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Intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery (Review)

Prabhakar H, Singh GP, Mahajan C, Kapoor I, Kalaivani M, Anand V

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[Intervention Review]

Intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery

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ABSTRACT

Background

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 agent over the other is a topic of ongoing debate. 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.

Objectives

To assess the effects of intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery.

Search 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 reran the searches for all databases in March 2016, and when we update the review, we will deal with the two studies of interest found through this search that are awaiting classification.

Selection criteria

We included randomized 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.

Data collection and analysis

We used standardized methods in conducting the systematic review, as described by the *Cochrane Handbook for Systematic Reviews of Interventions*. Two review authors independently extracted details of trial methods and outcome data from reports of all trials considered eligible for inclusion. We performed all analyses on an intention-to-treat basis. 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. For assessments of the overall quality of evidence for each outcome that included pooled data from RCTs only, we downgraded the evidence from 'high quality' by one level for serious (or by two levels for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect or potential publication bias.

Main 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 minutes, 95% confidence interval (CI) -5.41 to -1.18, low-quality evidence), and time to emergence from anaesthesia was not different with sevoflurane compared with propofol (MD 0.28 minutes slower with sevoflurane, 95% CI -0.56 to 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 to 0.91, low-quality evidence) or isoflurane (RR 0.45, 95% CI 0.26 to 0.78) and greater risk of haemodynamic changes with propofol than with sevoflurane (RR 1.85, 95% CI 1.07 to 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 to 1.17, low-quality evidence), but no difference when propofol is compared with sevoflurane.

Authors' 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. Use of isoflurane delays emergence from anaesthesia. These results should be interpreted with caution. Randomized controlled trials based on uniform and standard methods are needed. Researchers should follow proper methods of randomization and blinding, and trials should be adequately powered.

PLAIN LANGUAGE SUMMARY

Anaesthesia with injectable versus gaseous anaesthetic agents for rapid awakening following surgery for brain tumour

Review question: We reviewed and compared evidence on the usefulness of injectable and gaseous techniques for rapid awakening from anaesthesia in people undergoing surgery for brain tumour.

Background: Brain tumour surgery is carried out most often with the patient asleep and with the use of injectable agents or gases. Injectable agents are delivered to the patient through the veins, whereas gases are delivered to the lungs through a tube placed in the windpipe. Advantages of one over the other approach remain questionable. Smooth and quick awakening after surgery is important for these patients so that their mental status may be assessed easily. We aimed to discover whether injectable techniques were better or worse than gaseous techniques.

Study characteristics: The evidence is current to June 2014. We included studies with participants from all age groups except neonates (infants less than 28 days old) who received injectable or gas techniques of anaesthesia during surgery for brain tumour. We reran the searches for all databases in March 2016 and found two studies that are awaiting classification. We will deal with them when we update this review.

Key results: We found 15 eligible studies with 1833 participants. These studies compared one injectable drug (propofol) with two gaseous drugs (sevoflurane and isoflurane). Although isoflurane was associated with slower awakening (about three and a half minutes) compared with propofol, researchers found no important differences between propofol and sevoflurane. In terms of adverse effects, propofol was less likely to cause nausea and vomiting than either gas anaesthetic (about half as likely) but was more likely to be associated with changes in blood pressure. Overall, we found that isoflurane is associated with slower awakening, but we have found no evidence of important differences between sevoflurane and propofol.

Quality of evidence

We found evidence of low quality for our main outcome of quick wakefulness, and the effect of injectable anaesthetic technique in people undergoing brain tumour surgery is uncertain. Further research and well-designed studies are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Propofol versus sevoflurane for rapid emergence from anaesthesia in patients undergoing brain tumour surgery

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 vs sevoflurane

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Propofol vs sevoflurane				
Emergence from anaesthesia, minutes	Mean emergence from anaesthesia in control groups in minutes	Mean emergence from anaesthesia in intervention groups was 0.28 minutes longer (0.56 lower to 1.12 higher)		384 (4 studies)	⊕⊕⊕⊕ Low a,b	This was assessed by time needed to follow verbal commands (in minutes).
Adverse event - haemodynamic changes, number of events	Study population		RR 1.85 (1.07 to 3.17)	282 (2 studies)	⊕⊕⊕⊕ Low b,c	These were noted at the time of emergence from anaesthesia.
	120 per 1000	221 per 1000 (128 to 380)				
	Moderate					
	122 per 1000	226 per 1000 (131 to 387)				
Adverse event - nausea and vomiting, number of events	Study population		RR 0.68 (0.51 to 0.91)	952 (6 studies)	⊕⊕⊕⊕ Low a,b	These were noted at the time of emergence from anaesthesia.
	192 per 1000	130 per 1000 (98 to 174)				
	Moderate					
	138 per 1000	94 per 1000 (70 to 126)				
	Study population		RR 1.33 (0.88 to 1.99)	902 (5 studies)	⊕⊕⊕⊕ Low a,b	

Adverse event - shivering, number of events	80 per 1000	107 per 1000 (71 to 160)				These were noted at the time of emergence from anaesthesia.
	Moderate					
	54 per 1000	72 per 1000 (48 to 107)				
Adverse event - pain, visual analogue scale	Study population		RR 0.9 (0.71 to 1.14)	908 (5 studies)	⊕⊕⊕⊖ Low a,b	These were noted at the time of emergence from anaesthesia.
	230 per 1000	207 per 1000 (163 to 262)				
	Moderate					
	220 per 1000	198 per 1000 (156 to 251)				
Brain relaxation, scales or grades	Study population		RR 0.88 (0.67 to 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.
	197 per 1000	174 per 1000 (132 to 231)				
	Moderate					
	228 per 1000	201 per 1000 (153 to 267)				

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio

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.

^aDowngraded one level owing to serious concerns about allocation, blinding and potential sources of other bias noted in the included studies.

^bWide confidence intervals crossing the line of "no effect" were noted; we downgraded one level for imprecision.

^cDowngraded one level owing to serious concerns about allocation and performance bias noted in the included studies.

BACKGROUND

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 (Engelhard 2006; Lauts 2010; Magni 2005; Todd 1993). 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 (Citerio 2009; Lauts 2010; Talke 2002).

Description of the condition

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 (Lauts 2010). 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 (Lauts 2010).

Description of the intervention

Several studies have shown that maintenance of anaesthesia with propofol, an intravenous anaesthetic agent, results in shorter emergence time following surgical procedures (Ozkose 2001; Visser 2001). 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 (Citerio 2009). Propofol produces a dose-dependent reduction in both brain oxygen requirements and CBF (Alkire 1995). It maintains cerebrovascular reactivity to carbon dioxide (Craen 1992), preserves autoregulation of arterial blood pressure (Stephan 1987) and reduces intracranial pressure (Pinaud 1990). 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 (Gupta 2004).

How the intervention might work

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 (McKeage 2003). Anaesthesia for craniotomy must be conducted with emphasis on haemodynamic stability, sufficient cerebral perfusion pressure (CPP) and avoidance of agents and procedures that increase intracranial pressure (Petersen 2003). 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 (Hans 2006). 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 (Hans 2006).

Why it is important to do this review

Rapid emergence from anaesthesia is always desirable in neurosurgical patients. This allows early neurological assessment and prompt recognition of potential postoperative complications, such as haematoma formation and development of new neurological deficits. Rapid diagnosis and treatment of complications in these patients confers 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 (Gupta 2004). 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.

OBJECTIVES

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 randomized 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 less than 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 dichotomized 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 prioritized 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 (Lefebvre 2011). 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 (see [Differences between protocol and review](#)).

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 (HP and VA) independently performed this screening. We obtained and assessed for relevance the full articles and abstracts of all potentially eligible RCTs identified through the preplanned checklist (Appendix 4). 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 (GPS), who decided on inclusion or exclusion of the studies in dispute. We compiled a list of all eligible trials. When additional information was required, HP contacted the first named author of relevant trials.

Data extraction and management

Two review authors (CM and IK) independently extracted data and assessed trial quality using a standardized form (Appendix 4). We resolved disagreements by discussion with a third review author (HP). We performed assessment as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

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 (Figure 1; Figure 2).

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 study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ali 2009	+	+	-	-	+	+	+
Banevicius 2010	?	+	?	?	+	+	+
Bonhomme 2009	+	?	-	?	+	+	+
Cafiero 2007	+	?	?	+	+	+	+
Citerio 2012	?	-	-	+	+	+	+
Fabregas 1995	+	-	-	-	+	+	+
Grundy 1992	?	?	?	?	?	?	?
Ittichaikulthol 1997	?	?	?	?	?	?	?
Lauta 2010	+	+	-	+	+	+	+
Magni 2005	+	?	?	+	+	+	+
Magni 2007	+	?	?	+	+	+	+
Petersen 2003	+	+	?	+	+	+	+
Sneyd 2005	+	+	?	+	+	+	-
Talke 2002	?	+	-	-	+	+	+
Todd 1993	+	+	-	-	+	+	+

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 ([DerSimonian 1986](#)). 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 (ITT) 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 value ≤ 0.05 as indicating significant heterogeneity; we used the I^2 statistic to assess the magnitude of heterogeneity ([Higgins 2002](#)). 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 10 studies in the meta-analysis. However, we did not include 10 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 synthesized data only in the absence

of important clinical or statistical heterogeneity, and we expressed pooled estimates of the mean difference (MD) for continuous variables and the risk ratio (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, 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 ([Guyatt 2008](#)) 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 for the main comparison](#) (SoF) 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

See [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

See [Figure 3](#).

Figure 3. Study flow diagram.

Figure 3. (Continued)

Included studies

We included 15 studies in our review (Ali 2009; Banevicius 2010; Bonhomme 2009; Cafiero 2007; Citerio 2012; Fabregas 1995; Grundy 1992; Ittichaikulthol 1997; Laut 2010; Magni 2005; Magni 2007; Petersen 2003; Sneyd 2005; Talke 2002; Todd 1993). 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 (Grundy 1992). Isoflurane was the inhalational anaesthetic agent used in five studies (Fabregas 1995; Grundy 1992; Ittichaikulthol 1997; Talke 2002; Todd 1993), sevoflurane was used in eight studies (Banevicius 2010; Bonhomme 2009; Cafiero 2007; Citerio 2012; Laut 2010; Magni 2005; Magni 2007; Sneyd 2005) and both sevoflurane and isoflurane were used in two studies (Ali 2009; Petersen 2003). 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 (Ali 2009; Cafiero 2007; Fabregas 1995; Laut 2010; Magni 2005; Magni 2007; Sneyd 2005; Talke 2002; Todd 1993), and (2) adverse events were reported in eight studies (Cafiero 2007; Citerio 2012; Laut 2010; Magni 2005; Magni 2007; Sneyd 2005; Talke 2002; Todd 1993). Among our secondary outcomes, (1) time to eye opening was reported in three studies (Fabregas 1995; Ittichaikulthol 1997; Sneyd 2005); (2) recovery from anaesthesia in five studies (Cafiero 2007; Citerio 2012; Laut 2010; Talke 2002; Todd 1993); (3) opioid consumption in nine studies (Bonhomme 2009; Cafiero 2007; Citerio 2012; Fabregas 1995; Laut 2010; Petersen 2003; Sneyd 2005; Talke 2002; Todd 1993); (4) brain relaxation in six studies (Citerio 2012; Laut 2010; Magni 2007; Petersen 2003; Sneyd 2005; Todd 1993); and (5) complications of anaesthetic techniques in four studies (Bonhomme 2009; Citerio 2012; Fabregas 1995; Magni 2005).

Data from some studies were not reported in a manner suitable for pooling, including presentation of results in graphical form (Talke 2002) or as medians with a range (Talke 2002; Todd 1993). Others reported infusion rates for intravenous agents, but not total doses (Cafiero 2007; Petersen 2003; Talke 2002).

Excluded studies

We excluded three studies for the reasons detailed in the [Characteristics of excluded studies](#). These studies were not RCTs, as they included no control groups (Van Aken 1990; Van Hemelrijck 1991; Weninger 2004). We suspected possible duplication of data in two studies (Van Aken 1990; Van Hemelrijck 1991).

Ongoing studies

We found no ongoing studies.

Studies awaiting classification

Two studies are awaiting classification (Bastola 2015; Necib 2014). Please see [Characteristics of studies awaiting classification](#) for further information.

Risk of bias in included studies

We assessed the risk of bias of included studies by using the 'Risk of bias' tool developed by The Cochrane Collaboration (Higgins 2011). 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 [Figure 1](#) and [Figure 2](#) the characteristics of included studies used for our assessment of risk of bias. We found no studies of high methodological quality.

Allocation

Of the 15 included studies, only seven (Ali 2009; Banevicius 2010; Laut 2010; Petersen 2003; Sneyd 2005; Talke 2002; Todd 1993) reported allocation concealment. The remaining studies did not describe or did not perform allocation concealment.

Blinding

Among the 15 included studies, we observed performance bias in six studies (Bonhomme 2009; Citerio 2012; Fabregas 1995; Laut 2010; Talke 2002; Todd 1993), but the other studies did not report it. We noted detection bias in four studies (Ali 2009; Fabregas 1995; Talke 2002; Todd 1993) and found uncertain risk in four studies (Banevicius 2010; Bonhomme 2009; Grundy 1992; Ittichaikulthol 1997), as they did not describe or perform blinding of outcome assessment.

Incomplete outcome data

Thirteen studies reported data on all participants (Ali 2009; Banevicius 2010; Bonhomme 2009; Cafiero 2007; Citerio 2012; Fabregas 1995; Laut 2010; Magni 2005; Magni 2007; Petersen 2003; Sneyd 2005; Talke 2002; Todd 1993). However, this information remained unclear in two studies (Grundy 1992; Ittichaikulthol 1997), as they were presented as abstracts, and we could not contact study authors, whose contact details were not available.

Selective reporting

Thirteen studies reported data on all participants (Ali 2009; Banevicius 2010; Bonhomme 2009; Cafiero 2007; Citerio 2012; Fabregas 1995; Lauts 2010; Magni 2005; Magni 2007; Petersen 2003; Sneyd 2005; Talke 2002; Todd 1993). However, this information remained unclear in two studies (Grundy 1992; Ittichaikulthol 1997), 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 (Ali 2009; Banevicius 2010; Bonhomme 2009; Cafiero 2007; Citerio 2012; Fabregas 1995; Lauts 2010; Magni 2005; Magni 2007; Petersen 2003; Talke 2002; Todd 1993). One study (Sneyd 2005) 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 (Grundy 1992; Ittichaikulthol 1997).

Effects of interventions

See: [Summary of findings for the main comparison](#) Propofol versus sevoflurane for rapid emergence from anaesthesia in patients undergoing brain tumour surgery

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) (Ali 2009; Cafiero 2007; Magni 2005; Magni 2007). We found data from two studies (Lauts 2010; Sneyd 2005) 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 minutes shorter with sevoflurane, 95% CI -0.56 to 1.12; $I^2 = 22\%$; $P = 0.52$) (Analysis 1.1). 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 4).

Figure 4. Forest plot of comparison: 1 Propofol versus sevoflurane, outcome: 1.1 Emergence from anaesthesia.

Inhalational anaesthetic - isoflurane

Two studies enrolling 115 participants reported emergence from anaesthesia (6.27% of total participants in this review) (Ali 2009; Fabregas 1995). These two trials suggest that time to emergence

from anaesthesia was shorter with propofol than with isoflurane (MD -3.29 minutes, 95% CI -5.41 to -1.18; $I^2 = 0\%$, $P = 0.002$). We noted no heterogeneity in these studies (Analysis 2.1; Figure 5).

Figure 5. Forest plot of comparison: 2 Propofol versus isoflurane, outcome: 2.1 Emergence from anaesthesia.

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) (Magni 2005; Magni 2007). 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 to 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 (Analysis 1.2).

Agitation

A single trial (Citerio 2012) enrolling 274 participants reported agitation during emergence (14.9% of total participants in this review). This trial suggests that the incidence of agitation was seven of 136 (5.1%) in the sevoflurane group and nine of 138 (6.5%) in the propofol group ($P = 0.63$) (Table 1).

Nausea and vomiting

Six trials enrolling 952 participants reported nausea and vomiting during emergence (51.9% of total participants in this review) (Cafiero 2007; Citerio 2012; Lautá 2010; Magni 2005; Magni 2007; Sneyd 2005). 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 to 0.91; $I^2 = 23\%$, $P = 0.009$) (Analysis 1.2). 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) (Cafiero 2007; Citerio 2012; Lautá 2010; Magni 2005; Magni 2007). 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 to 1.99; $I^2 = 9\%$, $P = 0.17$) (Analysis 1.2). 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) (Citerio 2012; Lautá 2010; Magni 2005; Magni 2007; Sneyd 2005). 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 to 1.14; $I^2 = 14\%$, $P = 0.39$) (Analysis 1.2). 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 (Todd 1993) enrolling 80 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 (Table 1).

Agitation

A single trial (Todd 1993) enrolling 80 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 isoflurane group to three of 40 in the propofol group (Table 1).

Nausea and vomiting

Two trials enrolling 120 participants reported nausea and vomiting during emergence (6.54% of total participants in this review) (Talke 2002; Todd 1993). 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 to 0.78; $I^2 = 0\%$, $P = 0.005$) (Analysis 2.2).

Pain

A single trial (Talke 2002) enrolling 40 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 (Table 1).

Secondary outcomes

Time to eye opening

Inhalational anaesthetic - sevoflurane

A single trial (Sneyd 2005) enrolling 50 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) (Fabregas 1995; Ittichaikulthol 1997). These trials suggest that time to eye opening was shorter with propofol (MD -3.08, 95% CI -5.48 to -0.68; $I^2 = 81\%$, $P = 0.002$) (Analysis 2.3). 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 (Cafiero 2007; Citerio 2012; Lautá 2010) (Appendix 5). 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 (remifentanyl) consumption in mcg/kg/min (36.38% of total participants in this review) (Bonhomme 2009; Citerio 2012; Lautá 2010; Sneyd 2005). These trials suggest that remifentanyl was infused at a higher rate with propofol than with sevoflurane (MD 0.87 mcg/kg/min, 95% CI 0.60 to 1.14; $I^2 = 0\%$, $P < 0.00001$) (Analysis 1.3).

Inhalational anaesthetic - isoflurane

Two trials enrolling 138 participants reported total opioid (fentanyl) consumption in micrograms (7.53% of total participants in this review) (Fabregas 1995; Todd 1993). 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) (Citerio 2012; Lautá 2010; Magni 2007; Petersen 2003; Sneyd 2005). 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 to 1.17; $I^2 = 0\%$, $P = 0.38$) (Analysis 1.4). 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) (Petersen 2003; Todd 1993). 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 to 0.95; $I^2 = 54\%$, $P = 0.03$) (Analysis 2.4).

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) (Bonhomme 2009; Citerio 2012; Magni 2005; Magni 2007). 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 to 2.53; $I^2 = 67\%$, $P < 0.00001$) (Analysis 1.5). We noted significant heterogeneity.

Hypotension

Five trials enrolling 848 participants reported hypotension during the intraoperative period (46.26% of total participants in the review) (Bonhomme 2009; Citerio 2012; Magni 2005; Magni 2007; Petersen 2003). 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 to 0.95; $I^2 = 73\%$, $P = 0.02$) (Analysis 1.5). We noted significant heterogeneity.

Tachycardia

Three trials enrolling 708 participants reported tachycardia during the intraoperative period (38.63% of total participants in the review) (Citerio 2012; Magni 2005; Magni 2007). 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 to 1.68; $I^2 = 78\%$, $P = 0.85$) (Analysis 1.5). We noted significant heterogeneity.

Bradycardia

Three trials enrolling 708 participants reported tachycardia during the intraoperative period (38.63% of total participants in the review) (Citerio 2012; Magni 2005; Magni 2007). 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 to 1.42; $I^2 = 0\%$, $P = 0.87$) (Analysis 1.5). We noted no heterogeneity.

Inhalational anaesthetic - isoflurane

Hypertension

A single trial (Talke 2002) enrolling 40 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 four of 20 in the propofol group.

Hypotension

Three trials (Fabregas 1995; Petersen 2003; Talke 2002) 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 to 1.25; $I^2 = 18\%$, $P = 0.32$) (Analysis 2.5).

Tachycardia

A single trial (Talke 2002) enrolling 40 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 four of 20 in the propofol group.

Bradycardia

A single trial (Talke 2002) enrolling 40 participants reported hypertension (2.18% of total participants in the review). This trial suggests that the incidence of bradycardia increased from one of 20 in the isoflurane group to two of 20 in the propofol group.

DISCUSSION

Summary of main results

Evidence from 10 studies with 1188 participants contributing data to our primary outcome show 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 (mean difference (MD) 3.29 minutes, 95% confidence interval (CI) 5.41 to 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 (risk ratio (RR) 0.68, 95% CI 0.51 to 0.91, low-quality evidence) or isoflurane (RR 0.45, 95% CI 0.26 to 0.78) and greater risk of haemodynamic changes with propofol (RR 1.85, 95% CI 1.07 to 3.17), but no differences in the risk of shivering or pain.

Overall completeness and applicability of evidence

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.

Quality of the evidence

We selected randomized studies for our review, and many of these studies did not report details of randomization, 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, brain relaxation). For the outcomes of emergence from anaesthesia, adverse events (nausea and vomiting, shivering, pain) and brain relaxation, the quality of evidence was low, as is suggested by [Summary of findings for the main comparison](#). 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.

Potential biases in the review process

In an attempt to minimize 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 optimizing 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.

Agreements and disagreements with other studies or reviews

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.

AUTHORS' 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 suggesting 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 randomized controlled trials (RCTs) based on uniform and standard methods are needed. Investigators should follow proper methods of randomization and blinding and should examine standardized and clinically relevant outcomes. RCTs should be adequately powered. A multi-centre trial involving centres in different parts of the world would probably be useful.

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Prabhakar 2017

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Singh 2013

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ali 2009

Methods	<p>RCT, parallel design, India</p> <p>Sample size calculation: details on sample size calculation not mentioned</p> <p>Study period: March 2007 - January 2008</p> <p>Funding source: none</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 90 participants (43 females; 47 males)</p> <p>Inclusion criteria: ASA I and II, 18 - 65 years of age, undergoing transsphenoidal pituitary surgery, no previous pituitary surgery</p> <p>Exclusion criteria: psychiatric disorders, history of drug abuse, poorly controlled hypertension, Ischaemic heart disease, pituitary apoplexy</p>
Interventions	<p>Control (n = 30): sevoflurane at end-tidal concentration of 1%</p> <p>Control (n = 30): isoflurane at end-tidal concentration of 1%</p> <p>Intervention (n = 30): propofol @ 10 mg/kg/h, from induction of anaesthesia until beginning of gingival suturing</p>
Outcomes	<ol style="list-style-type: none"> Emergence time - time interval between nitrous oxide discontinuation and time to eye opening spontaneously or on command Extubation time - time interval between nitrous oxide discontinuation and extubation Cognitive functions at 5 and 10 minutes - modified, self devised questionnaire of short orientation memory concentration test Recovery from anaesthesia - Modified Aldrete score (1 - 10) Intraoperative haemodynamic variables at various stages of surgery Adverse event - emergence hypertension
Notes	Fentanyl 1 mcg/kg hourly during intraoperative period

Ali 2009 (Continued)

Study author contacted for details on number of participants with intraoperative haemodynamic changes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence of numbers
Allocation concealment (selection bias)	Low risk	Sealed envelope technique
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were blinded but person providing anaesthesia was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessor was not blinded to the anaesthetic technique.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all participants were reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods are reported.
Other bias	Low risk	Nothing suggestive

Banevicius 2010

Methods	<p>RCT, parallel design, Department of Anesthesiology, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50028 Kaunas, Lithuania</p> <p>Sample size calculation: "We calculated that approximately 49 patients would be needed to detect a 10-cm/s difference of Vmean between the groups with the power of 90% and α level of 0.05, with the assumed SD of 15 cm/s in the outcome variables".</p> <p>Study period: not mentioned</p> <p>Funding source: none</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 130 participants (87 females; 43 males)</p> <p>Inclusion criteria: ASA class I - III, 18 - 75 years of age, GCS = 15, first time elective surgery for supratentorial intracranial tumour</p> <p>Exclusion criteria: craniotomy, severe intracranial hypertension (> 5-mm midline shift on computed tomography scan with altered sensorium), history of cerebrovascular disorders, GCS score < 15, body mass index > 30, pregnancy, known allergy to any anaesthetic agent, history of drug or alcohol abuse, family or personal history of malignant hyperthermia</p>
Interventions	<p>Control (n = 65): sevoflurane at end-tidal concentration of 0.5% - 1.8% (entropy guided)</p>

Banevicius 2010 (Continued)

Intervention (n = 65): propofol infusion at 1.5 - 8.5 mg/kg/h

Outcomes	1. Cerebral haemodynamics and related index - using transcranial Doppler 2. Opioid consumption
Notes	Fentanyl infusion at 1 - 3 mcg/kg/h during intraoperative period Study authors contacted for details on other outcomes in the review No response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Low risk	Used sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants reported
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods are reported.
Other bias	Low risk	Nothing suggestive

Bonhomme 2009

Methods	RCT, parallel design, University Department of Anaesthesia and Intensive Care Medicine, Belgium Sample size calculation: not mentioned Study period: not mentioned Funding source: none Declaration of interest: none
Participants	Total: 61 participants (37 females; 24 males) Inclusion criteria: ASA I - III scheduled to undergo intracranial surgery Exclusion criteria: not mentioned

Bonhomme 2009 (Continued)

Interventions	<p>Control (n = 31): sevoflurane at end-tidal concentration between 1% and 2.5%</p> <p>Intervention (n = 30): propofol target controlled concentration of 1 - 3.5 mcg/mL</p>
Outcomes	<p>1. Acid-base balance on arterial blood samples</p> <p>2. Haemodynamic stability</p> <p>Mean arterial blood pressure < 60 mmHg = hypotension</p> <p>Mean arterial blood pressure > 90 mmHg = hypertension</p> <p>Heart rate < 50 beats/min = bradycardia</p> <p>Heart rate > 90 beats/min = tachycardia</p> <p>3. Opioid consumption</p>
Notes	<p>Remifentanyl infusion in both groups at 0.1 - 0.5 mcg/kg/min, during intraoperative period</p> <p>Participants also received a 5-gram bolus of magnesium sulphate and 125 mg methylprednisolone.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a Microsoft Excel 2003 random number function-generated list".
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The attending anesthesiologist was of course not blind to the randomization, because of evident practical reasons. Indeed, administration route is radically different between propofol and sevoflurane".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods are reported.
Other bias	Low risk	Nothing suggestive

Cafiero 2007

Methods	<p>RCT, parallel design, Department of Anaesthesiology and Postoperative Intensive Care, Cardarelli Hospital, Napoli, Italy</p> <p>Sample size calculation: "Applying a priori power analysis, at least 19 patients had to be enrolled in each treatment group to provide 80% power to detect a 3 min difference in recovery time ($\alpha = 0.05$; $\beta = 0.2$). Assuming a potential drop-out rate of 15%, we decided to recruit 22 patients per group".</p>
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Cafiero 2007 (Continued)

Study period: not mentioned

Funding source: none

Declaration of interest: none

Participants	Total: 44 participants (21 females; 23 males) Inclusion criteria: ASA I - III, adult patients scheduled for elective pituitary surgery Exclusion criteria: hypersensitivity to opioid, substance abuse, history of treatment with opioids or any psychoactive medication
Interventions	Control (n = 22): sevoflurane-remifentanil, at end-tidal concentration-hour between 0.8 and 1.5 Intervention (n = 22): propofol target control infusion to achieve target blood concentration of 3 mcg/mL
Outcomes	1. Intraoperative haemodynamic changes 2. Recovery profile - using Aldrete score 3. Surgical operative conditions 4. Emergence from anaesthesia - time to return of spontaneous respiration, extubation and response to verbal commands (opening eyes), time-space orientation 5. Level of postoperative pain - 4-point scale (0 = none and 3 = severe) 6. Incidence of nausea and vomiting - 4-point scale (0 = none and 3 = severe) 7. Adverse events, if any
Notes	Remifentanil infusion in both groups at 0.2 mcg/kg/min, during intraoperative period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomizations, drawing lots from a closed box
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An observer who was blinded to the group allocation of the patients carried out the assessments of all early recovery end-points".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods are reported.

Cafiero 2007 (Continued)

Other bias	Low risk	Nothing suggestive
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Citerio 2012

Methods	<p>RCT, parallel design, Neuroanaesthesia and Neurointensive Care Unit, Anestesia e Rianimazione, San Gerardo Hospital, via Pergolesi 33, Monza 20900, Milano</p> <p>Sample size calculation: "A sample size of 411 patients (137 in each group) was calculated to provide power of at least 84% to conclude equivalence, assuming a 10% drop-out rate and overall type I error (α) of 0.05, setting the α level of at 0.025 for each of the two comparisons".</p> <p>Study period: December 2007 - March 2009</p> <p>Funding source: Agenzia Italiana del Farmaco (AIFA, the national authority responsible for drug regulation in Italy under the direction of Ministry of Health)</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 411 participants (49% females; 51% males)</p> <p>Inclusion criteria: adults 18 - 75 years of age with GCS = 15, no clinical signs of intracranial hypertension</p> <p>Exclusion criteria: severe cardiovascular, renal or liver disease; pregnancy, allergy to any anaesthetic agent, body weight > 120 kg, drug abuse or psychiatric conditions and disturbance or surgery of the hypothalamic region, postoperative sedation or mechanical ventilation, warranted planned awakening in the ICU</p>
Interventions	<p>Control (n = 136): sevoflurane-remifentanyl, 0.75 - 1.25 minimal alveolar concentration (MAC) and remifentanyl 0.05 - 0.25 mcg/kg/min reduced to 0.05 to 0.1 mcg/kg/min after dural opening</p> <p>Intervention (n = 138): propofol infused continuously at 10 mg/kg/h for 10 minutes, reduced to 8 mg/kg/h for 10 minutes, then reduced to 6 mg/kg/h for the remainder of the procedure and remifentanyl infused at 0.05 to 0.25 mcg/kg/min, reduced to 0.05 to 0.1 mcg/kg/min after dural opening</p>
Outcomes	<ol style="list-style-type: none"> 1. Time to achieve Aldrete score of 9 2. Haemodynamic responses 3. Endocrine stress response 4. Quality of surgical field 5. Perioperative adverse events 6. Patient satisfaction score 7. Cost
Notes	<p>4-point brain relaxation score was used (1 = relaxed brain, 2 = mild brain swelling, 3 = moderate brain swelling, no therapy required, 4 = severe swelling, requiring treatment).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomised 1:1:1 to one of the three anaesthesia protocols; balanced randomisation was maintained at each clinical site using a

Criterio 2012 (Continued)

		stratified randomisation scheme provided by the centralised randomisation service".
Allocation concealment (selection bias)	High risk	Open-label study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To minimise bias in assessing treatment effects, a prospective randomised open blinded endpoint (PROBE) design was used in which primary endpoint data were assessed by anaesthesiologists not involved in the case and blinded to treatment assignment".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods are reported.
Other bias	Low risk	Nothing suggestive

Fabregas 1995

Methods	<p>RCT, parallel design, Servicio de Anestesiología, y Reanimación, Hospital Clínic i Provincial, Villarroel, 170.08036 Barcelona</p> <p>Study period: January 1992 - June 1993</p> <p>Funding source: none</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 58 participants (25 females; 33 males)</p> <p>Inclusion criteria: middle-aged patients (40 - 50 years) posted for intracranial surgery with GCS > 13</p> <p>Exclusion criteria: not mentioned</p>
Interventions	<p>Control (n = 27): isoflurane 0.6 - 1 minimal alveolar concentration (MAC)</p> <p>Intervention (n = 31): propofol 10 mg/kg/h for 30 minutes followed by 8 mg/kg/h for 30 minutes and 6 mg/kg/h until the end of surgery</p>
Outcomes	<ol style="list-style-type: none"> 1. Haemodynamic stability 2. Recovery time 3. Opioid consumption
Notes	<p>Article in Spanish</p> <p>Details obtained from study author</p>

Risk of bias

Fabregas 1995 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors contacted Quote: "Patients were randomly assigned to their study group by a computer obtained 'randomization sequence generation'".
Allocation concealment (selection bias)	High risk	Study authors contacted No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study authors contacted Quote: "There was no blinding".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study authors contacted Quote: "There was no blinding".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods are reported.
Other bias	Low risk	Nothing suggestive

Grundy 1992

Methods	<p>RCT, parallel design, Department of Anesthesiology, University of Florida College of Medicine, Gainesville</p> <p>Study period: not mentioned</p> <p>Funding source: none</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 30 participants (?females; ? males) Details not available as full text of the article could not be obtained.</p> <p>Inclusion criteria: patients undergoing elective craniotomy for aneurysm or tumour</p> <p>Exclusion criteria: not mentioned</p>
Interventions	<p>Control (n = 10): isoflurane 0.25% - 2% plus nitrous oxide</p> <p>Intervention (n = 10): thiopental with infusion of sufentanil 0.1 mcg/kg/h</p> <p>Intervention (n = 10): thiopental with infusion of fentanyl 1 mcg/kg/h</p>
Outcomes	<p>1. Intraoperative haemodynamic stability - percentage of time the participant required administration of an antihypertensive drug, measured from the first dose of thiopental to discontinuation of N₂O at the end of the procedure</p>

Grundy 1992 (Continued)

2. Emergence from anaesthesia - minutes from discontinuation of nitrous oxide to first opening of the eyes on command

Notes Study authors to be contacted for other details, as full text of the article could not be obtained.
Study author contact details not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study authors to be contacted for full text of article
Allocation concealment (selection bias)	Unclear risk	Study authors to be contacted for full text of article
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study authors to be contacted for full text of article
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study authors to be contacted for full text of article
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study authors to be contacted for full text of article
Selective reporting (reporting bias)	Unclear risk	Study authors to be contacted for full text of article
Other bias	Unclear risk	Study authors to be contacted for full text of article

Ittichaikulthol 1997

Methods RCT, parallel design, institute/hospital details not provided in the abstract

Study period: not mentioned

Funding source: not mentioned

Declaration of interest: not mentioned

Participants **Total:** 60 participants (? females; ? males) Details not available

Inclusion criteria: ASA class I - II, GCS = 15 undergoing elective intracranial surgery

Exclusion criteria: not mentioned

Interventions **Control** (n = 30): isoflurane

Intervention (n = 30): propofol infusion at 2 - 12 mg/kg/h

Outcomes 1. Haemodynamic instability

2. Recovery time

Ittichaikulthol 1997 (Continued)

Notes	Abstract
	Fentanyl used as analgesic
	Contact details of study author not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not mentioned in the abstract. Study authors could not be contacted.
Allocation concealment (selection bias)	Unclear risk	Details not mentioned in the abstract. Study authors could not be contacted.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not mentioned in the abstract. Study authors could not be contacted.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not mentioned in the abstract. Study authors could not be contacted.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not mentioned in the abstract. Study authors could not be contacted.
Selective reporting (reporting bias)	Unclear risk	Details not mentioned in the abstract. Study authors could not be contacted.
Other bias	Unclear risk	Details not mentioned in the abstract. Study authors could not be contacted.

Lauta 2010

Methods	<p>RCT, parallel design, Anaesthesia and Intensive Care Unit, Azienda Ospedaliero-Universitaria, Bari, Italy</p> <p>Sample size calculation: "We calculated the sample size considering the time to reach an Aldrete Score of more than equal to 9 as the primary variable based on the Todd et al study results testing for superiority of sevoflurane versus propofol, and taking into consideration Hartung and Cottrell's observation about the inferences of a sample size that is too small on the outcome measurements. We fixed a Δ of 5 minutes as an acceptable superiority limit for the median difference in minutes required to reach an Aldrete test score of more than equal to 9. Assuming, by means of 2 exponential life curves, the estimation of a hazard ratio of not less than 1.5, considering an α-level = 0.05 and a test power of $1-\beta = 0.90$, the trial was designed to include 313 adult patients, 18 to 75 years of age, over 4 years".</p> <p>Study period: February 2001 - February 2005</p> <p>Funding source: none</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 314 participants (165 females; 137 males) Data for 12 patients who were excluded from the study is not provided</p> <p>Inclusion criteria: ASA ≤ 3, GCS = 15, 18 – 75 years old, posted for elective resection of a supratentorial mass lesion</p>

Lauta 2010 (Continued)

Exclusion criteria: previous craniotomy; severe symptomatic cardiopulmonary, hepatic or renal disease; alcohol or other drug abuse, BMI > 35, should not have received general anaesthesia within previous 7 days and female patients could not be pregnant or breast feeding

Interventions	<p>Control (n = 155): sevoflurane (end-tidal concentration) maintained between 0.7% and 2%</p> <p>Intervention (n = 159): propofol 10 mg/kg/h for 10 minutes, reduced to 8 mg/kg/h for next 10 minutes and to 6mg/kg/h thereafter</p>
Outcomes	<ol style="list-style-type: none"> 1. Time to reach an Aldrete test score ≥ 9 2. Times to eye opening and extubation 3. Adverse events 4. Intraoperative haemodynamics 5. Brain relaxation score (4-point brain relaxation score) 6. Opioid consumption 7. Diuresis
Notes	Remifentanyl used as analgesic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A stratified randomized block selection was planned at each centre.
Allocation concealment (selection bias)	Low risk	Sealed envelope method was used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Attending anesthesiologist was aware of the treatment given".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to the study group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six participants were excluded in each group because of intraoperative complications requiring postoperative sedation and neurointensive care unit admission.
Selective reporting (reporting bias)	Low risk	Results of all outcomes mentioned in the methods have been reported.
Other bias	Low risk	Nothing suggestive

Magni 2005

Methods	RCT, parallel design, Department of Anesthesia and Intensive Care, Roma, Italy
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Magni 2005 (Continued)

Sample size calculation: "The study was powered to detect a difference in emergence time of at least 5 minutes between the two groups, assuming emergence time in group S as 15 ± 8 minutes, and to detect a 20% difference in postoperative impairment of cognitive functions between the two groups, with β set to 0.1 and α to 0.05. It was estimated that a minimum of 59 patients in each group was needed".

Study period: April 2002 and March 2003

Funding source: none

Declaration of interest: none

Participants	<p>Total: 120 participants (56 females; 64 males)</p> <p>Inclusion criteria: ASA I - III, 15 to 75 years of age, GCS = 15, undergoing craniotomy for supratentorial lesion</p> <p>Exclusion criteria: pregnancy, allergy to anaesthetic agents, GCS < 15, BMI > 30, history of drug or alcohol abuse, refusal to sign consent</p>
Interventions	<p>Control (n = 60): sevoflurane end-tidal concentration 1.5% - 2% and minimum alveolar concentration 1.3% - 1.8%</p> <p>Intervention (n = 60): propofol (10 mg/kg/h for 10 minutes; 8 mg/kg/h for next 10 minutes; 6 mg/kg/h thereafter)</p>
Outcomes	<ol style="list-style-type: none"> 1. Haemodynamics <ul style="list-style-type: none"> MAP < 70% of baseline value for > 1 minute - hypotension MAP > 130% of baseline value for > 1 minute - hypertension HR < 50 beats/min for > 1 minute - bradycardia HR > 90 beats/min for > 1 minute - tachycardia 2. Emergence time (time between drug interruption and time at which participant opened his or her eyes (spontaneous or on verbal prompting)) 3. Extubation time (time elapsing from anaesthetic discontinuation to extubation) 4. Postoperative vomiting, shivering, pain 5. Cognitive functions (Short Orientation Memory Concentration Test (SOMCT))
Notes	<p>Remifentanyl infusion 0.5 - 0.25 mcg/kg/min reduced to 0.05 - 0.1 mcg/kg/min after dural opening in the propofol group</p> <p>Fentanyl 0.7 mcg/kg when considered necessary by attending anaesthesiologist</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias)	Unclear risk	Not mentioned

Magni 2005 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors were blinded to the study group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were analysed.
Selective reporting (reporting bias)	Low risk	Results of all outcomes mentioned in the methods have been reported.
Other bias	Low risk	Nothing suggestive

Magni 2007

Methods	<p>RCT, parallel design, Department of Anaesthesia and Intensive Care, Policlinico, Rome, Italy</p> <p>Sample size calculation: "To compute the sample size for this study, a 70% incidence of at least one postoperative complication was hypothesized from the available literature in an unselected group of patients. We estimated that a clear clinical benefit could be established in the T group is a 30% or greater decrease in the complication incidence could be obtained in these patients. Therefore, with β set to 0.2 and α to 0.05 (single sided), it was estimated that a minimum of 76 patients were needed for each study group".</p> <p>Study period: not mentioned</p> <p>Funding source: none</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 162 participants (82 females; 80 males)</p> <p>Inclusion criteria: ASA I - III, scheduled for elective intracranial surgery</p> <p>Exclusion criteria: GCS < 15, complications during surgery, anticipated duration of surgery > 5 hours</p>
Interventions	<p>Control (n = 82): sevoflurane end-tidal concentration of 1.5% - 2% and minimum alveolar concentration 1.3% - 1.8%</p> <p>Intervention (n = 80): propofol (10 mg/kg/h for 10 minutes; 8 mg/kg/h for next 10 minutes; 6 mg/kg/h thereafter)</p>
Outcomes	<p>1. Postoperative complications (respiratory, neurological, haemodynamic, nausea, vomiting, pain and shivering)</p>
Notes	<p>Remifentanyl infusion 0.5 - 0.25 mcg/kg/min reduced to 0.05 - 0.1 mcg/kg/min after dural opening in the propofol group</p> <p>Fentanyl 0.7 mcg/kg when considered necessary by attending anaesthesiologist</p> <p>Study authors contacted for duplication of data from previous study (Magni 2005). Study authors confirmed that the 2 studies included different patient populations.</p>
Risk of bias	
Bias	Authors' judgement Support for judgement

Magni 2007 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor was blinded to anaesthetic management.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were analysed. However, 6 participants in whom early awakening was not considered safe were excluded.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods have been reported.
Other bias	Low risk	Nothing suggestive

Petersen 2003

Methods	<p>RCT, parallel design, Department of Neuroanaesthesia, Aarhus University Hospital, 8000 C Aarhus, Denmark</p> <p>Sample size calculation: "Based on a previous non-randomised study of ICP during three different anaesthetic techniques, given a minimum detectable difference of 3.6 mmHg, expected SD 5.0 mmHg, power of 0.8, and a significance level of P value < 0.05, the total number of patients was calculated to be 114".</p> <p>Study period: March 1998 - December 1999</p> <p>Funding source: none</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 117 participants (61 females; 56 males)</p> <p>Inclusion criteria: elective patients (18 - 70 years of age) scheduled for elective craniotomy for supratentorial cerebral tumours</p> <p>Exclusion criteria: arterial hypertension, chronic pulmonary insufficiency</p>
Interventions	<p>Control (n = 38): isoflurane - fentanyl: minimum alveolar concentration of isoflurane maximal at 1.5</p> <p>Control (n = 38): sevoflurane - fentanyl: minimum alveolar concentration of sevoflurane maximal at 1.5</p> <p>Intervention (n = 41): propofol - fentanyl: propofol infusion (6 - 10 mg/kg/h)</p>
Outcomes	<p>1. Subdural ICP before and after hyperventilation</p> <p>2. Incidence of cerebral swelling after dural opening (1. Very slack, 2. Normal, 3. Increased tension, 4. Pronounced increased tension)</p> <p>3. Brain relaxation (1. No swelling, 2. Moderate swelling, 3. Pronounced swelling)</p>

Petersen 2003 (Continued)

4. Cerebral perfusion pressure, arteriovenous oxygen difference, carbon dioxide reactivity

Notes

Fentanyl used as analgesic

Study authors contacted for details. Mail delivery failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization method used
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeon assessing brain relaxation and tension was blinded to the anaesthetic regimen.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all enrolled participants were analysed and reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods have been reported.
Other bias	Low risk	Nothing suggestive

Sneyd 2005

Methods

RCT, parallel design, University of Plymouth, UK

Sample size calculation: "The size of the study was determined by a priori power calculation using data from a previous study, which suggested that enrolment of 20 patients per group would determine a difference in time to tracheal extubation of 4 minutes with a power of 80% and P value < 0.05".

Study period: not mentioned

Funding source: supported by a grant from Abbott Laboratories Limited, the manufacturer of sevoflurane

Declaration of interest: Professor Sneyd has received lecture fees and research support from AstraZeneca, the manufacturers of propofol, and other research support from Abbott Laboratories.

Participants

Total: 50 participants (29 females; 21 males)

Inclusion criteria: unmedicated patients undergoing elective craniotomy

Exclusion criteria: not mentioned

Interventions

Control (n = 26): sevoflurane end-tidal concentration of 2%

Sneyd 2005 (Continued)

Intervention (n = 24): propofol - target controlled infusion with minimum concentration of 2 mcg/mL

Outcomes	<ol style="list-style-type: none"> 1. Haemodynamic responses 2. Time to adequate respiration 3. Time to extubation 4. Time to eye opening 5. Time to obeying commands 6. Nausea and vomiting 7. Time to discharge from recovery
Notes	Remifentanyl bolus 1 mcg/kg followed by infusion of 0.5 mcg/kg/min, reduced to 0.25 mcg/kg/min Brain conditions: soft/adequate/tight

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using random number function of Microsoft Excel version 7.0
Allocation concealment (selection bias)	Low risk	Individual opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Sevoflurane smell could have been easily detected by personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeons and nurses were unaware of the anaesthetic agents.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants enrolled in the study have been reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods have been reported.
Other bias	High risk	Study was funded by the pharmaceutical companies Abbott Laboratories Limited and AstraZeneca.

Talke 2002

Methods	RCT, parallel design, Department of Anaesthesia, Aarhus University Hospital, 8000 C Aarhus, Denmark Sample size calculation: not mentioned Study period: not mentioned Funding source: Department and University
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Talke 2002 (Continued)

Declaration of interest: none

Participants	<p>Total: 60 participants (31_ females; _29 males)</p> <p>Inclusion criteria: patients > 18 years old; ASA II, III or IV, scheduled for elective supratentorial neuro-surgical procedure</p> <p>Exclusion criteria: patients with increased intracranial pressure and those scheduled for emergency surgery</p>
Interventions	<p>Control (n = 20): isoflurane 0.55% end-tidal concentration</p> <p>Intervention (n = 20): propofol infusion 50 - 200 mcg/kg/min</p> <p>Balanced (n = 20): propofol/isoflurane, isoflurane 0.55% end-tidal concentration plus propofol infusion 50 - 200 mcg/kg/min</p>
Outcomes	<ol style="list-style-type: none"> 1. Haemodynamics 2. Recovery (using modified Aldrete score) 3. Emergence time (after discontinuation of propofol, time taken to follow commands) 4. Nausea and vomiting 5. Cost 6. Opioid consumption
Notes	<p>Fentanyl infusion at 2 mcg/kg/h</p> <p>Numerical data could not be retrieved. Study author reply: "I don't have data other than what is in the manuscript"</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not carried out
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not carried out
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants are reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods have been reported.
Other bias	Low risk	Nothing suggestive

Todd 1993

Methods	<p>RCT, parallel design, Department of Anesthesia, University of Iowa College of Medicine, GH6SE, Iowa City, Iowa 52242</p> <p>Sample size calculation: not mentioned</p> <p>Study period: April 1989 - December 1991</p> <p>Funding source: ICI Pharmaceuticals (Wilmington, DE)</p> <p>Declaration of interest: none</p>
Participants	<p>Total: 121 participants (60 females; 61 males)</p> <p>Inclusion criteria: patients 18 - 75 years old, ASA II and III, scheduled for elective craniotomy for a supratentorial mass lesion</p> <p>Exclusion criteria: patients with known aneurysms, arteriovenous malformation or posterior fossa tumours, severe ischaemic heart disease, congestive heart failure, renal or hepatic dysfunction or severe chronic respiratory disease, those who were ventilated postoperatively</p>
Interventions	<p>Control (n = 40): isoflurane titrated by attending anaesthesiologist</p> <p>Intervention (n = 40): propofol infusion at 200 mcg/kg/min; fentanyl infusion at 2 mcg/kg/h after a bolus of fentanyl 10 mcg/kg over 10 minutes</p> <p>Intervention (n = 41): fentanyl/nitrous oxide; fentanyl infusion at 2 mcg/kg/h after a bolus of fentanyl 10 mcg/kg over 10 minutes</p>
Outcomes	<ol style="list-style-type: none"> 1. Opioid consumption 2. Emergence (Aldrete score) 3. Time to extubation 4. Haemodynamic (emergence hypertension) changes during emergence 5. Intraoperative haemodynamic changes 6. Vomiting 7. Brain swelling after dural opening (1 = excellent, no swelling, 2 = minimal swelling but acceptable, 3 = serious swelling but no specific change in management required, 4 = severe brain swelling requiring some intervention) 8. Agitation on emergence
Notes	<p>Fentanyl used as analgesic</p> <p>Data for emergence time in median (range). Study author contacted for data in mean (SD). No response</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization done by a statistician
Allocation concealment (selection bias)	Low risk	Sealed envelopes used

Todd 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not a double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not a double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the methods have been reported.
Other bias	Low risk	Nothing suggestive

AIFA = Agenzia Italiana del Farmaco.

ASA = American Society of Anesthesiologists.

BIS = Bispectral Index.

BMI = Body mass index.

GCS = Glasgow Coma Scale.

HR = Heart rate.

ICP = Intracranial pressure.

ICU = Intensive care unit.

MAC = Minimum alveolar concentration.

MAP = Mean arterial pressure.

PROBE = Prospective randomized open blinded end point.

RCT = Randomized controlled trial.

SD = Standard deviation.

SOMCT = Short Orientation Memory Concentration Test.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Van Aken 1990	No control group
Van Hemelrijck 1991	No control group. Possible duplication of data from study by Van Aken 1990
Weninger 2004	No control group

Characteristics of studies awaiting assessment *[ordered by study ID]*
Bastola 2015

Methods	RCT, parallel design, Department of Anesthesia and Intensive Care, PSOT Graduate Institute of Medical Education and Research, Chandigarh, India
	Sample size calculation: "Sample size was estimated based on mean extubation time of 15.2 minutes with sevoflurane and 11.3 minutes with desflurane in a recent study.[5] To detect a 25% decrease in extubation time with standard deviation (SD) of 3.5, the calculated sample size was 17 per group at a power of 90% and confidence interval of

Bastola 2015 (Continued)

95% with an effect size of 1.1. To have adequate power of study despite possible dropouts and exclusion because of surgical reasons, the sample size was increased to 25 patients per group".

Study period: December 2009 and February 2011

Funding source: institutional resources

Declaration of interest: none

Participants	<p>Total: 75 participants (22 females; 53 males)</p> <p>Inclusion criteria: patients 20 - 60 years of age, ASA I and II, preoperative Glasgow coma score of 15</p> <p>Exclusion criteria: patients with ischaemic and/or congestive heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, hepatic and renal dysfunction; patients who had surgery-related complications such as vascular injury, massive intraoperative bleeding or injury to vital structures necessitating elective postoperative mechanical ventilation</p>
Interventions	<p>Control (n = 25): sevoflurane, end-tidal concentration 1% - 2% + 60% nitrous oxide in oxygen</p> <p>Control (n = 25): desflurane end-tidal concentration 2% - 4% + 60% nitrous oxide in oxygen</p> <p>Intervention (n = 25): propofol 5 - 10 mg/kg/h+ 60% nitrous oxide in oxygen</p>
Outcomes	<ol style="list-style-type: none"> 1. Intraoperative brain relaxation 2. Heart rate and mean arterial pressure 3. Emergence time 4. Coughing during extubation 5. Agitation following extubation 6. Postoperative complications such as pain, nausea, vomiting and convulsions
Notes	<p>Morphine used as analgesic</p> <p>Intraoperative brain relaxation scores were assessed by anaesthetists and surgeons.</p> <p>Anaesthesiologist's grading: (1) within the margin of the inner table of the skull, (2) within the margin of the outer table of the skull and (3) outside the margin of the outer table of the skull</p> <p>Surgeon's grading: (1) satisfied, (2) not satisfied but can manage and (3) not satisfied, and intervention is required</p>

Necib 2014

Methods	<p>RCT, parallel design, Department of Anesthesia, Intensive Care and Pain Management, Robert Debre Hospital, Paris, France</p> <p>Sample size calculation: "Assuming a mean time from discontinuing anesthesia to extubation of 14 minutes (SD, 6 min) in the SS arm²² we planned to involve 45 patients/arm to provide 80% power at a 2-sided α-level of 0.05 to detect a 30% decrease of the mean time from discontinuing anesthesia to extubation".</p> <p>Study period: November 2006 - March 2010</p> <p>Funding source: Department of Clinical Research and Development of the Assistance Publique Hôpitaux de Paris</p>
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Necib 2014 (Continued)

Declaration of interest: none

Participants	<p>Total: 66 participants (33 females; 33 males)</p> <p>Inclusion criteria: “patient aged 18 to 75 years, American Society of Anesthesiologists classification status 1 or 2, scheduled surgery for removal of supratentorial tumors (STTs), information and written consent for the protocol, the absence of inclusion in another study, the absence of susceptibility to one of the compounds of the protocol (allergy or malignant hyperthermia), pregnancy or planned intubation during the postoperative period”</p> <p>Exclusion criteria: “patients aged less than 18 years or more than 75 years, frontal tumors with the bone flap performed in the frontal region (absence of BIS monitoring), blindness and motor compromise of the upper limbs (this alters the ability of patient in performing the Mini Mental State [MMS] test), absence of French speaking (in order to understand questions and tests), or a decline to participate to the study”</p>
Interventions	<p>Control (n = 35): sevoflurane expiratory fraction guided by BIS maintained at 45 - 55</p> <p>Intervention (n = 31): propofol concentration guided by BIS maintained at 45 - 55</p>
Outcomes	<p>Primary outcome: time from discontinuation of anaesthesia to extubation</p> <p>Secondary outcomes: time from discontinuation of anaesthesia to response to a simple order (moving hands or opening eyes), time from discontinuation of anaesthesia to recover a spontaneous ventilation, agitation score at emergence (1 = calm, 2 = moderately agitated but easily calmed, 3 = agitated and hardly calmed, 4 = intense agitation and impossible to calm), postoperative AS, GCS, MMS score SSS pain scores (pVAS, monitored each 15 minutes during first postoperative hour and hourly during remaining 23 hours. Finally, 2 additional outcomes were added to assess haemodynamic stability of the 2 studied protocols: administration of intraoperative vasopressors or intraoperative nicardipine. To assess the effects of anaesthesia on cerebral relaxation and the difficulties of tumour resection, surgeons were asked to rate on a 10-point scale (0 - 10) predictable and effective difficulties of surgical resection before and after surgery, respectively. The difference in this score was considered as a surrogate of the relaxant effect of anaesthesia of the brain. Finally, the other data collected were sex, age, preoperative medication (antiepileptic and anti-oedema treatments), localization, histologic type and grade of tumours and duration of surgery.</p>
Notes	Remifentanyl used as analgesic in propofol group. Sufentanyl used in the sevoflurane group

ASA = American Society of Anesthesiologists.

AS = Aldrete score

BIS = Bispectral Index.

GCS = Glasgow Coma Scale.

MMS = Mini Mental State test.

pVAS = Pain visual analogical Scale.

SD = standard deviation.

STT = supratentorial tumor.

DATA AND ANALYSES

Comparison 1. Propofol versus sevoflurane

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Emergence from anaesthesia	4	384	Mean Difference (IV, Random, 95% CI)	0.28 [-0.56, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Adverse event	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Haemodynamic changes	2	282	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.07, 3.17]
2.2 Nausea and vomiting	6	952	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.91]
2.3 Shivering	5	902	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.88, 1.99]
2.4 Pain	5	908	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.71, 1.14]
3 Opioid consumption (remifentanyl)	4	667	Mean Difference (IV, Fixed, 95% CI)	0.87 [0.60, 1.14]
4 Brain relaxation	5	867	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.17]
5 Complication of technique	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Hypertension	3	455	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.47, 2.53]
5.2 Hypotension	4	534	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.56, 0.95]
5.3 Tachycardia	2	394	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.53, 1.68]
5.4 Bradycardia	2	394	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.42]

Analysis 1.1. Comparison 1 Propofol versus sevoflurane, Outcome 1 Emergence from anaesthesia.

Analysis 1.2. Comparison 1 Propofol versus sevoflurane, Outcome 2 Adverse event.

Analysis 1.3. Comparison 1 Propofol versus sevoflurane, Outcome 3 Opioid consumption (remifentanyl).

Analysis 1.4. Comparison 1 Propofol versus sevoflurane, Outcome 4 Brain relaxation.

Analysis 1.5. Comparison 1 Propofol versus sevoflurane, Outcome 5 Complication of technique.

Comparison 2. Propofol versus isoflurane

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Emergence from anaesthesia	2	115	Mean Difference (IV, Fixed, 95% CI)	-3.29 [-5.41, -1.18]
2 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Nausea and vomiting	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.26, 0.78]
3 Time to eye opening	2	118	Mean Difference (IV, Fixed, 95% CI)	-3.08 [-5.48, -0.68]
4 Brain relaxation	2	159	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.95]
5 Complication of technique	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Hypotension	2	137	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.51, 1.25]

Analysis 2.1. Comparison 2 Propofol versus isoflurane, Outcome 1 Emergence from anaesthesia.

Analysis 2.2. Comparison 2 Propofol versus isoflurane, Outcome 2 Adverse events.

Analysis 2.3. Comparison 2 Propofol versus isoflurane, Outcome 3 Time to eye opening.

Analysis 2.4. Comparison 2 Propofol versus isoflurane, Outcome 4 Brain relaxation.

Analysis 2.5. Comparison 2 Propofol versus isoflurane, Outcome 5 Complication of technique.

ADDITIONAL TABLES

Table 1. Adverse events

Adverse event	Study ID	Inhalational anaesthetic agent	Number of participants
Agitation	Citerio 2012	Sevoflurane	9 of 138 in propofol group and 7 of 136 in sevoflurane group
Agitation	Todd 1993	Isoflurane	3 of 40 in propofol group and none in isoflurane group
Haemodynamic disturbance	Todd 1993	Isoflurane	35 of 40 in propofol group and 37 of 40 in isoflurane group
Pain	Talke 2002	Isoflurane	16 of 20 in propofol group and 13 of 20 in isoflurane group

APPENDICES

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: [Anesthesia, Inhalation] explode all trees
#8 MeSH descriptor: [Anesthesia, 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 Anesthesia, Inhalation/ or Anesthesia, 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 anesthesia/ or intravenous anesthesia/ 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* or multicenter* 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

Appendix 4. Data extraction forms

Review title or ID

Study ID (*surname of first author and year first full report of study was published, e.g. Smith 2001*)

Report IDs of other reports of this study (*e.g. duplicate publications, follow-up studies*)

Notes:

1. General information

Date form completed (*dd/mm/yyyy*)

Name/ID of person extracting data

Report title

(*title of paper/abstract/report from which data are extracted*)

(Continued)

Report ID
(ID for this paper/abstract/report)
Reference details
Report author contact details
Publication type
(e.g. full report, abstract, letter)
Study funding sources
(including role of funders)
Possible conflicts of interest
(for study authors)
Notes:
2. Study eligibility

Study characteristics	Eligibility criteria	Yes	No	Unclear	Location in text
	(Insert eligibility criteria for each characteristic as defined in the Protocol)				(pg & ¶/fig/table)
Type of study	Randomized controlled trial				
	Controlled clinical trial				
	(quasi-randomized trial)				
Participants					
Types of interventions					
Types of outcome measures					
INCLUDE		EXCLUDE			
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW.

3. Population and setting

	Description	Location in text
	(Include comparative information for each group (i.e. intervention and controls) if available)	(pg & ¶/fig/table)
Population description		
(from which study participants are drawn)		
Setting		
(including location and social context)		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained	Yes No Unclear	
Notes:		

4. Methods

	Descriptions as stated in report/paper	Location in text
		(pg & ¶/fig/table)
Aim of study		
Design (e.g. parallel, cross-over, cluster)		
Unit of allocation		
(by individuals, clusters/groups or body parts)		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study		

(Continued)

Yes No Unclear

Notes:
5. Risk of bias assessment

See Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions.

Domain	Risk of bias			Support for judge- ment	Location in text (pg & ¶/fig/ta- ble)
	Low risk	High risk	Unclear risk		
Random sequence generation (selection bias)					
Allocation concealment (selection bias)					
Blinding of participants and per- sonnel (performance bias)				Outcome group: All/	
(if required)				Outcome group:	
Blinding of outcome assessment (detection bias)				Outcome group: All/	
(if required)				Outcome group:	
Incomplete outcome data (attrition bias)					
Selective outcome reporting? (reporting bias)					
Other bias					
Notes:					

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomized <i>(or total pop. at start of study for NRCTs)</i>		
Clusters <i>(if applicable, no., type, no. people per cluster)</i>		
Baseline imbalances		
Withdrawals and exclusions <i>(if not provided below by outcome)</i>		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Co-morbidities		
Other treatment received <i>(additional to study intervention)</i>		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

7. Intervention groups

Copy and paste table for each intervention and comparison group.

Intervention group 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)

(Continued)

Group name
No. randomized to group
(specify whether no. people or clusters)
Theoretical basis *(include key references)*
Description *(include sufficient detail for replication, e.g. content, dose, components)*
Duration of treatment period
Timing *(e.g. frequency, duration of each episode)*
Delivery *(e.g. mechanism, medium, intensity, fidelity)*
Providers
(e.g. no., profession, training, ethnicity etc. if relevant)
Co-interventions
Economic variables
(i.e. intervention cost, changes in other costs as result of intervention)
Resource requirements to replicate intervention
(e.g. staff numbers, cold chain, equipment)
Notes:
8. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text <i>(pg & ¶/fig/table)</i>
Outcome name	Mortality	
Time points measured		
Time points reported		
Outcome definition <i>(with diagnostic criteria if relevant)</i>		

(Continued)

Person measuring/reporting
Unit of measurement

(if relevant)

Scales: upper and lower limits (indicate whether high or low score is good)

Is outcome/tool validated?

Yes No Unclear

Imputation of missing data

(e.g. assumptions made for ITT analysis)

Assumed risk estimate

(e.g. baseline or population risk noted in Background)

Power
Notes:
Outcome 2

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name	Emergence from anaesthesia	
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Unit of measurement		
(if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data		

(Continued)

(e.g. assumptions made for ITT analysis)

Assumed risk estimate

(e.g. baseline or population risk noted in Background)

Power
Notes:
Outcome 3

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name	Brain relaxation	
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Unit of measurement (if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data (e.g. assumptions made for ITT analysis)		
Assumed risk estimate (e.g. baseline or population risk noted in Background)		
Power		
Notes:		

Outcome 4

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name	Intraoperative haemodynamic instability	
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Unit of measurement (if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data (e.g. assumptions made for ITT analysis)		
Assumed risk estimate (e.g. baseline or population risk noted in Background)		
Power		
Notes:		

Outcome 5

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name	Hospital stay	
Time points measured		

(Continued)

Time points reported
Outcome definition (with diagnostic criteria if relevant)

Person measuring/reporting
Unit of measurement

(if relevant)

Scales: upper and lower limits (indicate whether high or low score is good)

Is outcome/tool validated?

Yes No Unclear

Imputation of missing data

(e.g. assumptions made for ITT analysis)

Assumed risk estimate

(e.g. baseline or population risk noted in Background)

Power
Notes:
Outcome 6

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name	3 months outcome	
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Unit of measurement		
(if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?		

(Continued)

Yes No Unclear

Imputation of missing data

(e.g. assumptions made for ITT analysis)

Assumed risk estimate

(e.g. baseline or population risk noted in Background)

Power
Notes:

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome (Mortality)

Description as stated in report/paper				Location in text (pg & ¶/fig/table)
Comparison				
Outcome				
Subgroup				
Time point (specify whether from start or end of intervention)				
Results	Intervention		Comparison	
	No. events	No. participants	No. events	No. participants
No. missing participants and reasons				
No. participants moved from other group and reasons				
Any other results reported				

(Continued)

Unit of analysis *(by individuals, clusters/groups or body parts)*
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*
Reanalysis required? *(specify)*

Yes No Unclear

Reanalysis possible?

Yes No Unclear

Reanalysed results
Notes:
Dichotomous outcome *(Brain relaxation)*

Description as stated in report/paper

Location in text
(pg & ¶/fig/table)
Comparison
Outcome
Subgroup
Time point
(specify whether from start or end of intervention)
Results
Intervention
Comparison

No. events

No. participants

No. events

No. participants

No. missing participants and reasons
No. participants moved from other group and reasons
Any other results reported

(Continued)

Unit of analysis *(by individuals, clusters/groups or body parts)*
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*
Reanalysis required? *(specify)*

Yes No Unclear

Reanalysis possible?

Yes No Unclear

Reanalysed results
Notes:
Dichotomous outcome *(Three-month outcome)*

Description as stated in report/paper		Location in text <i>(pg & ¶/fig/table)</i>	
Comparison			
Outcome			
Subgroup			
Time point <i>(specify whether from start or end of intervention)</i>			
Results	Intervention		Comparison
	No. events	No. participants	No. events No. participants
No. missing participants and reasons			
No. participants moved from other group and reasons			
Any other results reported			

(Continued)

Unit of analysis *(by individuals, clusters/groups or body parts)*

Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*

Reanalysis required? *(specify)*

Yes No Unclear

Reanalysis possible?

Yes No Unclear

Reanalysed results

Notes:

Continuous outcome *(Emergence from anaesthesia)*

Description as stated in report/paper				Location in text <i>(pg & ¶/fig/table)</i>		
Comparison						
Outcome						
Subgroup						
Time point <i>(specify whether from start or end of intervention)</i>						
Post-intervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants
No. missing participants and reasons						
No. participants moved from other group and reasons						
Any other results reported						
Unit of analysis <i>(individuals, clusters/groups or body parts)</i>						
Statistical methods used and appropriateness of these methods <i>(e.g. adjustment for correlation)</i>						
Reanalysis required? <i>(specify)</i>						
Yes No Unclear						
Reanalysis possible?						

Yes No Unclear

(Continued)

Reanalysed results

Notes:

Continuous outcome (Intraoperative haemodynamic instability)

Description as stated in report/paper				Location in text (pg & ¶/fig/table)		
Comparison						
Outcome						
Subgroup						
Time point (specify whether from start or end of intervention)						
Post-intervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants
No. missing participants and reasons						
No. participants moved from other group and reasons						
Any other results reported						
Unit of analysis (individuals, clusters/groups or body parts)						
Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation)						
Reanalysis required? (specify)						
Yes No Unclear						
Reanalysis possible?						

Yes No Unclear

(Continued)

Reanalysed results

Notes:

Continuous outcome (Hospital stay)

Description as stated in report/paper				Location in text <i>(pg & ¶/fig/table)</i>		
Comparison						
Outcome						
Subgroup						
Time point <i>(specify whether from start or end of intervention)</i>						
Post-intervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants
No. missing participants and reasons						
No. participants moved from other group and reasons						
Any other results reported						
Unit of analysis <i>(individuals, clusters/groups or body parts)</i>						
Statistical methods used and appropriateness of these methods <i>(e.g. adjustment for correlation)</i>						
Reanalysis required? <i>(specify)</i>						
Yes No Unclear						
Reanalysis possible?						

Yes No Unclear

(Continued)

Reanalysed results

Notes:

Other outcome

Description as stated in report/paper					Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Time point (specify whether from start or end of intervention)					
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis (by individuals, clusters/groups or body parts)					
Statistical methods used and appropriateness of these methods					
Reanalysis required? (specify)					
	Yes	No	Unclear		
Reanalysis possible?					
	Yes	No	Unclear		
Reanalysed results					
Notes:					

10. Applicability

Have important populations been excluded from the study? <i>(Consider disadvantaged populations and possible differences in the intervention effect)</i>	Yes	No	Unclear
Is the intervention likely to be aimed at disadvantaged groups? <i>(e.g. lower socioeconomic groups)</i>	Yes	No	Unclear
Does the study directly address the review question? <i>(any issues of partial or indirect applicability)</i>	Yes	No	Unclear
Notes:			

11. Other information

	Description as stated in report/paper	Location in text <i>(pg & ¶/fig/table)</i>
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information <i>(from whom, what and when)</i>		
Notes:		

Appendix 5. Modified Aldrete Scale score

Modified Aldrete score	Score
Activity	2
1. Moves all extremities	1
2. Moves 2 extremities	0
3. Unable to move extremities	
Respiration	2

(Continued)

1. Breathes deeply, coughs freely	1
2. Dyspnoeic, shallow or limited breathing	0
3. Apnoeic	
Circulation (blood pressure)	2
1. 20 mmHg > preanaesthetic level	1
2. 20 - 50 mmHg > preanaesthetic level	0
3. 50 mmHg > preanaesthetic level	
Consciousness	2
1. Fully awake	1
2. Arousable on calling	0
3. Not responding	
Oxygen saturation	2
1. SpO ₂ > 92% on room air	1
2. Supplemental O ₂ required to maintain SpO ₂ > 90%	0
3. SpO ₂ < 90% with O ₂ supplementation	

WHAT'S NEW

Date	Event	Description
4 January 2017	Amended	Co-published in the Journal of Neuroanaesthesiology and Critical Care (Prabhakar 2017)

CONTRIBUTIONS OF AUTHORS

Hemanshu Prabhakar (HP), Gyaninder Pal Singh (GPS), Charu Mahajan (CM), Indu Kapoor (IK), Mani Kalaivani (MK), Vidhu Anand (VA).

Conceiving the review: GPS.

Co-ordinating the review: GPS, HP.

Undertaking manual searches: GPS, VA.

Screening search results: HP, VA.

Organizing retrieval of papers: GPS, HP.

Screening retrieved papers against inclusion criteria: HP, VA.

Appraising quality of papers: HP, VA.

Abstracting data from papers: CM, IK.

Writing to authors of papers for additional information: HP.

Providing additional data about papers: CM, IK.

Obtaining and screening data on unpublished studies: CM, IK.

Managing data for the review: HP, CM, IK.

Entering data into Review Manager ([RevMan 5.3](#)): HP, CM.

Analysing RevMan statistical data: MK, HP.

Performing other statistical analysis not using RevMan: MK.

Interpreting data: MK, HP, CM.

Making statistical inferences: MK, HP.

Writing the review: HP.

Securing funding for the review: None

Performing previous work that was the foundation of the present study: None

Serving as guarantor for the review (one author): CM.

Taking responsibility for reading and checking the review before submission: HP, CM.

DECLARATIONS OF INTEREST

Gyaninder Pal Singh: none known.

Hemanshu Prabhakar: none known.

Mani Kalaivani: none known.

Vidhu Anand: none known.

Charu Mahajan: none known.

Indu Kapoor: none known.

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Internal sources

- All India Institute of Medical Sciences, New Delhi, India.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between [Singh 2013](#) and the review include the following.

1. The lead author of the review has changed from Gyaninder Pal Singh to Hemanshu Prabhakar.
2. Two new review authors (Charu Mahajan and Indu Kapoor) have joined the review team.
3. The new review authors (IK and CM) were assigned tasks at different stages of preparation of the review, such as Abstracting data from papers, Providing additional data about papers, Obtaining and screening data on unpublished studies, Managing data for the review, Entering data into Review Manager, Interpreting data, Serving as guarantor for the review and Taking responsibility for reading and checking the review before submission.
4. We have changed the title to "Intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery".
5. We had not described in the protocol assessment of the outcome of Brain relaxation. We have replaced the 4- to 5-point scales with 3- to 4-point scales, as we found no included study that described brain relaxation on a 5-point scale.
6. Under Types of interventions, we have added thiopentone sodium to the existing list of propofol and etomidate.

7. We did not create the planned Summary of findings table for the outcomes of Mortality, Intraoperative haemodynamic instability, Hospital stay and Three-month outcomes, as none of these were outcomes for this review.
8. We have included in our review full texts and abstracts of relevant randomized controlled trials (RCTs).
9. We have rephrased the review objectives.
10. We have added a sentence to the end of the section [Why it is important to do this review](#).
11. Under "Methods of Study - Data Collection and Analysis - Data extraction and management", we have changed review author names.
12. We have added a sentence to the end of the section summarizing review findings.