,[28,29] as they were presented as abstracts, and we could not contact study authors, whose contact details were not available.

Selective reporting (reporting bias)

Thirteen studies reported data on all participants.[2-4,6,15,22-27,30] However, this information remained unclear in two studies,[28,29] as they were presented as abstracts, and we could not contact study authors, whose contact details were not available.

Other potential sources of bias

We could find no other potential sources of bias in 12 of the included studies.[2-4,6,15,22-27,30] One study[31] received funding from the pharmaceutical companies Abbott Laboratories Limited and AstraZeneca, and this could have introduced bias into the study. The source of the supply of anaesthetics remained unclear in two studies.[28,29]

EFFECTS OF INTERVENTIONS

Primary outcomes

Emergence from anaesthesia

Inhalational anaesthetic - sevoflurane

Four studies enrolling 384 participants reported emergence from anaesthesia (20.95% of total participants in this review).[3,22,25,30] We found data from two studies[2,31] to be skewed, so we excluded them from the analysis. We found no difference in time to emergence from anaesthesia with sevoflurane compared with propofol (MD 0.28 min shorter with sevoflurane; 95% CI – 0.56–1.12; I^2 = 22%; P = 0.52). We downgraded the quality of evidence from high to very low owing to risk of bias and imprecise results and the magnitude of effect. As studies were few, a funnel plot was inappropriate [Figure 4a].

Inhalational anaesthetic - isoflurane

Two studies enrolling 115 participants reported emergence from anaesthesia (6.27% of total participants in this review).[22,27] These two trials suggest that time to emergence from anaesthesia was shorter with propofol

than with isoflurane (MD – 3.29 min; 95% CI – 5.41––1.18; I^2 = 0%; P = 0.002). We noted no heterogeneity in these studies [Figure 4b].

Adverse events during emergence

Inhalational anaesthetic - sevoflurane

- Haemodynamic changes: Two studies enrolling 282 participants reported haemodynamic changes during emergence (15.4% of total participants in this review).[3,30] The incidence of haemodynamic disturbance was increased from 17 of 142 (11.9%) in the sevoflurane group to 31 of 140 (22.1%) in the propofol group (RR for haemodynamic changes with propofol 1.85; 95% CI 1.07–3.17; I^2 = 0%; P = 0.03). We downgraded the quality of evidence from high to low owing to risk of bias and imprecise results. We noted no heterogeneity in these studies
- Agitation: A single trial[26] enrolling 274 participants reported agitation during emergence (14.9% of total participants in this review). This trial suggests that the incidence of agitation was 7 of 136 (5.1%) in the sevoflurane group and 9 of 138 (6.5%) in the propofol group (P = 0.63)
- Nausea and vomiting: Six trials enrolling 952 participants reported nausea and vomiting during emergence (51.9% of total participants in this review).[2,3,25,26,30,31] These trials suggest that the incidence of nausea and vomiting decreased from 91 of 475 (19.2%) in the sevoflurane group to 62 of 477 (12.9%) in the propofol group (RR for nausea and vomiting with propofol 0.68; 95% CI 0.51–0.91; I^2 = 23%; P = 0.009). We downgraded the quality of evidence from high to low owing to risk of bias and imprecise results. As studies were few, a funnel plot was not appropriate
- Shivering: Five trials enrolling 902 participants reported shivering during emergence (49.2% of total participants in this review).[2,3,25,26,30] These trials suggest that the incidence of shivering increased from 36 of 449 (8%) in the sevoflurane group to 48 of 453 (10.6%) in the propofol group (RR for shivering with propofol 1.33; 95% CI 0.88–1.99; I^2 = 9%; P = 0.17). We downgraded the quality of evidence from high to low owing to risk of bias and imprecise results. As studies were few, we did not create a funnel plot, although it might have been useful
- Pain: Five trials enrolling 908 participants reported pain during emergence (49.53% of total participants in this review).[2,3,26,30,31] The incidence of pain decreased from 104 of 453 (22.9%) in the sevoflurane group to 93 of 455 (20.4%) in the propofol group (RR for pain with propofol 0.90; 95% CI 0.71–1.14; I^2 = 14%; P = 0.39). We downgraded the quality of evidence from high to low owing to risk of bias and imprecise results. As studies were few, we did not create a funnel plot although it might have been useful.

Inhalational anaesthetic - isoflurane

- Haemodynamic changes: A single trial[4] enrolling eighty participants reported haemodynamic changes during emergence (4.36% of total participants in this review). This trial suggests that the incidence of haemodynamic changes decreased from 37 of 40 in the isoflurane group to 35 of 40 in the propofol group
- Agitation: A single trial[4] enrolling eighty participants reported haemodynamic changes during emergence (4.36% of total participants in this review). This trial suggests that the incidence of haemodynamic changes increased from 0 of 40 in the

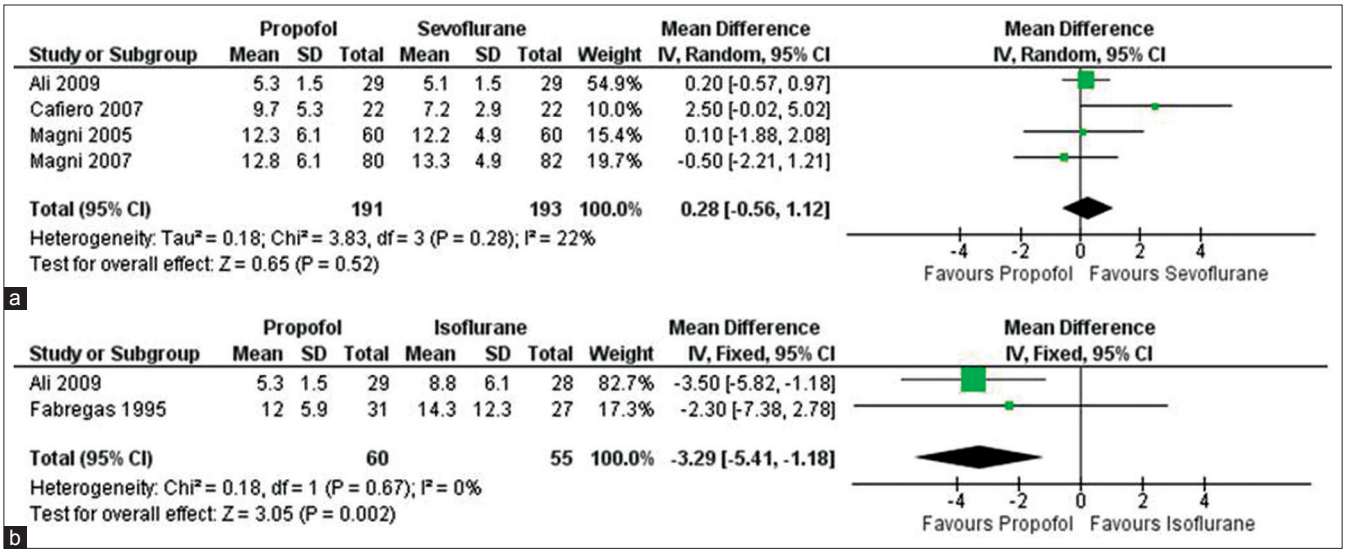

Figure 4: Forest plot of comparison (a) one propofol versus sevoflurane, outcome: Emergence from anaesthesia. (b) Forest plot of comparison: Two propofol versus isoflurane, outcome: Emergence from anaesthesia

isoflurane group to 3 of 40 in the propofol group.

- Nausea and vomiting: Two trials enrolling 120 participants reported nausea and vomiting during emergence (6.54% of total participants in this review).[4,6] These trials suggest that the incidence of nausea and vomiting decreased from 20 of 60 (33.3%) in the isoflurane group to 9 of 60 (30%) in the propofol group (RR for nausea and vomiting with propofol 0.45; 95% CI 0.26–0.78; I^2 = 0%; P = 0.005)
- Pain: A single trial[6] enrolling forty participants reported pain on emergence (2.18% of total participants in this review). This trial suggests that the incidence of pain increased from 13 of 20 in the isoflurane group to 16 of 20 in the propofol group.

Secondary outcomes

Time to eye opening

Inhalational anaesthetic - sevoflurane

A single trial[31] enrolling fifty participants reported time to eye opening (2.7% of total participants in this review). The mean (standard deviation) time to eye opening was 10.55 (7.39) minutes in the propofol group and 12.4 (6.22) minutes in the sevoflurane group.

Inhalational anaesthetic - isoflurane

Two trials enrolling 118 participants reported time to eye opening (6.44% of total participants in this review).[27,29] These trials suggest that time to eye opening was shorter with propofol (MD – 3.08; 95% CI – 5.48–-0.68; I^2 = 81%; P = 0.002). We noted significant heterogeneity.

Recovery from anaesthesia

Inhalational anaesthetic - sevoflurane

Three trials enrolling 598 participants (32% of the total) reported recovery from anaesthesia using an 11-point Aldrete scale (higher number means greater degree of recovery) expressed as time in minutes required to reach a score of 9.[2,25,26] We determined that meta-analysis was not appropriate as the data from all three studies were skewed.

Inhalational anaesthetic - isoflurane

No trial reported recovery from anaesthesia.

Opioid consumption

Inhalational anaesthetic - sevoflurane

Four trials enrolling 667 participants reported opioid (remifentanil) consumption in mcg/kg/min (36.38% of total participants in this review).[2,24,25,31] These trials suggest that remifentanil was infused at a higher rate with propofol than with sevoflurane (MD 0.87 mcg/kg/min; 95% CI 0.60–1.14; I^2 = 0%; P < 0.00001).

Inhalational anaesthetic - isoflurane

Two trials enrolling 138 participants reported total opioid (fentanyl) consumption in micrograms (7.53% of total participants in this review).[4,27] We noted significant heterogeneity between the two studies and did not perform a meta-analysis.

Brain relaxation

Inhalational anaesthetic - sevoflurane

Five trials enrolling 867 participants reported brain relaxation (47.29% of total participants in this review).[2,15,26,30,31] These trials suggest that the incidence of brain relaxation decreased from 85 of 431 (19.7%) in the sevoflurane group to 76 of 436 (17.4%) in the propofol group (RR for brain relaxation with propofol 0.88; 95% CI 0.67–1.17; I^2 = 0%; P = 0.38). We downgraded the quality of evidence from high to low owing to risk of bias and imprecise results.

Inhalational anaesthetic - isoflurane

Two trials enrolling 159 participants reported brain relaxation (8.67% of total participants in the review).[4,15] These trials suggest that the incidence of brain relaxation decreased from 39 of 78 (50%) in the isoflurane group to 26 of 81 (32%) in the propofol group (RR of brain relaxation with propofol 0.64; 95% CI 0.44–0.95; I^2 = 54%; P = 0.03).

Complications of anaesthetic technique

Inhalational anaesthetic - sevoflurane

- Hypertension: Four trials enrolling 769 participants reported hypertension during the intraoperative period (41.95% of total participants in the review).[3,24,26,30] These trials suggest that the incidence of hypertension increased from 120 of 382 (31.4%) in the sevoflurane group to 173 of 387 (44.7%) in the propofol group (RR of hypertension with propofol 1.93; 95% CI 1.47–2.53; I^2 = 67%; P < 0.00001). We noted significant heterogeneity
- Hypotension: Five trials enrolling 848 participants reported hypotension during the intraoperative period (46.26% of total participants in the review).[3,15,24,26,30] These trials suggest that the incidence of hypotension decreased from 153 of 420 (36.4%) in the sevoflurane group to 115 of 428 (26.8%) in the propofol group (RR of hypotension with propofol 0.72; 95% CI 0.56–0.95; I^2 = 73%; P = 0.02). We noted significant heterogeneity
- Tachycardia: Three trials enrolling 708 participants reported tachycardia during the intraoperative period (38.63% of total participants in the review).[3,26,30] These trials suggest that the incidence of tachycardia decreased from 34 of 351 (9.6%) in the sevoflurane group to 32 of 357 (8.9%) in the propofol group (RR of tachycardia with propofol 0.95; 95% CI 0.53–1.68; I^2 = 78%; P = 0.85). We noted significant heterogeneity
- Bradycardia: Three trials enrolling 708 participants reported bradycardia during the intraoperative period (38.63% of total participants in the review).[3,26,30] These trials suggest that the incidence of tachycardia

increased from 57 of 351 (16.2%) in the sevoflurane group to 56 of 357 (15.6%) in the propofol group (RR of bradycardia with propofol 1.03; 95% CI 0.74–1.42; I^2 = 0%; P = 0.87) We noted no heterogeneity.

Inhalational anaesthetic - isoflurane

- Hypertension: A single trial[6] enrolling forty participants reported hypertension (2.18% of total participants in the review). This trial suggests that the incidence of hypertension decreased from 12 of 20 in the isoflurane group to 4 of 20 in the propofol group
- Hypotension: Three trials[6,15,27] enrolling 177 participants reported hypotension (9.66% of total participants in the review). These trials suggest that the incidence of hypotension increased from 36 of 85 (42.3%) in the isoflurane group to 43 of 92 (46.7%) in the propofol group (RR of hypotension with propofol 0.79; 95% CI 0.51–1.25; I^2 = 18%; P = 0.32)
- Tachycardia: A single trial[6] enrolling forty participants reported tachycardia (2.18% of total participants in the review). This trial suggests that the incidence of tachycardia decreased from 12 of 20 in the isoflurane group to 4 of 20 in the propofol group
- Bradycardia: A single trial[6] enrolling forty participants reported bradycardia (2.18% of total participants in the review). This trial suggests that the incidence of bradycardia increased from 1 of 20 in the isoflurane group to 2 of 20 in the propofol group.

DISCUSSION

Evidence from ten studies with 1188 participants contributing data to our primary outcome shows that propofol (intravenous anaesthetic technique) administered to patients undergoing brain tumour surgery resulted in emergence from anaesthesia comparable with an inhalational technique when sevoflurane was used as the anaesthetic agent. However, propofol provides early emergence when compared with isoflurane as the inhalational agent. Pooled results from two trials suggest that time to emergence from anaesthesia was longer with isoflurane than with propofol (MD 3.29 min, 95% CI 5.41–1.18, low-quality evidence). Adverse events were comparable between the two anaesthetic techniques, except that haemodynamic changes were significantly greater in the intravenous anaesthetic group than in the inhalational group when sevoflurane was used. Nausea and vomiting was significantly less in the intravenous group. Pooled analyses for adverse events suggest lower risk of nausea and vomiting with propofol than with sevoflurane (RR 0.68, 95% CI 0.51–0.91, low-quality evidence) or isoflurane (RR 0.45, 95% CI 0.26–0.78) and greater risk of haemodynamic changes with propofol (RR 1.85, 95% CI 1.07–3.17), but no differences in the risk of shivering or pain.

A limited number of studies provided the evidence presented in this review. We found no significant difference in our primary outcome of emergence from anaesthesia when inhalational (sevoflurane) or intravenous (propofol) technique was used in patients undergoing surgery for brain tumour. Emergence was definitely delayed when isoflurane as the inhalational anaesthetic agent was compared with propofol as the intravenous anaesthetic agent. From limited studies, we were able to retrieve data on some clinically useful outcomes of adverse events such as nausea and vomiting, shivering and pain, recovery from anaesthesia, opioid consumption, brain relaxation and complications of the technique. The evidence produced by this review cannot be considered complete and should be interpreted with caution, with awareness that only intraoperative brain relaxation can be achieved more effectively with propofol than with sevoflurane.

We selected randomised studies for our review, and many of these studies did not report details of randomisation, allocation concealment and blinding. The overall methodological quality of these studies could not be considered good. The included studies did not have homogeneous populations, and heterogeneity was evident but was not clinically significant for some outcomes (adverse events, opioid consumption and brain relaxation). For the outcomes of emergence from anaesthesia, adverse events (nausea and vomiting, shivering and pain) and brain relaxation, the quality of evidence was low as is suggested by SoF [Table 1]. The main limiting factors that accounted for a decrease in quality among outcomes were risk of bias and inconsistency of results. Although we judged studies to be at varying risks of bias overall, the evidence for our main outcomes is drawn from studies at low risk of bias. We downgraded the quality of evidence to low or very low for the main outcomes owing mainly to risk of bias, inconsistency or imprecision. Subgroup analyses did not provide a convincing explanation for observed variation between study results.

In an attempt to minimise bias, we followed the guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions. Two review authors independently determined eligibility for inclusion and exclusion and assessed risk of bias of included studies. We made no decisions about the analysis of heterogeneity after seeing the study data. We made no assumptions about the class or intensity of interventions. We noted no limitations in our search process related to factors such as

challenges in optimising search terms/poor indexing of studies, limitations of databases used or grey literature sources accessed, restrictions on dates of search and incomplete correspondence with study investigators or sponsors. No relevant departures from the protocol could have affected our findings or introduced any risk of bias.

We are unaware of any systematic review conducted to compare intravenous with inhalational anaesthetic techniques in patients undergoing surgery for brain tumour. However, our review does support the findings of studies suggesting that intraoperative brain relaxation is better with intravenous techniques when propofol is the anaesthetic agent. At the same time, our review disproves the notion that inhalational techniques with isoflurane or sevoflurane result in rapid emergence from anaesthesia when compared with intravenous anaesthetic agents.

CONCLUSIONS

Implications for practice

Our review indicates that isoflurane delays emergence from anaesthesia, and sevoflurane has equivalent effects to propofol in terms of emergence from anaesthesia. At the same time, propofol has a better profile in terms of adverse events, as it causes less nausea and vomiting. Evidence from our review provides only limited support for use of the intravenous anaesthetic technique. Findings of our review suggest that the intravenous technique is not superior to the inhalational technique with sevoflurane in providing early emergence from anaesthesia were derived from a limited number of studies that generated evidence of low quality for desired outcomes. Therefore, the authors of this review cannot draw firm conclusions on the benefits of any technique over another for use during brain tumour surgery. We do not have sufficient evidence to determine the effects of intravenous over inhalational anaesthetic techniques for rapid emergence in patients undergoing brain tumour surgery.

Implications for research

Additional RCTs based on uniform and standard methods are needed. Investigators should follow proper methods of randomisation and blinding and should examine standardised and clinically relevant outcomes. RCTs should be adequately powered. A multicentre trial involving centres in different parts of the world would probably be useful. This article is based on a systematic review published by the Cochrane Collaboration.[37]

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Conflicts of interest

There are no conflicts of interest.

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APPENDICE

Appendix 1: Search strategy for CENTRAL

#1. MeSH descriptor: [Brain neoplasms] explode all trees.
#2. MeSH descriptor: [Neurosurgery] explode all trees.
#3. MeSH descriptor: [Neurosurgical procedures] explode all trees.
#4. (((Brain or neuro*) near (tumor* or neoplasm* or cancer or carcinoma or sarcoma)) and (operat* or surg*)).
#5. #1 or #2 or #3 or #4.
#6. MeSH descriptor: [Anesthetics, inhalation] explode all trees.
#7. MeSH descriptor: [Anaesthesia, inhalation] explode all trees.
#8. MeSH descriptor: [Anaesthesia, intravenous] explode all trees.
#9. ((Inhalat* and intraven*) near an?esth*).
#10. #6 or #7 or #8 or #9.
#11. #5 and #10.

Appendix 2: Search strategy for MEDLINE (Ovid SP)

1. Exp brain neoplasms/or neurosurgery/or neurosurgical procedures/or (((brain or neuro*) adj3 (tumor* or neoplasm* or cancer or carcinoma or sarcoma)) and (operat* or surg*)).mp.
2. Anesthetics, inhalation/or anaesthesia, inhalation/or anaesthesia, intravenous/or ((Inhalat* and intraven*) adj3 an?esth*).mp.
3. 1 and 2.
4. ((Randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
5. 3 and 4.

Appendix 3: Search strategy for EMBASE (Ovid SP)

1. exp brain tumor/or neurosurgery/or neurosurgery/or (((brain or neuro*) adj3 (tumor* or neoplasm* or cancer or carcinoma or sarcoma)) and (operat* or surg*)).mp. (181696).
2. Inhalation anesthetic agent/or inhalation anaesthesia/or intravenous anaesthesia/or ((Inhalat* and intraven*) adj3 an?esth*).mp. (28944).
3. (Randomized-controlled-trial/or randomization/or controlled-study/or multicenter-study/or phase-3-clinical-trial/or phase-4-clinical-trial/or double-blind-procedure/or single-blind-procedure/or (random* or cross?over* ormulticenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti, ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh. (4821980).
4. 1 and 2 and 3.