

1 **Title Page**

2 **Comparison of Asleep-Awake-Asleep and Monitored Anesthesia Care in reducing Awake Craniotomy**  
3 **failure during brain surgery: A Systematic Review and Meta-Analysis of the literature from 2014 to**  
4 **2018.**

6 **Authors**

7 Daniele Natalini, MD<sup>1,2,3</sup>, Mario Ganau, MD, PhD, FEBNS, FACS<sup>4</sup>, Ruben Rosenkranz, PhD<sup>5</sup>, Tatjana  
8 Petrinic<sup>6</sup>, Karina Fitzgibbon, MB BChir, BAO, MSc, FCAI<sup>2</sup>, Massimo Antonelli, MD<sup>1,3</sup>, Lara Prisco, MD,  
9 MSc, AFRCA, AFFICM<sup>\*2,7</sup>

11 <sup>1</sup> Istituto di Anestesia e Rianimazione, Università Cattolica del Sacro Cuore Rome, Italy

12 <sup>2</sup> Neuroanaesthesia and Neurosciences Intensive Care Unit, John Radcliffe Hospital, Oxford, United  
13 Kingdom

14 <sup>3</sup> Dipartimento di Scienze dell’Emergenza Anestesiologiche e della Rianimazione, Fondazione Policlinico  
15 Universitario A.Gemelli IRCCS

16 <sup>4</sup> Department of Neurosurgery, John Radcliffe Hospital, Oxford, United Kingdom

17 <sup>5</sup> IsTerre, Institut des Sciences de la Terre, Grenoble University, Grenoble, France

18 <sup>6</sup> Bodleian Healthcare Libraries, University of Oxford

19 <sup>7</sup> Anaesthesia Neuroimaging Research Group, Wellcome Centre for Integrative Neuroimaging,  
20 Nuffield Department of Clinical Neurosciences, University of Oxford, United Kingdom

22 **\*Corresponding Author**

23 Lara Prisco

24 Neuro-Anaesthesia and Neurosciences Intensive Care Unit

25 John Radcliffe Hospital, Level 1 West Wing, Headley Way – OX3 9DU, Oxford

26 Email: [lara.prisco@ndcn.ox.ac.uk](mailto:lara.prisco@ndcn.ox.ac.uk)

27 Tel: 00441865857772

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33 **Abstract**

34 Awake Craniotomy (AC) is the preferred surgical option for intractable epilepsy and resection of tumors  
35 adjacent or within eloquent cortical areas. The two most widely used anesthetic protocols for AC are:

monitored anesthesia care (MAC), and asleep-awake-asleep (SAS). In this study we used a random-effects modelled meta-analysis, following the Cochrane methodology for Meta-Analysis and Systematic Reviews to synthesize the most recent evidence and establish which anesthetic technique is safer and more effective for AC.

We included both randomized controlled trials and observational studies that explored the incidence of AC failure, the duration of surgery and the length of hospital stay (LOS) in adult patients (age  $\geq 18$  years) undergoing AC.

Eighteen studies were included in the final analysis. We found a lower risk of AC failure in the MAC group compared to SAS, which was statistically significant (AC failure global pooled proportion MAC vs SAS: 1% vs 4%; OR, 0.28; 95% CI 0.11–0.71;  $p=0.007$ ) and a shorter procedure time (global pooled mean MAC vs SAS: 224.44 vs 327.94 min; MD -48.76 min; 95% CI -61.55 to -35.97;  $p<0.00001$ ). SAS was associated with less intraoperative seizures (seizures global pooled proportion MAC vs SAS: 10% vs 4%; OR 2.38; 95% CI 1.05–5.39;  $p=0.04$ ). The difference in intraoperative nausea and vomiting was not statistically significant (global pooled proportion MAC vs SAS: 4% vs 8%; OR 0.86; 95% CI 0.30-2.45;  $p=0.78$ ). LOS was shorter in the MAC group (MAC vs SAS: 3.96 vs 6.75 days; MD -1.30; 95% CI -2.69-0.10;  $p=0.07$ ).

MAC is associated with lower AC failure rate and shorter procedure time compared with SAS, whereas SAS leads to a lower incidence of intraoperative seizures. However, the superiority of one technique over the other needs to be confirmed in large randomized studies.

**Keywords:** neuroanesthesia, awake craniotomy, monitored anesthesia care, asleep-awake-asleep, epilepsy neurosurgery, neurooncological surgery

## INTRODUCTION

Awake Craniotomy (AC) is considered “gold standard” for resection of brain lesions close to eloquent areas<sup>1</sup>. Modern AC techniques have evolved in combination with cortical mapping, a method of intraoperative neurophysiological monitoring used for intractable epilepsy or resection of anatomically challenging tumors<sup>2, 3</sup>. Over the years, optimization of cortical and subcortical mapping facilitated progressive improvement in resection of tumors, without injuring functional areas of the brain<sup>4, 5</sup>. A recent meta-analysis by Lu et al. compared AC to surgery performed under continuous General Anesthesia (GA), and concluded that operative and functional outcomes are comparable<sup>6</sup>. However, AC generates less postoperative nausea and vomiting, a shorter length of hospital stay (LOS), and lower medium- and long-term costs, achieving a decrease in morbidity and a faster return to work<sup>7, 8</sup>.

Sedation and analgesia must be finely tuned to maintain hemodynamic stability, with the lucid cooperation required to perform neuropsychological tasks <sup>9, 10</sup>. Moreover, expertise in regional anesthesia of the scalp, and in advanced airway management are essential <sup>11-13</sup>.

Authors describe two main protocols for anesthetic management during AC: the monitored anesthesia care (MAC) technique and the Asleep-Awake-Asleep (SAS) technique. MAC is a conscious sedation technique where patients maintain spontaneous breathing and airway control throughout the procedure. Sedation and analgesia are used mostly to allow respectively a tolerable and pain-free incision, craniotomy and closure. The SAS technique provides GA and airway protection by means of an airway device insertion (i.e. a laryngeal mask) until the dura mater is opened and the brain exposed. At this point the patient is woken up and the airway device removed. GA and airway protection are then regained after brain mapping (and sometimes resection) is complete <sup>9, 14</sup>.

Other authors propose an approach based solely on optimal local anesthesia, an “awake throughout” method, where only local scalp block and infiltration with local anesthetic of pin sites, incision site, and dura leaflets are performed <sup>15-17</sup>.

The use of continuous infusion or intermittent boluses of short-acting anesthetic medications, such as propofol, remifentanyl, fentanyl is widely documented in the literature. Increasingly, anesthesiologists are using dexmedetomidine for conscious sedation. Dexmedetomidine is a highly selective  $\alpha_2$ -adrenoceptor agonist with sedative, sympatholytic and anxiolytic effects, with little risk of respiratory depression <sup>18</sup>. Although well-established techniques, their safety and efficacy remain a topic of discussion in the literature; as are patient compliance, outcomes, and the balance between new neurological deficits and extent of tumor resection. Most studies involving these techniques are retrospective case series and prospective cohort studies, with few randomized controlled trials.

In the largest review published to date, Stevanovic et al. <sup>19</sup> described different AC anesthetic techniques concluding that both SAS and MAC have similar safety and efficacy profiles with similar complications rates. <sup>20, 21</sup>. However, no studies comparing SAS to MAC were included in the review, and their findings arose from indirect evidence <sup>19</sup>.

More recently Lu et al. published a systematic review and meta-analysis comparing AC to GA <sup>6</sup> but few studies were included, and only surgical outcomes were assessed

Both reviews included studies published over a wide time period, resulting in large heterogeneity of anesthetic approaches, therefore increasing the risk of bias <sup>6, 19</sup>.

AC with intraoperative mapping and direct electrical stimulation became popular for neuro-oncology and epilepsy surgery <sup>9</sup>. Nowadays, these traditional indications are being extended to other types of neurosurgical procedures, such as resection of cerebrovascular malformations, with the aim of improving surgical safety and clinical outcomes <sup>22</sup>.

Since 2015, four new RCT's and three studies comparing SAS to MAC were published. Therefore, this review is important in the context of establishing which anesthetic technique for AC has the best outcomes.

## Objectives

In this systematic review we aim to synthesize the evidence published from 2014 to 2018 on anesthetic management for AC.

The primary objectives are to compare SAS and MAC by describing the rate of: a) AC failure, defined as the premature interruption of the process of brain mapping; b) intraoperative complications; and c) postoperative variables with these two techniques.

Secondly, we aim to use the evidence synthesis to try to establish which is more effective in reducing adverse events rate and improving outcomes.

## METHODS

The systematic review protocol was published with the National Institute for Health Research international prospective register of scientific reviews (PROSPERO, CRD42018108057, see Supplementary materials Appendix S1) and was updated according to the progress of the evidence synthesis.

The original protocol has been modified in light of the results of the database search. The present review was conducted and reported following the PRISMA guidelines and recommendations (see Supplementary Materials Appendix S2 for PRISMA Checklist)<sup>23-25</sup>.

### Type of studies

The following study designs were considered eligible for inclusion: randomized controlled trials, retrospective and prospective observational studies (cohort studies, and case series). These had to be written in English and published between 2014 and 2018. Eligible studies had to specify which anesthetic approach was adopted and report on at least one of the outcome measures considered.

We excluded studies with mixed cohorts, pediatric populations, animal studies, and neuropsychological studies, as well as reviews, conference abstracts, editorials, letters and expert opinions.

### Type of participants

Adults (aged 18 or above), undergoing AC and brain mapping for resection of epileptic foci or brain tumors involving any functional cortex.

### Type of interventions

We included studies comparing SAS to MAC, studies that reported on at least one AC technique (SAS, MAC or “awake throughout”), and studies comparing AC to surgery under GA.

### Type of outcomes measures

#### Primary outcomes

As a primary outcome, we considered the incidence of AC failure, defined as failure to achieve complete intraoperative awake mapping of the brain.

## **Secondary outcomes**

We explored the following secondary outcomes:

- incidence of peri-operative nausea and vomiting;
- intraoperative seizures;
- intraoperative respiratory adverse events and hypertensive episodes;
- duration of the procedure;
- length of Stay (LOS).

## **Search methods**

The electronic search was performed with the assistance of a senior librarian expert in perioperative medicine (TP, Bodleian Health Care Libraries: Cairns Library, University of Oxford). We searched Medline and Embase databases for studies published between 01/01/2014 and 01/09/2018 (see Supplementary Material Appendix S3 for details of the search strategy).

## **Data collection and analysis**

### **Study selection**

Two independent reviewers (DN and MG) screened all studies resulting from the initial search. Studies were then screened from titles and abstracts after removal of all duplicates. Full-text articles of potentially eligible articles were assessed for inclusion. Disagreements over the eligibility of particular studies were resolved through Delphi approach between two other authors (KF, LP). The statistical analysis was conducted by a reviewer (RR), with expertise in biostatistics and data analysis, belonging to an independent institution.

### **Data extraction**

Data extraction was conducted using an Excel Data Extraction Form. It included: type of study, population size, summary of aims and results for each study, anesthetic management, intraoperative and postoperative variables and outcome measures.

### **Assessment of risk of bias in included studies**

The risk of bias for RCTs and prospective cohort studies was assessed using the Cochrane Collaboration tool and RevMan5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) <sup>26</sup>. Two reviewers (DN, MG) attributed a judgment of low, high, or unclear risk of bias for each domain.

The risk of bias and quality rating for non-randomized studies were assessed using the Newcastle-Ottawa scale <sup>27</sup>. A “good” quality score required 3 or 4 stars in selection, 1 or 2 star(s) in comparability, and 2 or 3

stars in outcomes. A “fair” quality score required 2 stars in selection, 1 or 2 star(s) in comparability, and 2 or 3 stars in outcomes. A “poor” quality score reflected 0 or 1 star in selection, or 0 star in comparability, or 0 or 1 star in outcomes.

The assessment was performed independently by two authors. For the studies comparing SAS directly to MAC, we selected five outcomes (AC failure, intraoperative seizures, intraoperative nausea and vomiting, duration of surgery and LOS) and we determined the quality of the evidence for each outcome using the GRADE approach<sup>28</sup> (RevMan 5.3, GRADEpro GDT: GRADEpro Guideline Development Tool Software. McMaster University, 2015. Developed by Evidence Prime, Inc.). The quality of evidence was downgraded in the presence of a high risk of bias in at least one study, heterogeneity, inconsistency, indirectness or imprecision of results. The grading was reduced by one level when the limitation was serious and by two levels when the limitation was very serious.

### Measures of treatment effect

We assessed the treatment effect size only for studies comparing SAS to MAC. For each dichotomous outcome measure (AC failure, intraoperative seizures, intraoperative nausea and vomiting) the Odds Ratio (OR) with 95% confidence interval (CI) was calculated using the Mantel-Haenszel method (M-H). For continuous measurements (duration of procedure and LOS) we analyzed the data as mean difference (MD) or standardized mean difference (SMD) using the inverse variance method. For both types of variables, data were combined using a random effect model.

Results are presented as forest plots. Analyses with  $p < 0.05$  were interpreted as significant.

### Data synthesis

For the qualitative analysis, we performed a descriptive synthesis of the findings from the included studies. In the quantitative analysis, after excluding three studies presenting a sub analysis of the same population<sup>7, 9, 29</sup> described in the original study by Eseonu et al.<sup>30</sup>, we compared the following five outcomes variables:

- AC failure;
- intraoperative seizures;
- intraoperative nausea and vomiting;
- duration of surgery;
- LOS.

We were not able to include the rate of conversion to GA in the meta-analysis of proportions, because in many studies the rate of conversion to GA was not reported. We defined AC failure as premature interruption or non-performance of mapping. Due to the inability to systematically assess AC failure as outcome measure, we considered the percentage of global AC failures a more relevant and bias-free parameter. Early and late neurological dysfunction were not considered in the analysis because of the heterogeneity of available data. In fact, pooling all of the neurological dysfunction would have led to a high

risk of bias, because different types of deficits reflect different locations of brain lesions or epileptogenic foci across the studies. Moreover, there was a high heterogeneity in the timing criteria used to define permanent neurological deficit.

Two authors (DN and RR) pooled the data for each outcome measure using the random-effects model for meta-analysis and presented the results with 95% confidence intervals (95%CI). The proportions were grouped into SAS and MAC, and forest plots were produced using and the “meta” package within the “R” environment<sup>31</sup>.

We performed additional comparative meta-analysis and forest plots for each one of the mentioned five outcomes including all the studies comparing SAS directly to MAC using RevMan 5.3.

### **Missing data**

Missing data such as standard deviations (SD) were imputed following the Cochrane Handbook for Systematic Reviews<sup>26</sup> borrowing the values from other comparable studies. No additional information was sought from the authors.

### **Assessment of heterogeneity**

We assessed the variation between studies using a standard Chi<sup>2</sup> test and I<sup>2</sup> statistic<sup>32</sup>. The Chi<sup>2</sup> test is a statistical test for heterogeneity, I<sup>2</sup> estimates the quantity of inconsistency across studies in the meta-analysis. The following ranges of I<sup>2</sup> are used to interpret heterogeneity: 0% to 40%: might not be significant; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.

### **Assessment of reporting bias**

We assessed publication bias using Funnel plots and study effect using Baujat plots.

## **RESULTS**

### **Results of the search**

After de-duplication, we obtained 408 studies (Figure 1). Two additional studies were identified from backward searches. We excluded 371 studies after applying inclusion and exclusion criteria, and 37 full-text articles were assessed. 21 studies were included in the qualitative and descriptive analysis. Four studies by Eseonu et al. partially reported on the same cohort<sup>7, 9, 29, 30</sup>; hence we included only the largest study in the quantitative analysis<sup>30</sup>. A total of 18 studies were included in the final quantitative analysis (Appendix S4).

## Included studies

Study characteristics are described in Table 1. A total of four RCTs<sup>16, 18, 33, 34</sup>, four prospective observational studies<sup>30, 35-37</sup>, five observational retrospective studies<sup>38-42</sup> and five case series<sup>17, 43-46</sup> were included in the quantitative analysis. The anesthetic techniques used in each study are described in Table 2.

## Risk of bias of the studies included

We assessed the risk of bias for four RCTs and one prospective cohort using the Cochrane Collaboration tool and RevMan 5.3 (Figure 2). Two RCTs were globally judged at low risk of bias, with an unclear risk of reporting bias due to insufficiency of available information<sup>18, 33</sup>. The study by Cao et al. was judged as unclear risk for selection bias because of insufficient reporting about the sequence generation process and method of concealment, and as unclear risk of detection and reporting bias due to lack of available information<sup>16</sup>. The last RCT by Wang et al. presented a high risk of performance bias because of impossibility of blinding of both participants and clinical staff and a high risk of reporting bias. The study presented an unclear risk of selection bias because neither the randomization system nor the method of concealment were described<sup>34</sup>. The only prospective cohort study included was considered at high risk of bias with a low risk of detection bias and attrition bias<sup>30</sup>.

The risk of bias for the other non-randomized studies was assessed using the Newcastle-Ottawa scale<sup>27</sup>. We rated the quality of the studies as “good” for four studies<sup>7, 29, 30, 37</sup>, and “poor” for twelve studies<sup>17, 35, 36, 38-46</sup>. We assessed the quality of evidence for every outcome measure in the studies comparing SAS to MAC using the GRADE approach<sup>28</sup>. We found a very low grade for all the five outcomes assessed (Appendix S5).

## Synthesis of results

### SAS vs MAC

The comparison between SAS and MAC was based on three studies (Figure 3)<sup>30, 38, 42</sup>. MAC was associated with a statistically significant lower risk of AC failure compared to SAS (OR, 0.28; 95% CI, 0.11–0.71;  $p=0.007$ ;  $I^2=0\%$ ). The study by Suero Molina et al. contributed largely to this, thus leading to a large-study effect on the result.

SAS was associated with less risk of intraoperative seizures compared to MAC (OR, 2.38; 95% CI, 1.05–5.39;  $p=0.04$ ;  $I^2=0\%$ ). No differences in the risk of intraoperative nausea and vomiting between MAC and SAS were described (OR 0.86; 95% CI 0.30-2.45;  $p=0.78$ ).



MAC was associated with a statistically significant shorter procedure time compared to SAS (MD, -48.76 mins; 95% CI, -61.55 to -35.97;  $p < 0.00001$ ;  $I^2 = 0\%$ ). MAC was not associated with a statistically significant shorter length of stay compared to SAS (MD, -1.30 days; 95% CI, -2.69 to 0.10;  $p = 0.07$ ;  $I^2 = 12\%$ ).

## AC failure

The pooled proportions of AC failure in the two subgroups MAC and SAS were 1% [95% CI 0-3] and 5% [95% CI 1-10] respectively (Figure 4). Heterogeneity was moderate in the MAC subgroup ( $I^2 = 49\%$ ) and substantial in the SAS subgroup ( $I^2 = 81\%$ ). With reference to the SAS subgroup, the study published by Suero Molina et al. contributes substantially to the overall heterogeneity compared to other included studies (Appendix S6) <sup>42</sup>. The overall proportion was 2% [95% CI 1-5] in a pooled sample of 1105 patients. The primary cause of AC failure was intraoperative agitation or lack of compliance during the intraoperative mapping (19/54, 35%), followed by intraoperative seizures (7/54; 13%), drowsiness or over-sedation (5/54; 9%), pain (5/54; 9%), acute neurological deterioration (4/54; 7%) (Fig. 4). Other causes were reported in 9/54 patients (17%). Elbakry et al. did not describe the cause of AC failure (5/54; 9%) <sup>33</sup>.

## Intraoperative seizures

Intraoperative seizures are a frequent and undesirable complication during cortical and subcortical mapping; they are usually induced by direct electrical stimulation and tend to stop spontaneously or after irrigation with cold saline solution. The pooled proportion of intraoperative seizures in the two subgroups, MAC and SAS, was 10% [95% CI 5-17] and 4% [95% CI 2-8] respectively (Figure 4). Heterogeneity was substantial in the both (MAC  $I^2 = 71\%$ , SAS  $I^2 = 67\%$ ). The overall proportion of intraoperative seizures was 7% [95% CI 4-11] in a pooled sample of 1019 patients (Appendix S7 and S8). In the SAS subgroup, Wang et al. included adults undergoing elective epilepsy surgery, which could explain the higher proportion of intraoperative seizures <sup>34</sup>. In two studies by Eseonu et al. and Groshev et al. preoperative anticonvulsants were given to all patients, which could account for a lower rate of seizures <sup>30, 46</sup>. In the other studies included in the MAC subgroup, with the exception of a retrospective analysis by Dilmen et al. <sup>38</sup>, no prophylactic dose of anticonvulsant was given. Goettel et al. did not specify whether any prophylactic antiepileptic medication was given <sup>18</sup>.

## Intraoperative nausea and vomiting

Intraoperative nausea and vomiting can adversely affect the quality of mapping and patient satisfaction. The pooled proportion of intraoperative nausea and vomiting in the MAC and SAS subgroups was 4% [95% CI 1-9] and 8% [95% CI 1-19], respectively (Figure 4). Heterogeneity was moderate in the MAC subgroup ( $I^2 = 56\%$ ) and substantial in the SAS subgroup ( $I^2 = 91\%$ ). The high incidence of nausea and vomiting in the study by Kamata et al. related to their study design: half of the population did not receive prophylactic dexamethasone, which had a significant impact on the pooled proportion in the SAS subgroup (Appendix S9

and S10)<sup>37</sup>. The overall proportion of intraoperative nausea and vomiting was 6% [95% CI 2-11] in a pooled sample size of 862 patients (Appendix S8 and S9).

### Duration of surgery

Where explicitly reported, we considered the duration of the surgical procedure, without including the time needed for anesthetic preparation. Dilmen et al. and Eseonu et al. did not specify how they measured time<sup>30, 38</sup>. This introduces a potential risk of bias and could possibly explain why longer times are described in these two studies. In a few cases, the SD value was not available, hence it was imputed in order to perform the statistical analysis. The pooled mean duration of surgery in the two subgroups, MAC and SAS, was 224.44 mins [95% CI 186.59-262.29] and 327.94 mins [95% CI 260.28-395.59], respectively (Figure 4). Heterogeneity was considerable in both subgroups:  $I^2=97\%$  for MAC, and  $I^2=99\%$  for SAS. The pooled mean duration of surgery was 269 mins [95% CI 225.94-312.13] (Appendix S11 and S12).

### Length of Stay

The pooled mean LOS in the MAC and SAS subgroups was 3.96 days [95% CI 2.88-5.54] and 6.75 days [95% CI 3.93-11.58], respectively (Figure 4). Heterogeneity was again considerable in both:  $I^2=94\%$  for MAC, and  $I^2=98\%$  for SAS. The overall pooled LOS was 5.06 days [95% CI 225.94-312.13] (Appendix S13 and S14). Dilmen et al. and Pallud et al. described a longer LOS<sup>38, 44</sup>.

### Other Outcomes

The rate of intraoperative respiratory adverse events and hypertensive episodes was minimal and not described in enough studies to allow a systematic analysis (Appendix S15 and S16).

Suero Molina et al. described a longer period of hypertension before induction of anesthesia in the SAS subgroup and less antihypertensive drug use in the MAC group<sup>42</sup>. Dilmen et al. concluded that blood pressure was higher in the MAC group during pinning and incision, while higher in the SAS group during neurological examination<sup>38</sup>. Kulikov et al. used an inhalational anesthetic, Xenon, and 50% of included patients experienced at least one hypertensive episode (SBP > 150 mmHg) during the incision and craniotomy phases<sup>36</sup>.

Goettel et al. and Elbakry et al. reported more respiratory adverse events when propofol and remifentanyl were used together for MAC<sup>18, 33</sup>. Dilmen et al. described a higher incidence of desaturation in the MAC group using dexmedetomidine<sup>38</sup>. Suero Molina et al. included 180 patients and in only four cases, two in the MAC group and two in the SAS group, was intraoperative hypoxia reported<sup>42</sup>. Eseonu et al. reported no respiratory adverse events. In the last two comparative studies, dexmedetomidine was used alone or in combination<sup>30</sup>.

No deaths due to operative complications were reported.

## DISCUSSION

With the increasing use of AC in neurosurgery, MAC and SAS have emerged as the preferred anesthetic techniques.

This systematic review and meta-analysis synthesize the evidence published from 2014 to 2018 to explore the most effective technique of reducing the risk of AC failure, defined as the inability to complete cortical/subcortical mapping and brain lesion resection.

The pooled rate of AC failure in our meta-analysis was 3%. This is slightly higher than that reported by Stevanovic et al. (2%)<sup>19</sup>. A deviation towards a higher pooled rate of AC failure (5%) in the SAS subgroup is mostly due to a single study effect. Suero Molina et al. described an AC failure rate of 21% in the SAS subgroup mainly due to the lack of patient compliance<sup>42</sup>. Indeed, in the studies included in this systematic review, agitation and lack of compliance were the main reasons for AC failure (35%). This supports the maxim of adequate patient preparation.

Intraoperative seizures represent the second cause of AC failure (13%) and one of the most frequent intraoperative complications. The majority of intraoperative seizures are caused by DES and are usually terminated by irrigation of the brain with cold saline solution, without administration of anticonvulsant drugs. The pooled rate of intraoperative seizures in our systematic review was 7%, slightly lower than the 8% reported by Stevanovic et al.<sup>19</sup>. In only 5 of the 18 studies included in the statistical analysis were anticonvulsant drugs routinely administered preoperatively<sup>30, 33, 38, 39, 46</sup>. Of note, anticonvulsant-induced excessive sedation could affect intraoperative mapping<sup>47</sup>. In the MAC subgroup, we identified a higher incidence of seizures (10%) compared with the SAS subgroup (4%) and compared with the same subgroup analysis performed by Stevanovic et al. (8%)<sup>19</sup>. Our comparative analysis between MAC and SAS based on three studies confirmed this trend, with more events in the MAC subgroup. The MAC subgroup reported a higher use of dexmedetomidine, whereas none was used to perform SAS technique in these three studies. There has been an increase in use of dexmedetomidine in the last four years, primarily for MAC, whereas for SAS management a classical regimen using propofol and remifentanyl is still preferred. Animal models describe a possible dexmedetomidine-induced reduction in the epileptogenic threshold; this likely represents a drug-mediated reduction in the central noradrenergic activity that leads to a facilitatory effect on seizure expression<sup>48, 49</sup>. Although these results have not been reproduced in humans, this could have played a role in the observed difference, in addition to the lack of routine use of preoperative anticonvulsants in the majority of the cases.

Intraoperative nausea and vomiting can be unpleasant for patients and interferes with intraoperative mapping. 4% of patients during MAC and 8% during SAS experienced this complication, with a pooled rate of 6%. A single dose of dexamethasone preoperatively helps to reduce the risk of vomiting as described by Kamata et al.<sup>37</sup>, and propofol can have a role in reducing the rate of nausea and vomiting during SAS due to its anti-emetic properties. No statistically significant differences were found between MAC and SAS with

regard to postoperative nausea and vomiting (PONV). Dexamethasone was routinely given to prevent PONV in majority of the studies.

The incidence of major respiratory and cardiovascular adverse events was low, thus potentially expanding the indication for this technique to patients with cardiorespiratory contraindications to GA. During SAS the LMA (Laryngeal Mask Airway) was the preferred device. Joswig et al. routinely performed fiberoptic intubation to protect the airway during closure <sup>45</sup>. No airway devices were generally used during conscious sedation, and supplemental oxygen was typically delivered through nasal prongs.

MAC was associated with a statistically significant shorter procedure time compared to SAS. This is because no airway devices are usually involved, and a shorter time is needed for emergence from sedation and readiness to perform neurological tasks. Bispectral Index (BIS) monitoring, a useful but non-essential tool to guide the anesthetist through the phases of the procedure by allowing a targeted modulation of the hypnotic agents, was not routinely used <sup>50</sup>.

There were no significant differences between MAC and SAS in the LOS, and the majority of patients were discharged from hospital during the first week. In the review by Lu et al. AC had a significantly shorter LOS compared to craniotomy performed under GA <sup>6</sup>. In very select cases, same-day discharge is feasible <sup>51</sup>.

In 9 out of the 11 studies that adopted MAC, dexmedetomidine was the first line sedative, either alone or in combination with propofol or remifentanyl. In the systematic review by Stevanovic et al. in 2016, only in 8 out of 28 studies was dexmedetomidine used for MAC <sup>19</sup>. This increase in its use could be due to its optimal pharmacological profile which enhances patients' safety. The quality of intraoperative mapping using dexmedetomidine alone, or in combination, is comparable to propofol and remifentanyl alone, but dexmedetomidine can reduce the risk of respiratory adverse events and the demand for postoperative analgesia. Dexmedetomidine for MAC is also associated with shorter arousal times, thus making the procedure more comfortable for patients, with an acceptably low risk of bradycardia and hypotension <sup>20, 35, 40, 42, 43, 52, 53</sup>.

A propofol/remifentanyl combination remains the most frequently used regimen for the SAS technique, where dexmedetomidine was used in only two cases out of eight.

Kulikov et al. introduced Xenon as the primary hypnotic agent for AC <sup>36</sup>. The use of Xenon was feasible and safe and resulted in a shorter period of intraoperative emergence for brain mapping but with more hypertensive episodes during craniotomy and pinning.

We performed a new literature search at the end of the systematic review to assess literature published between September 2018 and March 2019. We found 36 new items in Medline and 43 in Embase. After excluding duplicates, four full-text articles were assessed. Only one study by Wang et al. could be considered eligible for inclusion in our review <sup>54</sup>. In this retrospective analysis of 41 elective MAC awake craniotomies for epileptic tumor resection, the only outcome explored was the rate of seizures (7%), which

was comparable with the results of our meta-analysis, but of note the entire cohort had a history of preoperative seizures.

Three studies were not eligible for inclusion. Two retrospective studies by Gerritsen et al. and Zelitzki et al. compared MAC to GA<sup>55, 56</sup>. These studies did not assess intraoperative outcome or rate of AC failure. Frati et al. in 2018 published an interesting analysis on the role of hypnosis in awake surgery<sup>57</sup>. Only six patients were included, and the authors integrated their data with other literature. The result was a comparison between a hypnosis-based approach and a classical SAS technique. According to this study, hypnosis seems to decrease the incidence of intraoperative pain and complications and postpones refractoriness to intraoperative neuropsychological testing.

### **Limitations**

Our systematic review is based on a large number of observational, mainly retrospective, studies with a high risk of bias. This is more apparent in the higher incidence of AC failure in the SAS group, that is mainly influenced by the result of the study by Suero Molina et al<sup>42</sup>, a cohort study significantly larger than other studies included.

In the analysis of the LOS and the duration of surgery data was often missing. Hence, we had to impute the SD value. Furthermore, a lack of reporting in many studies led to the exclusion of several potential outcomes of interest from our statistical analysis.

The initial aim of producing a meta-analysis of new and permanent postoperative neurological deficit was difficult to assess because of the presence of a significant biological bias and the numerous surgical confounders involved. Indeed, the brain regions affected in the included population are very heterogeneous.

### **Conclusions**

The rate of AC failure is minimal and comparable to the rate described in previous studies.

MAC is demonstrated to be statistically associated with lower AC failure rate and shorter procedure time, and a tendency (non-statistically significant) towards reduced LOS and incidence of PONV compared with SAS.

We found a slightly higher rate of intraoperative seizures in patients sedated with dexmedetomidine. A relative effect of seizure reduction in the SAS group cannot be excluded, possibly due to the anticonvulsant effect of propofol.

Due to the abovementioned limitations of this systematic review and meta-analysis, further randomized studies directly comparing MAC vs SAS are required to confirm our findings, and adequately powered studies are necessary to explore subgroups of patients. Finally, bench to bedside translation of evidence from animal studies of the association between dexmedetomidine and seizures warrants further exploration.

## AUTHORS' CONTRIBUTION

DN, MG and LP designed the study, developed the protocol for the systematic review and drafted the first version of the manuscript; TP provided professional input on the protocol development and on the search strategy; DN and MG extracted data from the studies; RR and LP provided third assessment of the studies if requested; RR performed the statistical analysis and meta-analysis; KF and MA provided professional expertise in the critical analysis of the results; KF revised the manuscript for English language.

All authors comply with the ICMJE recommendations: a) all authors provided substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data; b) all authors drafted the article or revised it critically for important intellectual content; c) all authors have given final approval of the version to be published; and d) all authors agreed to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## REFERENCES

1. Kulikov A, Lubnin A. Anesthesia for awake craniotomy. *Curr Opin Anaesthesiol*. 2018;31(5):506-10.
2. July J, Manninen P, Lai J, Yao Z, Bernstein M. The history of awake craniotomy for brain tumor and its spread into Asia. *Surg Neurol*. 2009;71(5):621-4; discussion 4-5.
3. Ganau L, Ligarotti GKI, Ganau M. Predicting complexity of tumor removal and postoperative outcome in patients with high-grade gliomas. *Neurosurg Rev*. 2018;41(1):371-3.
4. Talacchi A, Turazzi S, Locatelli F, Sala F, Beltramello A, Alessandrini F, et al. Surgical treatment of high-grade gliomas in motor areas. The impact of different supportive technologies: a 171-patient series. *J Neurooncol*. 2010;100(3):417-26.
5. Aleem Bhatti AU, Jakhrani NK, Parekh MA. Awake Craniotomy with Noninvasive Brain Mapping by 3-Tesla Functional Magnetic Resonance Imaging for Excision of Low-grade Glioma: A Case of a Young Patient from Pakistan. *Asian J Neurosurg*. 2018;13(2):471-4.
6. Lu VM, Phan K, Rovin RA. Comparison of operative outcomes of eloquent glioma resection performed under awake versus general anesthesia: A systematic review and meta-analysis. *Clin Neurol Neurosurg*. 2018;169:121-7.
7. Eseonu CI, Rincon-Torroella J, ReFaey K, Quinones-Hinojosa A. The Cost of Brain Surgery: Awake vs Asleep Craniotomy for Perirolandic Region Tumors. *Neurosurgery*. 2017;81(2):307-14.
8. Martino J, Gomez E, Marco de Lucas E, Martinez M, Ocon R, Valle-Folgueral JM, et al. [Controversy in the management of WHO grade II gliomas in eloquent brain areas: recent literature review]. *Neurocirugia (Astur)*. 2012;23(2):70-8.
9. Eseonu CI, ReFaey K, Garcia O, John A, Quinones-Hinojosa A, Tripathi P. Awake Craniotomy Anesthesia: A Comparison of the Monitored Anesthesia Care and Asleep-Awake-Asleep Techniques. *World Neurosurg*. 2017;104:679-86.
10. Gravesteyn BY, Keizer ME, Vincent A, Schouten JW, Stolker RJ, Klimek M. Awake craniotomy versus craniotomy under general anesthesia for the surgical treatment of insular glioma: choices and outcomes. *Neurol Res*. 2018;40(2):87-96.
11. Osborn I, Sebeo J. "Scalp block" during craniotomy: a classic technique revisited. *J Neurosurg Anesthesiol*. 2010;22(3):187-94.

12. Potters JW, Klimek M. Local anesthetics for brain tumor resection: current perspectives. *Local Reg Anesth.* 2018;11:1-8.
13. Bilotta F, Titi L, Lanni F, Stazi E, Rosa G. Training anesthesiology residents in providing anesthesia for awake craniotomy: learning curves and estimate of needed case load. *J Clin Anesth.* 2013;25(5):359-66.
14. Chung YH, Park S, Kim WH, Chung IS, Lee JJ. Anesthetic management of awake craniotomy with laryngeal mask airway and dexmedetomidine in risky patients. *Korean J Anesthesiol.* 2012;63(6):573-5.
15. Hansen E, Seemann M, Zech N, Doenitz C, Luerding R, Brawanski A. Awake craniotomies without any sedation: the awake-awake-awake technique. *Acta Neurochir (Wien).* 2013;155(8):1417-24.
16. Cao SE, Gao BQ, Zhang YQ, Yang SM, Liu GZ, Zhang XR. Clinical application of remifentanyl in local anesthesia for tumor resection in functional brain area. *Eur Rev Med Pharmacol Sci.* 2014;18(21):3212-6.
17. Khan SA, Nathani KR, Ujjan BU, Barakzai MD, Enam SA, Shafiq F. Awake craniotomy for brain tumours in Pakistan: An initial case series from a developing country. *J Pak Med Assoc.* 2016;66(Suppl 3)(10):S68-S71.
18. Goettel N, Bharadwaj S, Venkatraghavan L, Mehta J, Bernstein M, Manninen PH. Dexmedetomidine vs propofol-remifentanyl conscious sedation for awake craniotomy: a prospective randomized controlled trial. *Br J Anaesth.* 2016;116(6):811-21.
19. Stevanovic A, Rossaint R, Veldeman M, Bilotta F, Coburn M. Anaesthesia Management for Awake Craniotomy: Systematic Review and Meta-Analysis. *PLoS One.* 2016;11(5):e0156448.
20. Shen SL, Zheng JY, Zhang J, Wang WY, Jin T, Zhu J, et al. Comparison of dexmedetomidine and propofol for conscious sedation in awake craniotomy: a prospective, double-blind, randomized, and controlled clinical trial. *Ann Pharmacother.* 2013;47(11):1391-9.
21. Gupta DK, Chandra PS, Ojha BK, Sharma BS, Mahapatra AK, Mehta VS. Awake craniotomy versus surgery under general anesthesia for resection of intrinsic lesions of eloquent cortex--a prospective randomised study. *Clin Neurol Neurosurg.* 2007;109(4):335-43.
22. Abdulrauf SI. Awake craniotomies for aneurysms, arteriovenous malformations, skull base tumors, high flow bypass, and brain stem lesions. *J Craniovertebr Junction Spine.* 2015;6(1):8-9.
23. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.
24. Shamseer L, Moher D, Clarke M, Ghera D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015;350:g7647.
25. Welch V, Petticrew M, Tugwell P, Moher D, O'Neill J, Waters E, et al. PRISMA-Equity 2012 extension: reporting guidelines for systematic reviews with a focus on health equity. *PLoS Med.* 2012;9(10):e1001333.
26. Higgins JPT, Green S, Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions.* Chichester, England ; Hoboken, NJ: Wiley-Blackwell; 2008. xxi, 649 p. p.
27. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Loso M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. 2009.
28. Schünemann H, Brożek J, Guyatt G, O'xman A, Group. *TGW. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations.* 2013.
29. Eseonu CI, Rincon-Torroella J, Lee YM, ReFaey K, Tripathi P, Quinones-Hinojosa A. Intraoperative Seizures in Awake Craniotomy for Periolandic Glioma Resections That Undergo Cortical Mapping. *J Neurol Surg A Cent Eur Neurosurg.* 2018;79(3):239-46.

30. Eseonu CI, Rincon-Torroella J, ReFaey K, Lee YM, Nangiana J, Vivas-Buitrago T, et al. Awake Craniotomy vs Craniotomy Under General Anesthesia for Periolandic Gliomas: Evaluating Perioperative Complications and Extent of Resection. *Neurosurgery*. 2017;81(3):481-9.
31. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2014.
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-60.
33. Elbakry AE, Ibrahim E. Propofol-dexmedetomidine versus propofol-remifentanil conscious sedation for awake craniotomy during epilepsy surgery. *Minerva Anesthesiol*. 2017;83(12):1248-54.
34. Wang X, Wang T, Tian Z, Brogan D, Li J, Ma Y. Asleep-awake-asleep regimen for epilepsy surgery: a prospective study of target-controlled infusion versus manually controlled infusion technique. *J Clin Anesth*. 2016;32:92-100.
35. Mahajan C, Rath GP, Singh GP, Mishra N, Sokhal S, Bithal PK. Efficacy and safety of dexmedetomidine infusion for patients undergoing awake craniotomy: An observational study. *Saudi J Anaesth*. 2018;12(2):235-9.
36. Kulikov A, Bilotta F, Borsellino B, Sel'kov D, Kobayakov G, Lubnin A. Xenon anesthesia for awake craniotomy: safety and efficacy. *Minerva Anesthesiol*. 2019;85(2):148-55.
37. Kamata K, Morioka N, Maruyama T, Komayama N, Nitta M, Muragaki Y, et al. The effect of single low-dose dexamethasone on vomiting during awake craniotomy. *J Anesth*. 2016;30(6):941-8.
38. Dilmen OK, Akcil EF, Oguz A, Vehid H, Tunali Y. Comparison of Conscious Sedation and Asleep-Awake-Asleep Techniques for Awake Craniotomy. *J Clin Neurosci*. 2017;35:30-4.
39. Gernsback JE, Kolcun JPG, Starke RM, Ivan ME, Komotar RJ. Who Needs Sleep? An Analysis of Patient Tolerance in Awake Craniotomy. *World Neurosurg*. 2018;118:e842-e8.
40. McAuliffe N, Nicholson S, Rigamonti A, Hare GMT, Cusimano M, Garavaglia M, et al. Awake craniotomy using dexmedetomidine and scalp blocks: a retrospective cohort study. *Can J Anaesth*. 2018;65(10):1129-37.
41. Shinoura N, Midorikawa A, Yamada R, Hiromitsu K, Itoi C, Saito S, et al. Operative Strategies during Awake Surgery Affect Deterioration of Paresis a Month after Surgery for Brain Lesions in the Primary Motor Area. *J Neurol Surg A Cent Eur Neurosurg*. 2017;78(4):368-73.
42. Suero Molina E, Schipmann S, Mueller I, Wolfer J, Ewelt C, Maas M, et al. Conscious sedation with dexmedetomidine compared with asleep-awake-asleep craniotomies in glioma surgery: an analysis of 180 patients. *J Neurosurg*. 2018;129(5):1223-30.
43. Prontera A, Baroni S, Marudi A, Valzania F, Feletti A, Benuzzi F, et al. Awake craniotomy anesthetic management using dexmedetomidine, propofol, and remifentanil. *Drug Des Devel Ther*. 2017;11:593-8.
44. Pallud J, Dezamis E. Functional and oncological outcomes following awake surgical resection using intraoperative cortico-subcortical functional mapping for supratentorial gliomas located in eloquent areas. *Neurochirurgie*. 2017;63(3):208-18.
45. Joswig H, Bratelj D, Brunner T, Jacomet A, Hildebrandt G, Surbeck W. Awake Craniotomy: First-Year Experiences and Patient Perception. *World Neurosurg*. 2016;90:588-96 e2.
46. Groshev A, Padalia D, Patel S, Garcia-Getting R, Sahebjam S, Forsyth PA, et al. Clinical outcomes from maximum-safe resection of primary and metastatic brain tumors using awake craniotomy. *Clin Neurol Neurosurg*. 2017;157:25-30.
47. Khandelwal A, Sokhal N, Kumar N, Singh S, Sokhal S. Phenytoin-induced Excessive Sedation During Awake Craniotomy: An Unusual Observation. *J Neurosurg Anesthesiol*. 2019;31(1):87-8.
48. Miyazaki Y, Adachi T, Kurata J, Utsumi J, Shichino T, Segawa H. Dexmedetomidine reduces seizure threshold during enflurane anaesthesia in cats. *Br J Anaesth*. 1999;82(6):935-7.



49. Mirski MA, Rossell LA, McPherson RW, Traystman RJ. Dexmedetomidine decreases seizure threshold in a rat model of experimental generalized epilepsy. *Anesthesiology*. 1994;81(6):1422-8.
50. Conte V, L'Acqua C, Rotelli S, Stocchetti N. Bispectral index during asleep-awake craniotomies. *J Neurosurg Anesthesiol*. 2013;25(3):279-84.
51. Venkatraghavan L, Bharadwaj S, Au K, Bernstein M, Manninen P. Same-day discharge after craniotomy for supratentorial tumour surgery: a retrospective observational single-centre study. *Can J Anaesth*. 2016;63(11):1245-57.
52. Turgut N, Turkmen A, Ali A, Altan A. Remifentanyl-propofol vs dexmedetomidine-propofol--anesthesia for supratentorial craniotomy. *Middle East J Anaesthesiol*. 2009;20(1):63-70.
53. Ard JL, Jr., Bekker AY, Doyle WK. Dexmedetomidine in awake craniotomy: a technical note. *Surg Neurol*. 2005;63(2):114-6; discussion 6-7.
54. Wang YC, Lee CC, Takami H, Shen S, Chen KT, Wei KC, et al. Awake craniotomies for epileptic gliomas: intraoperative and postoperative seizure control and prognostic factors. *J Neurooncol*. 2019.
55. Zelitzki R, Korn A, Arial E, Ben-Harosh C, Ram Z, Grossman R. Comparison of Motor Outcome in Patients Undergoing Awake vs General Anesthesia Surgery for Brain Tumors Located Within or Adjacent to the Motor Pathways. *Neurosurgery*. 2019.
56. Gerritsen JKW, Vietor CL, Rizopoulos D, Schouten JW, Klimek M, Dirven CMF, et al. Awake craniotomy versus craniotomy under general anesthesia without surgery adjuncts for supratentorial glioblastoma in eloquent areas: a retrospective matched case-control study. *Acta Neurochir (Wien)*. 2019;161(2):307-15.
57. Frati A, Pesce A, Palmieri M, Iasanzaniro M, Familiari P, Angelini A, et al. Hypnosis-Aided Awake Surgery for the Management of Intrinsic Brain Tumors versus Standard Awake-Asleep-Awake Protocol: A Preliminary, Promising Experience. *World Neurosurg*. 2019;121:e882-e91.

## Manuscript Figures' Captions

**Figure 1.** Flowchart of search strategy.

**Figure 2.** Risk of bias graphs. A) Review authors' judgments about each risk of bias item presented as percentages across all included randomized controlled trials and observational prospective studies. B) Review authors' judgement of risk of bias items presented as traffic-light for each included randomized controlled trial and observational prospective study. C) Review authors' judgement about each risk of bias according to the Newcastle–Ottawa Quality Assessment Scale criteria for all included retrospective observational studies.

**Figure 3.** Comparison: MAC vs SAS. Outcome measures: AC Failure, PONV, Intraoperative Seizures, Duration of Surgery and Hospital Length of Stay. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy; PONV, Post-Operative Nausea and Vomiting; CI, Confidence Interval; SD, Standard Deviation.

**Figure 4.** Pooled meta-analysis of MAC and SAS studies for AC Failure. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

## Supplementary Material Captions

**Appendix S1.** Protocol as published on Prospero.

**Appendix S2.** PRISMA Checklist.

**Appendix S3.** Details of the search strategy.

**Appendix S4.** Details of included and excluded studies.

**Figure S5.** Certainty assessment per outcome measures.

**Figure S6.** Assessment of heterogeneity and publication bias. Baujat and Funnel plots for AC Failure.

**Figure S7.** Pooled meta-analysis of MAC and SAS studies for Seizures. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

**Figure S8.** Assessment of heterogeneity and publication bias. Baujat and Funnel plots for Seizures.

**Figure S9.** Pooled meta-analysis of MAC and SAS studies for Nausea. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

**Figure S10.** Assessment of heterogeneity and publication bias. Baujat and Funnel plots for Nausea.

**Figure S11.** Pooled meta-analysis of MAC and SAS studies for Duration of the Surgical Procedure. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

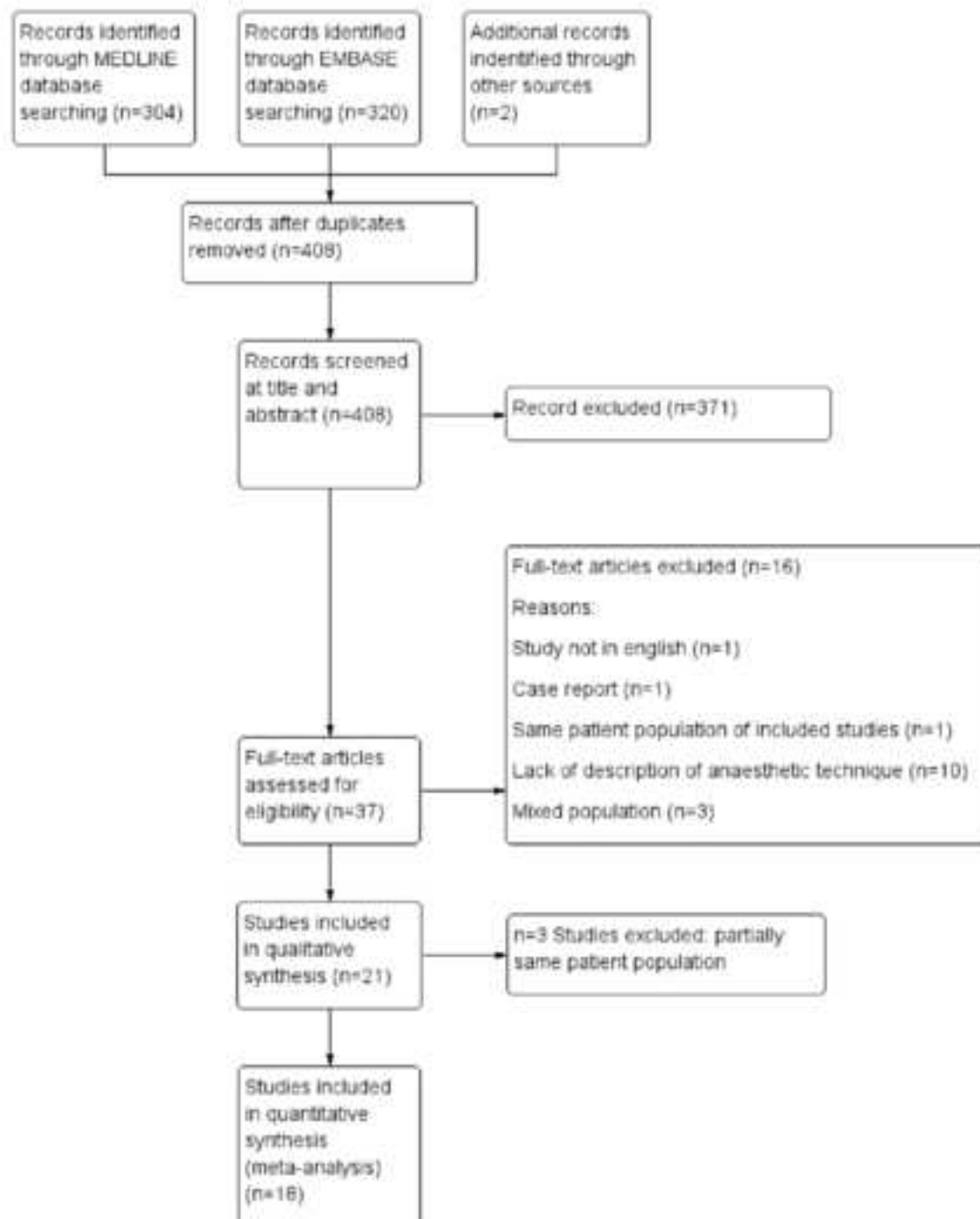
**Figure S12.** Assessment of heterogeneity and publication bias. Baujat and Funnel plots for Duration of the Surgical Procedure.

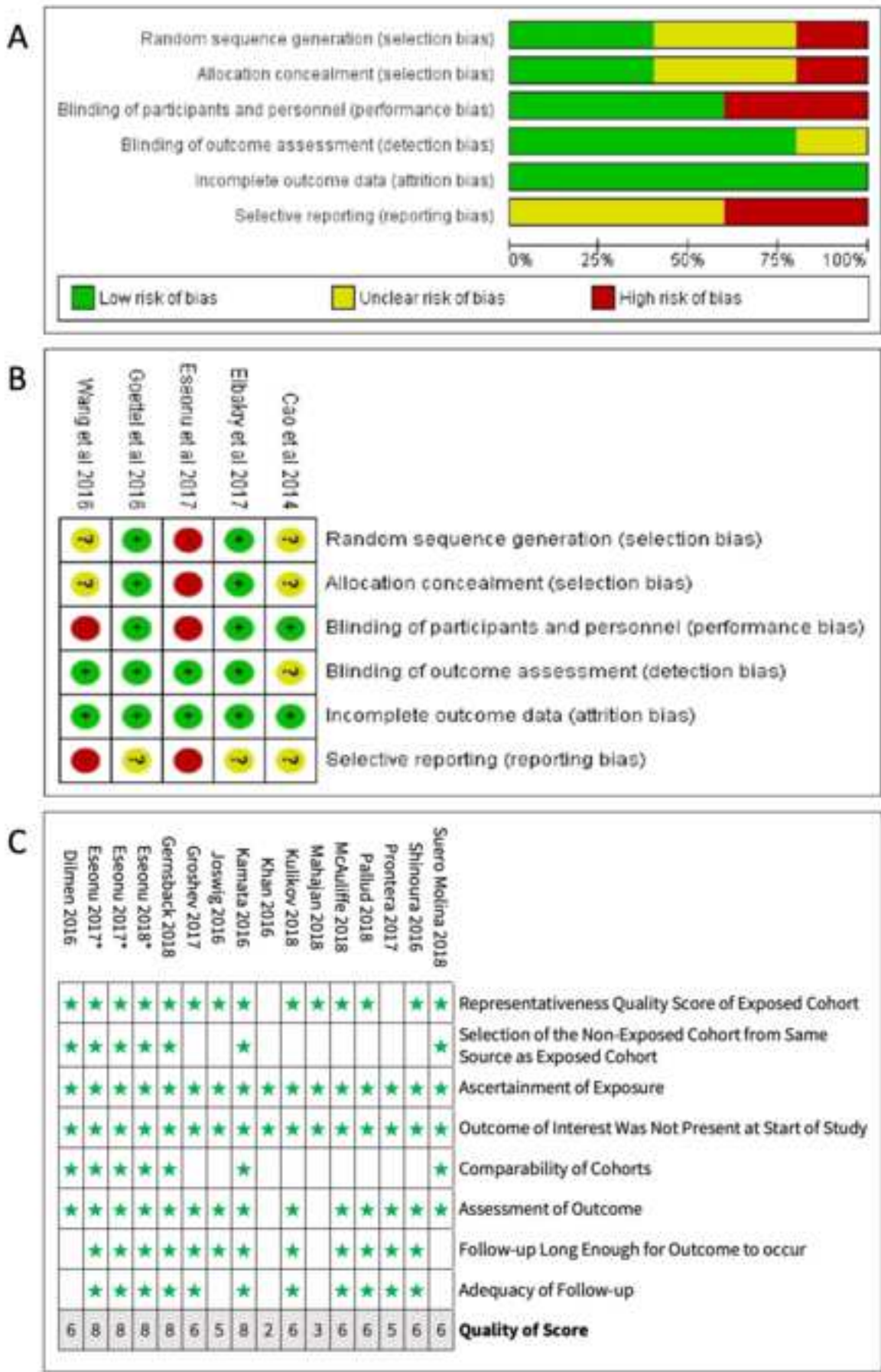
**Figure S13.** Pooled meta-analysis of MAC and SAS studies for Hospital Length of Stay. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

**Figure S14.** Assessment of heterogeneity and publication bias. Baujat and Funnel plots for Hospital Length of Stay.

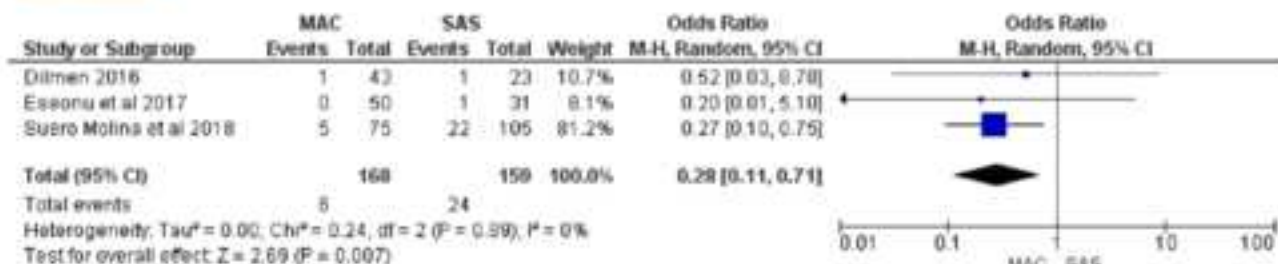
**Appendix Table S15.** Perioperative outcomes not included in the quantitative analysis.

**Appendix Table S16.** Neurosurgical characteristics and outcomes not included in the quantitative analysis.

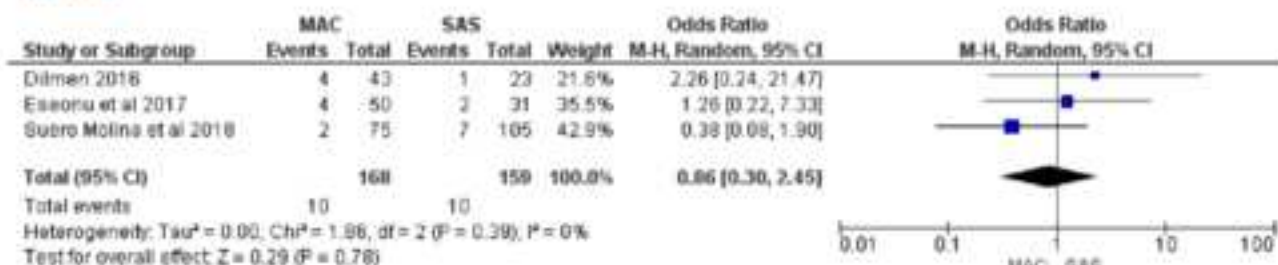




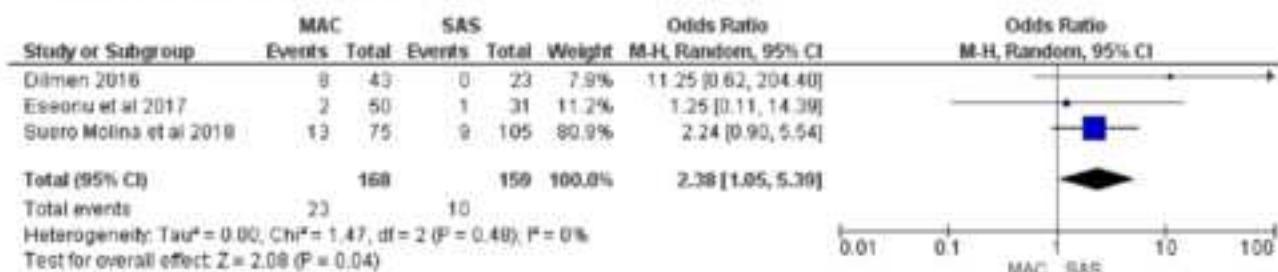
## AC failure



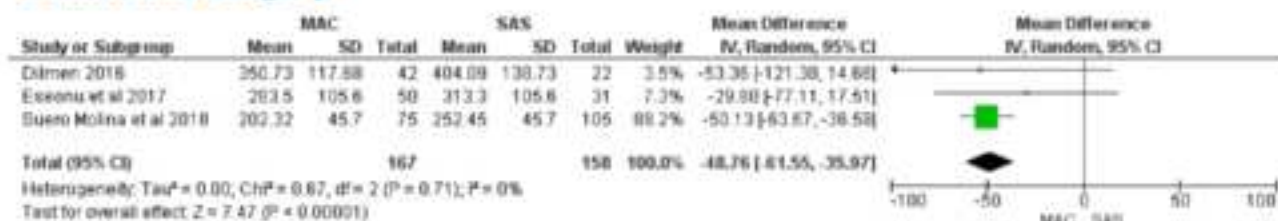
## PONV



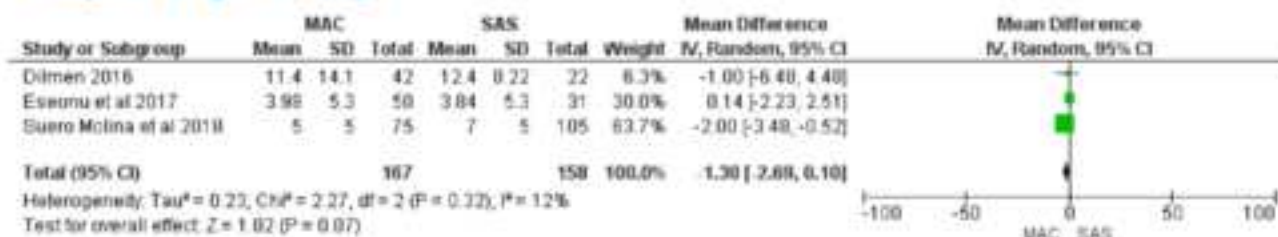
## Intraoperative Seizures

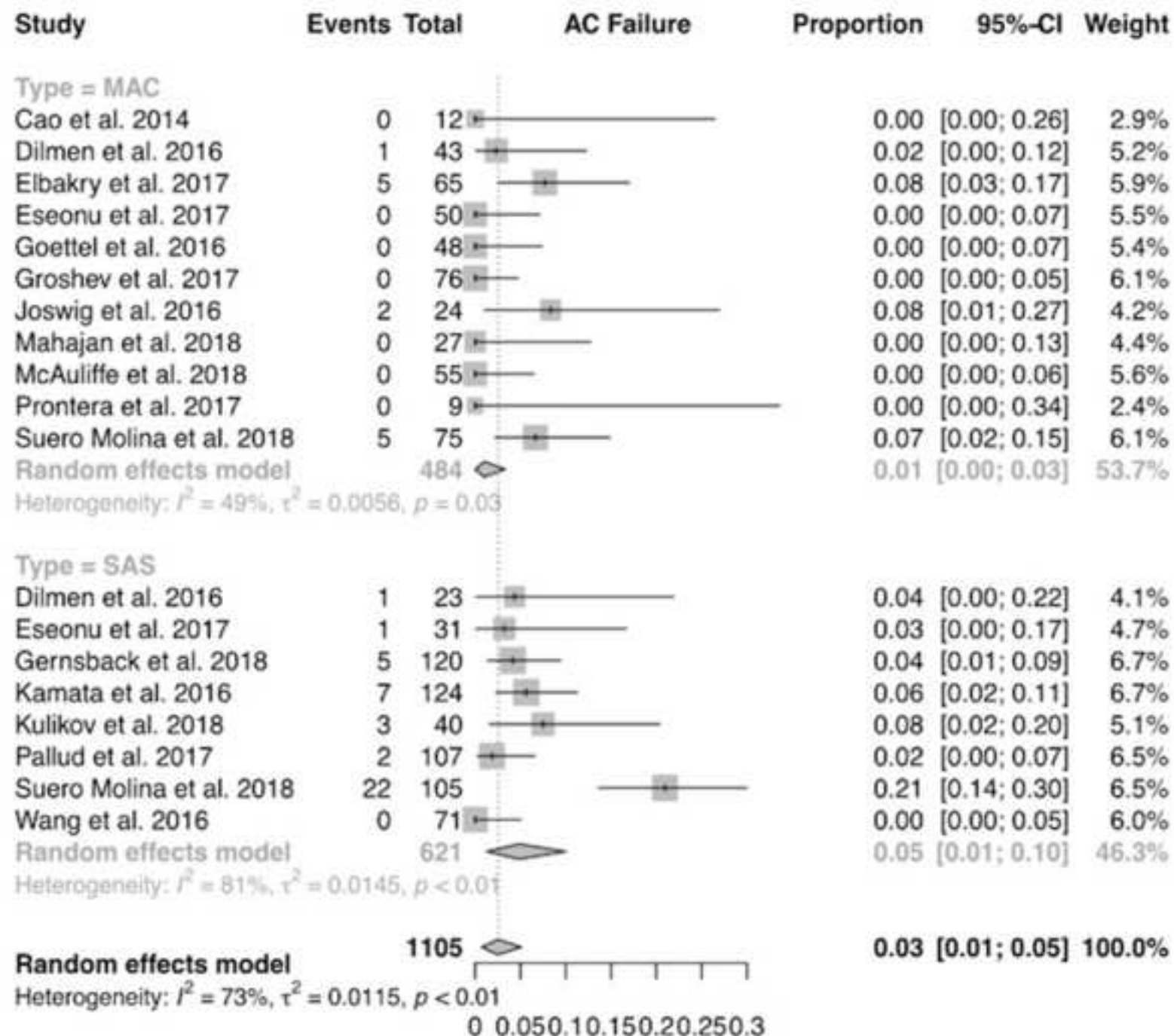


## Duration of Surgery



## Hospital length of stay







**Table 1.** Description of included studies.

Author	Study Design	Recruitment Period	Sample Size	Aim of Study	Main Findings
Cao SE et al 2014	RCT	2009-2010	24	To investigate clinical applications of remifentanyl in AC	AC can be safely performed with remifentanyl in infusion and good LA
Dilmen OK et al 2016	RCS	2011-2016	64	To compare effectiveness of MAC vs SAS for supratentorial tumor resection	SAS technique may provide better results with respect to agitation and seizure, but intraoperative hypertension needs a vigilant follow up
Elbakry A et al 2017	RCT	Not Documented	60	To evaluate the effect of propofol-dexmedetomidine (PD) vs propofol-remifentanyl (PR) during AC	RASS was higher in the PR group compared to the PD group at all times. Nausea, vomiting and respiratory depression were higher in the PR group
Eseonu CI et al 2017*	RCS	2005-2015	27	To evaluate a single surgeon's experience with AC vs surgery under GA	AC can be performed with more frequent total resections, better postoperative KPS (Karnofsky performance score), shorter hospitalizations
Eseonu CI et al 2018*	PCS	2005-2016	57	To evaluate the role of awake craniotomy and motor mapping on neurologic outcome and extent of resection of brain tumors	AC can be safely performed with a similar incidence of intraoperative seizures as reported for the language cortex
Eseonu CI et al 2017*	RCS	2005-2015	17	To evaluate the cost effectiveness and clinical outcomes between AC and GA patients	The total inpatient costs for awake craniotomies were lower than surgery under GA
Eseonu CI et al 2017*^	PCS	2007-2016	81	To compare effectiveness of MAC to SAS techniques	MAC and SAS techniques provide efficacious and safe methods for managing awake craniotomy cases that produce similar perioperative outcomes
Gernsback JE et al 2018	RCS	2011-2016	120	To assess the safety and efficacy of AC	AC remains an effective treatment option. The majority of patients tolerate the procedure without issue
Goettel N et al 2016	RCT	2012-2014	48	To compare dexmedetomidine to propofol-remifentanyl during AC	There were no differences between dexmedetomidine and propofol-remifentanyl groups. Respiratory adverse events were more frequent in the propofol-remifentanyl group
Groshev A et al 2017	CS	2012-2015	76	To analyze outcomes in patients undergoing awake craniotomies	AC can be performed with good oncological and functional outcomes
Joswig H et al 2016	CS	2014-2015	24	To analyze the feasibility, complications and outcomes of AC	AC is feasible with reasonable operation time, complication rates and high patient satisfaction

Kamata K et al 2016	PCS	2012-2015	91	To investigate the effect of single low-dose dexamethasone on the incidence of vomiting during AC	A single low-dose of dexamethasone prevents intraoperative vomiting for AC
Khan SA et al 2016	CS	2015-2016	16	An initial case series from a developing country	AC is effective and safe and is associated with shorter hospital course and lower cost of management.
Kulikov A et al 2018	PCS	2011-2015	40	To test the use of Xenon in the first asleep phase of AC	Xenon was successfully used for the sedative phase of AC
Mahajan C et al 2018	PCS	Not Documented	27	To evaluate the efficacy of dexmedetomidine sedation for AC	The use of dexmedetomidine infusion with regional scalp block in patients undergoing awake craniotomy is safe and efficacious
McAuliffe N et al 2018	RCS	2012-2016	55	To report a single center experience of using dexmedetomidine and scalp block for AC	AC for tumor resection using dexmedetomidine and scalp blocks resulted in no airway complications or conversion to general anesthesia
Pallud J et al 2017	CS	2010-2016	107	The authors detailed functional results along with oncological results after a functional-based resection of gliomas	Maximal functional-based resection improves the onco-functional balance of adult patients harboring a glioma located within eloquent region
Prontera A et al 2017	CS	2013-2014	9	To evaluate the use of dexmedetomidine as the primary hypnotic medication during AC	AC entails specific anesthetic management. Dexmedetomidine is a unique sedative agent that does not directly cause respiratory depression
Shinoura N et al 2016	RCS	2004-2014	61	To analyze the relationship between operative strategies and worsened motor function at 1 month after AC	Stopping tumor resection on deterioration of motor function during awake surgery may help prevent worsened paresis at 1-month follow-up
Suero Molina E et al 2018	RCS	2009-2015	180	To compare SAS to MAC with dexmedetomidine	Use of dexmedetomidine creates excellent conditions for awake surgeries. It sedates moderately and acts as an anxiolytic
Wang X et al 2016	RCT	2011-2013	71	To examine whether IV anesthesia using the TCI system with propofol-remifentanyl would be a more effective method than manually controlled infusion in SAS epilepsy surgery	TCI promoted quicker recovery from sedation, and reached the satisfactory awake state accompanied with higher BIS values. TCI achieved a less disturbed condition of hemodynamic

RCT, Randomized Controlled Trial; RCS, Retrospective Cohort Study; PCS, Prospective Cohort Study; CS, Case Series; AC, awake craniotomy; GA, general anesthesia, LA, local anesthesia; MAC, monitored anesthesia care; SAS, asleep-awake-asleep protocol; RASS, Richmond agitation-sedation scale; TCI, Target Controlled Anesthesia.

\* Four studies by Eseonu et al. partially reported on the same cohort.

\*^ Only the largest study by Eseonu et al. was included in the quantitative analysis.

**Table 2.** Anesthetics techniques described in the included studies.

Study	Premedication/Additional medication	SAS/MAC Technique	Awake phase	Surgical closure
Cao SE et al (2014)	<p><i>Premedication:</i> Midazolam 0.02-0.05 mg/kg Hydrochloric acid penethyclidine microphone 1 mg iv</p> <p><i>LA</i> (pins &amp; dura)</p> <p><i>RSNB:</i> 0.2% ropivacaine</p>	<p><i>No SAS</i> <i>No NMBA</i></p> <p><b>MAC</b> Remifentanyl group (n=12, starting rate 0.1 mcg/kg/min) vs control group with saline infusion (n=12)</p> <p><i>Airway:</i> Own + Oxygen mask</p>	NA	NA
Dilmen OK et al (2016)	<p><i>PONV prophylaxis:</i> Ondansetron 8 mg Intraoperative</p> <p><i>AED prophylaxis:</i> Phenytoin 20 mg/kg</p> <p><i>PONV treatment:</i> Metoclopramide</p> <p><i>Other:</i> Esmolol infusion 0.05-0.2 mg/kg/min for hypertension</p> <p><i>LA</i> (pins &amp; dura)</p> <p><i>RSNB:</i> 0.5% bupivacaine 2 mg/kg</p>	<p><b>SAS (n=23)</b> Induction with propofol 1.5 mg/kg, remifentanyl 0.15 mcg/kg/min in 5 min, rocuronium 0.6 mg/kg. Maintenance with propofol 50-250 mcg/kg/min and remifentanyl 0.05-0.1 mcg/kg/min</p> <p><i>Airway:</i> LMA</p> <p><b>MAC (n=43)</b> Induction with dexmedetomidine 1 mcg/kg over 10 min. Maintenance with dexmedetomidine infusion 0.2-0.7 mcg/kg/h (RASS 2-4).</p> <p><i>Airway:</i> Own + 2-6 l/min oxygen via nasal cannula</p> <p><i>Analgesia:</i> Remifentanyl infusion 0.02-0.05 mcg/kg/min + intermittent fentanyl boluses 25-50 mcg.</p> <p><i>Agitation:</i> Propofol infusion 20 mcg/kg/min or propofol boluses 10-20 mg.</p>	<p><i>SAS (n=23)</i> Infusions interrupted 15 min before the neurological examination.</p> <p>Sugammadex IV and LMA removed when obeying commands.</p>	<p><i>SAS (n=23)</i> Propofol 1.5 mg/kg, remifentanyl 0.15 mcg/kg/min, atracurium 0.6 mg/kg.</p> <p><i>NMBA reversal:</i> IV atropine 0.01 mg/kg and neostigmine 0.02 mg/kg</p> <p><i>Analgesia:</i> Tramadol 2 mg/kg for postoperative analgesia at the closure of dura.</p>
Elbakry A et al (2017) *	<p><i>AED prophylaxis:</i> Drug not specified</p> <p><i>PONV treatment:</i> Ondansetron 4 mg</p> <p><i>Seizures treatment:</i> Thiopental sodium 1-2 mg/kg</p> <p><i>LA</i> (pins &amp; dura)</p> <p><i>RSNB:</i> 0.5% bupivacaine and 2% lidocaine with epinephrine 1:200000. lidocaine mx 4.5 mg/kg and bupivacaine max 3 mg/kg</p>	<p><i>No SAS</i> <i>No NMBA</i></p> <p><b>MAC</b> Induction with 1% propofol infusion dose of 250 mcg/kg/min for 15 min Followed by an infusion dose of 50 mcg/kg/min</p> <p><i>PD group:</i> Dexmedetomidine infusion dose of 1 mcg/kg/h was started for 15 min then titrated down to 0.2 mcg/kg/hr.</p> <p><i>PR group:</i> Remifentanyl bolus dose of 0.5 mcg/kg over 60 sec then an infusion of 0.1 mcg/kg/min. Insufficient sedation treated with boluses of 250 mcg/kg.</p>	<p><b>MAC</b> Propofol infusion was stopped for 15 minutes before intraoperative neurophysiologic monitoring in both groups</p>	NA

Eseonu CI et al (2017) *	<p><i>AED prophylaxis:</i> Levetiracetam 500-1500 mg</p> <p><i>Seizures treatment:</i> Midazolam and/or Propofol</p> <p>LA (pins &amp; dura)</p> <p><i>RSNB:</i> 0.5% ropivacaine with 1:200000 epinephrine</p>	<p><b>SAS (n=31)</b> Propofol induction Maintenance with sevoflurane <i>No NMBA</i></p> <p><i>Airway:</i> LMA</p> <p><b>MAC (n=50)</b> Midazolam, dexmedetomidine 0.2-0.5 mcg/kg/h or propofol 25-100 mcg/kg/min</p> <p><i>Analgesia:</i> Remifentanyl infusion 0.02-0.09 mcg/kg/min</p> <p><i>Airway:</i> Oxygen via nasal trumpet</p>	<p><b>SAS (n=31)</b> Sevoflurane stopped and LMA removed as soon as dura mater was exposed</p>	<p><b>SAS(n=31)</b> Sedation restarted with propofol or dexmedetomidine</p>
Eseonu CI et al (2017) *	<p><i>Seizures treatment:</i> Levetiracetam 500-1500 mg and/or Midazolam 0.1-0.3 mg/kg</p> <p>LA (pins &amp; dura)</p> <p><i>RSNB:</i> 0.5% bupivacaine with 1:200000 epinephrine</p>	<p><b>No SAS</b> <i>No NMBA</i></p> <p><b>MAC NA</b></p>	NA	NA
Eseonu CI et al (2018) *	<p><i>Premedication:</i> Midazolam 2 mg Fentanyl 50 mcg</p> <p><i>AED prophylaxis:</i> Levetiracetam 500-1500 mg or Fosphenytoin 15-20 mg/kg</p> <p><i>Seizures treatment:</i> Midazolam or Levetiracetam</p> <p>LA (pins &amp; dura)</p> <p><i>RSNB:</i> 0.5% bupivacaine with 1:200000 epinephrine</p>	<p><b>No SAS</b> <i>No NMBA</i></p> <p><b>MAC</b> PM (n= 33) NM (n=24) Propofol up to 100 mcg/kg/min or dexmedetomidine up to 0.2-0.7 mcg/kg/h</p>	Patient awakened before the mapping	NA
Eseonu CI et al (2017) *	<p>LA (pins &amp; dura)</p> <p><i>RSNB:</i> 0.5% bupivacaine with 1:200000 epinephrine</p>	<p><b>No SAS</b> <i>No NMBA</i></p> <p><b>MAC</b> Midazolam, dexmedetomidine 0.2-0.5 mcg/kg/h or propofol 25-100 mcg/kg/min</p> <p><i>Analgesia:</i> Remifentanyl infusion 0.02-0.09 mcg/kg/min</p> <p><i>Airway:</i> Oxygen via nasal trumpet</p>	Sedation titrated down to allow the patient to wake up	NA

Gernsback JE et al (2018)	<p><i>PONV prophylaxis:</i> Dexamethasone</p> <p><i>AED prophylaxis:</i> Levetiracetam</p> <p><i>LA</i> (pins &amp; dura)</p>	<p><b>SAS</b> Propofol, ketamine, and dexmedetomidine, in varying combinations, at the discretion of the attending anesthetist during awake phase. <i>NMBA</i> NA</p> <p><i>Analgesia:</i> Remifentanyl infusion</p> <p><i>Airway:</i> LMA</p> <p><b>No MAC</b></p>	Anesthetics stopped	General anesthesia was resumed for closure.
Goettel N et al (2016)	<p><i>Premedication:</i> Fentanyl 50 mcg premedication</p> <p><i>Intraoperative analgesia:</i> Fentanyl 25-50 mcg</p> <p><i>Rescue sedation:</i> Propofol bolus IV 20-30 mg</p> <p><i>PONV treatment:</i> Ondansetron 4 mg and/or Dimenhydrinate 50 mg and/or Metoclopramide 20 mg and/or Dexamethasone 4 mg post op</p> <p><i>LA</i> (pins &amp; dura)</p> <p><i>RSNB:</i> 0.25% bupivacaine with 1:200000 epinephrine</p>	<p><b>No SAS</b> <i>No NMBA</i></p> <p><b>MAC (n=48)</b></p> <p><i>DEX group (n=23)</i> Dexmedetomidine loading dose 1 mcg/kg over 10 min, followed by a maintenance infusion titrated to effect 0.2-1 mcg/kg/h</p> <p><i>P-R group (n=25)</i> Propofol 25-150 mcg/kg/min</p> <p><i>Analgesia:</i> Remifentanyl infusion 0.01-0.1 mcg/kg/min</p> <p><i>Airway:</i> 4 l/min oxygen via nasal cannula</p>	<p>Propofol discontinued and dexmedetomidine and remifentanyl reduced 10 min before mapping</p> <p>Minimal infusions rates of dexmedetomidine 0.1-0.4 mcg/kg/h and remifentanyl 0.01-0.05 mcg/kg/min continued during mapping</p>	Study drug infusions resumed were resumed. Fentanyl 0.5-1 mcg/kg if headache or pain
Groshev A et al (2017)	<p><i>PONV prophylaxis:</i> Corticosteroids</p> <p><i>AED prophylaxis:</i> Drug not specified</p> <p><i>RSNB:</i> bupivacaine with 1:200000 epinephrine</p>	<p><b>No SAS</b> <i>No NMBA</i></p> <p><b>MAC</b> Dexmedetomidine</p> <p><i>Analgesia:</i> Remifentanyl infusion</p>	NA	NA
Joswig H et al (2016)	<p><i>PONV treatment:</i> Dexamethasone and/or Ondansetron</p> <p><i>Seizures treatment:</i> Drug not specified</p> <p><i>RSNB:</i> 0.25% bupivacaine</p>	<p><b>SAS</b> TIVA-TCI propofol <i>NMBA:</i> Rocuronium for end of surgery intubation</p> <p><i>Analgesia:</i> Remifentanyl infusion</p> <p><i>Airway:</i> 5.5 mm flexible bronchoscope endotracheal intubation</p> <p><b>No MAC</b></p>	Propofol/remifentanyl stopped before mapping	Propofol, remifentanyl TCI, rocuronium
Kamata K et al (2016)	<p><i>PONV prophylaxis:</i> Dexamethasone 5 mg (anesthetist-dependent)</p> <p><i>Intraoperative analgesia:</i> Fentanyl during awake phase</p> <p><i>LA</i> (pins &amp; dura)</p> <p><i>RSNB:</i> 0.3 % ropivacaine</p>	<p><b>SAS</b> Fentanyl iv, TCI Propofol <i>NMBA</i> NA</p> <p><i>Analgesia:</i> Remifentanyl infusion</p> <p><i>Airway:</i> LMA, nasal cannula during awake phase</p> <p><b>No MAC</b></p>	<p>All anesthetics stopped. The supraglottic device and gastric tube were removed after the patient regained consciousness</p>	IV sedatives if required Fentanyl boluses during surgical site closure

Kahn SA et al (2016)	LA (pins & dura)	<i>No SAS</i> <i>No NMBA</i>	NA	NA
		<i>No MAC</i>		
Kulikov A et al (2018)	<i>Premedication:</i> Lornoxicam 8 mg  <i>PONV prophylaxis:</i> Ondansetron 4 mg Dexamethasone 8 mg  LA (pins & dura)  <i>RSNB:</i> 0.75% ropivacaine	<i>SAS</i> Induction with propofol 1.5 - 2 mg/kg, fentanyl 100 mcg IV. After ten minutes of mechanical ventilation with a FiO2 of 100%, the ventilator was switched to the Xenon mode (closed loop ventilation) with FiO2 30% and Xenon concentration of 55% - 60% were set. Propofol infusion stopped when BIS ~40.  <i>NMBA:</i> Rocuronium 0.8±0.4 mg/kg.  <i>Airway:</i> LMA	Xenon was switched off and washed out with an oxygen flow Sugammadex before mapping	Propofol and fentanyl restarted, LMA reapplied. Maintenance with Xenon, or more often Propofol continuous infusion.
Mahajan C et al (2018)	<i>PONV prophylaxis:</i> Ondansetron 4 mg  LA (pins & dura)  <i>RSNB:</i> 0.25% bupivacaine, 2% xylocaine for incision site and pins	<i>No MAC</i> <i>No SAS</i> <i>No NMBA</i>  <i>MAC</i> Induction with dexmedetomidine 1.0 µg/kg infused over 10 min Maintenance with dexmedetomidine infusion of 0.5–0.7 µg/kg/h to maintain BIS 60–80.  <i>Analgesia:</i> Fentanyl 0.5 µg/kg was administered before anticipated noxious stimuli  <i>Airway:</i> 3 l/min oxygen via nasal cannula	Dexmedetomidine reduced to 0.2 µg/kg/h after dura was opened	Dexmedetomidine increased to 0.5–0.7 µg/kg/h once the tumor excision was complete
McAuliffe N et al (2018)	<i>Premedication:</i> Midazolam 0.01-0.05 mg/kg Fentanyl 1 mcg/kg  LA (pins & dura)  <i>RSNB:</i> 0.375% bupivacaine with epinephrine	<i>No SAS</i> <i>No NMBA</i>  <i>MAC</i> Induction with dexmedetomidine loading dose 1 mcg/kg over 15 min Maintenance infusion started at 0.3-0.4 mcg/kg/h. Bolus doses of dexmedetomidine 0.05-0.1 mcg/kg and infusion rates were increased as necessary.  <i>Analgesia:</i> Fentanyl during bone flap and dura opening. If required a low dose remifentanyl infusion for supplemental analgesia.  <i>Airway:</i> Facemask or nasal cannula	Infusions stopped at dura opening	Infusions restarted. Hydromorphone for postoperative analgesia
Pallud J et al (2016)	NA	<i>SAS NA</i> <i>NMBA NA</i>  <i>No MAC</i>	NA	NA
Prontera A et al (2017)	<i>Premedication:</i> Ranitidine 50 mg  <i>PONV prophylaxis:</i> Metoclopramide 10 mg 2 h before induction of anesthesia  LA (pins & dura)	<i>No SAS</i> <i>No NMBA</i>  <i>MAC</i> Propofol, dexmedetomidine  Induction dexmedetomidine dose of 0.7 µg/kg/h Maintenance dexmedetomidine infusion of 0.2–1.4 µg/kg/h Infusion rate progressively increased until adequate sedation was obtained.	All anesthetics stopped	Propofol, remifentanyl, dexmedetomidine restarted

	<i>RSNB</i> : bupivacaine with epinephrine (1:200,000) and ropivacaine 7.5 mg/mL	RASS between 4 and 6 was considered adequate.  <i>Analgesia</i> : Remifentanyl infusion  <i>Airway</i> : Nasal cannula O2 2 l/min		
Shinoura N et al (2016)	<i>LA</i> (pins & dura)  <i>RSNB</i> : 1% xylocaine with epinephrine and 0.75% anapain	<i>SAS</i> Propofol, dexmedetomidine, or remifentanyl <i>NMBA</i> NA  <i>Airway</i> : LMA, oxygen mask during awake phase	All anesthetics stopped. The supraglottic device was removed after the patient regained consciousness	Anesthetics restarted (propofol)
Suero Molina E et al (2018)	<i>PONV prophylaxis</i> : Dexamethasone 8 mg  <i>LA</i> (pins & dura)  <i>RSNB</i> : 0.5% ropivacaine with 1:200000 epinephrine	<i>No MAC</i> <i>SAS (n=105)</i> TIVA propofol <i>No NMBA</i>  <i>Analgesia</i> : Remifentanyl infusion  <i>MAC (n=75)</i> Dexmedetomidine 0.5-1.6 mcg/kg/h  <i>Analgesia</i> : In some cases, remifentanyl up to 0.05 mcg/kg/min	NA	NA
Wang X et al (2016)	<i>Premedication</i> : Penehyclidine 0.1-0.3 mg  <i>PONV prophylaxis</i> : Tropisetron 2,5-5 mg  <i>LA</i> (pins & dura)  <i>RSNB</i> : 50:50 mixture of 1% lidocaine with 1:100,000 epinephrine; and 0.25% bupivacaine	<i>SAS</i>  <i>TCI group</i> : Induction with TCI propofol Cp 3 mcg/ml, remifentanyl cp 4 ng/ml, cisatracurium 0,2 mg/kg Maintenance with propofol 1 to 3 mcg/ml  <i>Analgesia</i> : remifentanyl infusion 2 to 4 ng/ml.  <i>MCI group</i> : Induction with propofol 2 mg/kg, remifentanyl 1 mcg/kg, cis-atracurium 0.2 mg/kg. Maintenance with propofol 2 to 4 mg/kg/h  <i>Analgesia</i> : remifentanyl infusion 0.05-0.2 mcg/kg/min  Dexmedetomidine adjunct for pin fixation and awake phase 0.1 mcg/kg/h.  NMBA: cis-atracurium 0,2 mg/kg  <i>Airway</i> : LMA  <i>No MAC</i>	Ten minutes before wake-up:  TCI group Propofol adjusted to 0.5 to 1 mcg/ml and remifentanyl adjusted to 1.5 to 2 ng/ml  MCI group Propofol adjusted to 1 to 2 mg/kg/h, remifentanyl to 0.05 to 0.1 mcg/kg/min.  Dexmedetomidine 0.1 mcg/kg/h was used in all four groups during this phase.  LMA not removed for motor areas mapping	Propofol and remifentanyl infusions restored to their previous concentrations until the end of surgery in all groups  NMBA given if laryngeal mask insertion was required again

NA, Not Available; LA, local anesthesia; MAC, monitored anesthesia care; SAS, asleep-awake-asleep protocol; IV, Intra-Venous; RASS, Richmond agitation-sedation scale; BIS, BISpectral Index; RSNB, Regional Surgical Nerve Block; AED, Anti-Epileptic Drugs; PONV, Post-Operative Nausea and Vomiting; NMBA, Neuro-Muscular Blocking Agents; TCI, Target Controlled Anesthesia; MCI, Manually Controlled Anesthesia; TIVA, Total Intra-Venous Anesthesia; LMA, Laryngeal Mask Airway.

\* Four studies by Eseonu et al. partially reported on the same cohort.



\*^ Only the largest study by Eseonu et al. was included in the quantitative analysis.

## Systematic review

### 1. \* Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Comparison of Asleep-Awake-Asleep and Monitored Anaesthesia Care in reducing Awake Craniotomy failure during brain surgery: Protocol for a Systematic Review and Meta-Analysis of the literature from 2014 to 2018.

### 2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

English

### 3. \* Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/08/2018

### 4. \* Anticipated completion date.

Give the date by which the review is expected to be completed.


01/04/2019

### 5. \* Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: 

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

Initial registration on Prospero in November 2018. Update in March 2019: Systematic review now complete.

Initial registration on Prospero in November 2018. Update in March 2019: Systematic review now complete.

## 6. \* Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Lara Prisco

## Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Prisco

## 7. \* Named contact email.

Give the electronic mail address of the named contact.

lara.prisco@ndcn.ox.ac.uk

## 8. Named contact address

Give the full postal address for the named contact.

Neurosciences Intensive Care Unit John Radcliffe Hospital, West Wing Level 1 Headley Way - OX3 9DU

## 9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+44 (0)1865857772

## 10. \* Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Oxford University Hospitals NHS Foundation Trust

## Organisation web address:

## 11. \* Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Daniele Natalini. Neurosciences Intensive Care Unit, Oxford University Hospitals NHS Foundation Trust  
Dr Mario Ganau. Department of Neurosurgery, Oxford University Hospitals NHS Foundation Trust  
Dr Ruben Rosenkranz. Centre de Recherches Pédrographiques et Géochimiques, Université de Lorraine  
Mrs Tatjana Petrinic. Bodleian Healthcare Libraries, University of Oxford  
Dr Karina Fitzgibbon. Neuroanaesthesia and Neurointensive Care Unit, Oxford University Hospitals NHS Foundation Trust  
Professor Massimo Antonelli. Dipartimento di Scienze dell'Emergenza Anestesiologiche e della Rianimazione, Fondazione Policlinico Universitario A.Gemelli IRCCS  
Dr Lara Prisco. Neuroanaesthesia and Neurointensive Care Unit, Oxford University Hospitals NHS Foundation Trust

## 12. \* Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

None

## 13. \* Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

## 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

## 15. \* Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

In this systematic review we aim to synthesize the evidence published from 2014 to 2018 on anaesthetic

The primary objectives are to compare SAS and MAC by describing the rate of: a) AC failure, defined as the premature interruption of the process of brain mapping; b) intraoperative complications; and c) postoperative variables with these two techniques.

Secondly, we aim to use the evidence synthesis to try to establish which is more effective in reducing adverse events rate and improving outcomes, cost-effectiveness and patient satisfaction.

## 16. \* Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We will systematically search MEDLINE, EMBASE for the period 01/01/2014 until 01/08/2018. The search strategies will be developed with the assistance of an experienced research librarian. We will analyse the

bibliographies of all included studies for additional relevant articles.

### 17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

### 18. \* Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Anaesthesia techniques for operative resection of brain tumours or epileptogenic foci

### 19. \* Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Adult patients with brain tumours or epileptogenic foci scheduled for intraoperative resection under awake anaesthesia

### 20. \* Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Monitored anaesthesia care (MAC), or conscious sedation, in which spontaneous ventilation is maintained during the whole surgery and sedation is guaranteed by controlled infusions of propofol and a short acting opioid such as remifentanyl.

### 21. \* Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

2) the awake-awake-awake (AAA) technique, using GA and an airway device before and after brain mapping; and

3) the newest awake-awake-awake (AAA), or "fully awake" method, where no sedation is required and only local anaesthesia of the scalp is performed.

### 22. \* Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

In the analysis we will include randomised controlled trials, observational case-control and cohort studies (both prospective and retrospective), clinical series with more than 4 cases. We will include all the publications written in English.

We will exclude from the analysis: animal trials, other reviews, paediatric trials, trials on pregnant women, abstracts, letters, records in Non-English language, case reports including fewer than four patients and publication with no description of the anaesthetic strategy.

### 23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

We will include all the studies performed on adult patients (older than 18 years at time of surgery) undergoing AC and brain mapping for resection of epileptic foci or tumours involving any functional cortex. As previously specified, the anaesthetic approach has to be described; additionally, to be included the studies have to report data for at least one of the outcome variables: intraoperative seizures, hypoxia, hypertension episodes, intra/postoperative PONV, new neurological dysfunction, conversion to GA and failure of AC. We will include studies reporting at least one between SAS, MAC and AAA strategy.

### 24. \* Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

As a primary outcome, we considered the incidence of AC failure, defined as failure to achieve complete intraoperative awake mapping of the brain.

### Timing and effect measures

### 25. \* Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

We will explore the following secondary outcomes:

- intraoperative seizures;
- intraoperative respiratory adverse events and hypertensive episodes;
- duration of the procedure;
- length of Stay (LOS).

### Timing and effect measures

Perioperative outcomes

## 26. \* Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Titles and abstracts will be screened to identify studies that meet the inclusion criteria. Of the eligible studies we will assess the full text. Doubts over the eligibility of particular studies will be resolved through Delphi approach among all other authors. An Excel form will be used to extract data from the individual studies for the assessment of study quality and evidence synthesis. Extracted information will include: population and demographic characteristics and baseline parameters; description of the anaesthesia technique; type of study, intraoperative and postoperative variables, outcome measures.

## 27. \* Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two authors will independently assess the risk of bias in each included study. We will use the GRADE approach to assess the certainty of the evidence for each outcome for RCT and the Ottawa Newcastle Scale for assessing the quality of nonrandomised studies. We have written this protocol following the PRISMA-P guidelines, and will report the review according to the PRISMA statement.

## 28. \* Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A descriptive synthesis of the findings from the included studies will be described, underlying the type of anaesthesia and target population outcomes. If the data extracted from the included studies is consistent and homogeneous a meta-analysis will be performed. Considering the three different techniques of anaesthesia management and depending on the data availability and homogeneity a network meta-analysis could be taken into consideration.

## 29. \* Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Should the necessary data be available, a subgroup analysis will be done for SAS, MAC, AAA .

## 30. \* Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

### Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

No

Individual patient data (IPD) meta-analysis

No

Intervention

Yes

Meta-analysis

Yes

Methodology

No

Narrative synthesis

Yes

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Review of reviews

No

Service delivery

No

Synthesis of qualitative studies

No

Systematic review

Yes

Other

No

### Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system

No

Cancer

No

Cardiovascular

No

Care of the elderly

No

Child health



No

Complementary therapies

No

Crime and justice

No

Dental

No

Digestive system

No

Ear, nose and throat

No

Education

No

Endocrine and metabolic disorders

No

Eye disorders

No

General interest

No

Genetics

No

Health inequalities/health equity

No

Infections and infestations

No

International development

No

Mental health and behavioural conditions

No

Musculoskeletal

No

Neurological

Yes

Nursing

No

Obstetrics and gynaecology

No

Oral health

No

Palliative care

No

Perioperative care

Yes

Physiotherapy

No

Pregnancy and childbirth

No

Public health (including social determinants of health)

No

Rehabilitation

No

Respiratory disorders  
No

Service delivery  
No

Skin disorders  
No

Social care  
No

Surgery  
No

Tropical Medicine  
No

Urological  
No

Wounds, injuries and accidents  
No

Violence and abuse  
No

### 31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.  
English

There is not an English language summary

### 32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

England

### 33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

### 34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

**No I do not make this file publicly available until the review is complete**

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

### 35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate

audiences.

We aim to publish the results of the systematic review and meta-analysis on peer-reviewed medical journals.

### Do you intend to publish the review on completion?

No

### 36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Awake craniotomy; Brain tumours; Epilepsy surgery; Anaesthesia; Neurosurgery

### 37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

### 38. \* Current review status.

Review status should be updated when the review is completed and when it is published. For new registrations the review must be Ongoing.

Please provide anticipated publication date

Review\_Completed\_not\_published

### 39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

The two reviews published in 2016 and 2018, respectively by Stevanovic et al. and Lu et al., have multiples limitations.

First of all both include studies published in a very wide period of time, with an obvious variation in the anaesthetic management.

Lu et al. in their systematic review and meta-analysis comparing AC vs GA did not provide any information about the anaesthetic regime adopted during AC, and only surgical outcomes were taken in consideration.

Only 8 observational studies and 1 RCT were included in the analysis.

Moreover, the systematic review and meta-analysis performed by Stevanovic et al. analyzed only 4 outcome variables: AC failures; seizures; conversion into general anaesthesia; new postoperative neurologic dysfunction based on the anaesthetic approach of MAC or SAS. The monitored anaesthesia care and AAA techniques were compared against the same 4 previous mentioned outcome measures. AC failures included all cases where a complete intraoperative awake mapping of the brain during tumour resection could not be

achieved. AC failure was not restricted to the cases where conversion to GA was required. 47 studies were included of which only 2 were RCT. In the last 3 years several observational studies and one new randomised controlled trial (RCT) comparing different anaesthetic strategies were published.

Although AC represents the "gold standard" in neuro-oncology and functional neurosurgery, many team are more and more extending these traditional indications (for instance to surgery for neuro-vascular malformations) aiming to increase the safety of the procedures and obtaining better clinical outcomes. In light of the above, it is essential to keep the evidence up to date.

#### 40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.



# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2-3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4-5 Suppl
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6 Suppl
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7 Fig.1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 Fig.2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	10-11-12



# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7 Fig.2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tab.1/2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Suppl.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Suppl.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12-13-14 Fig.3/4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Suppl.
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

## Appendix S3. Search Strategy

### EMBASE SEARCH STRATEGY

1 exp CRANIOTOMY/

2 "craniotom\*".af.

3 1 or 2

4 CONSCIOUS SEDATION/

5 WAKEFULNESS/

6 (awake or sedation\* or sedated or conscious).af.

7 4 or 5 or 6

8 3 and 7

9 limit 8 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)

10 limit 8 to animal studies

11 9 or 10

12 8 not 11

13 limit 12 to (english language and yr="2014 -Current")

14 limit 13 to (article or article in press or "review")

### MEDLINE SEARCH STRATEGY

1 exp CRANIOTOMY/

2 "craniotom\*".af.

3 1 or 2

4 CONSCIOUS SEDATION/

5 WAKEFULNESS/

6 (awake or sedation\* or sedated or conscious).af.

7 4 or 5 or 6

8 3 and 7

9 limit 8 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)")

10 limit 8 to animals

11 9 or 10

12 8 not 11

13 limit 12 to (english language and yr="2014 -Current")

## Appendix S4. RCTs and Prospective Studies Characteristics

### Characteristics of included studies

#### *Cao et al 2014*

<b>Methods</b>	Randomized controlled trial
<b>Participants</b>	24 participants (12 remifentanil group, 12 control group) with intracranial frontal glioma
<b>Interventions</b>	Intervention: remifentanil infusion Control: saline infusion
<b>Outcomes</b>	Patient satisfaction, Haemodynamic changes, Intraoperative complications
<b>Notes</b>	The authors declare they have no conflict of interests

#### Risk of bias table

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote: patients were randomly allocated. Comment: Insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described
Blinding of participants and personnel (performance bias)	Low risk	Comment: the outcome is not likely to be influenced by possible lack of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'Low risk or High risk '
Incomplete outcome data (attrition bias)	Low risk	Quote: "All patients successfully completed the operation." Comment: No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'Low risk or High risk. No protocol available

#### *Elbakry et al 2017*

<b>Methods</b>	Randomized controlled trial
<b>Participants</b>	60 participants (30 propofol-dexmedetomidine, 30 propofol-remifentanil) scheduled for awake craniotomy for the treatment of epilepsy
<b>Interventions</b>	Intervention: propofol-dexmedetomidine Control: propofol-remifentanil
<b>Outcomes</b>	Sedation score, patients'/surgeons' satisfaction, haemodynamic changes. Intraoperative complications
<b>Notes</b>	



#### Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly divided using a computerized system or software program into two groups"
Allocation concealment (selection bias)	Low risk	Quote: "An independent anaesthetist prepared the infusions and handed them to the research team."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patients, surgeons and the research team were blinded to the randomization."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "An anaesthetist (who was blinded to the randomization) started the infusions and collected the data." Comment: Blinding of outcome assessment ensured
Incomplete outcome data (attrition bias)	Low risk	Quote: "The number of patients required general anaesthesia and excluded from the results were two patients in PD group versus three patients in PR group." Comment: Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information to permit judgement of 'Low risk' or High risk. No protocol available

#### Eseonu et al 2017

<b>Methods</b>	Prospective cohort study
<b>Participants</b>	81 participants (50 conscious sedation, 31 SAS technique) scheduled for awake craniotomy for eloquent brain lesion
<b>Interventions</b>	conscious sedation versus asleep-awake-asleep for awake craniotomy
<b>Outcomes</b>	Intraoperative complications, postoperative complications and new motor deficit, pain management, duration of surgery
<b>Notes</b>	

#### Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: Allocation by judgement of the clinician
Allocation concealment (selection bias)	High risk	Quote: "Patients with a history of anesthesia complications, such as inflammatory reactions and 8 hypersensitivity, or poor blood pressure control were placed in the AAA group, in order

		to have more intraoperative time with a secure airway. Patients that could follow sensorimotor and language commands easily in the preoperative clinic evaluation were often placed in the MAC group as they were able to cooperate with the surgical team throughout the operative case" Comment: Allocation by judgement of the clinician
Blinding of participants and personnel (performance bias)	High risk	Comment: No blinding, and the outcome is likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All statistical analyses were done using STATA 14 by a biostatistician (O.G.) blinded to the cohorts." Comment: Blinding of outcome assessment ensured
Incomplete outcome data (attrition bias)	Low risk	Comment: No missing outcome data
Selective reporting (reporting bias)	High risk	Quote: "In addition, the types of medications used for each sedation approach differed for some patients which add additional variables to the anesthetic techniques that are not accounted for in this study." Comment: no study protocol available

#### *Goettel et al 2016*

<b>Methods</b>	Randomized controlled trial
<b>Participants</b>	50 participants (25 dexmedetomidine group, 25 propofol-remifentanyl group) scheduled for awake craniotomy for supratentorial tumour resection
<b>Interventions</b>	Intervention: dexmedetomidine Control: propofol-remifentanyl
<b>Outcomes</b>	Ability to perform intraoperative brain mapping assessed on a numeric rating scale (NRS). Efficacy of sedation. Haemodynamic and respiratory variables, pain, sedation and anxiety scores, adverse events, patients' satisfaction.
<b>Notes</b>	Funding: Study drug was supplied by Hospira inc.

#### Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We performed simple randomization of participants to the DEX and P-R groups. One investigator generated the random allocation sequence and provided allocation concealment by using sequentially numbered, sealed, opaque envelopes"
Allocation concealment (selection bias)	Low risk	Quote: "One investigator generated the random allocation sequence and provided allocation concealment by using sequentially numbered, sealed, opaque envelopes"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patient and neurosurgeon were blinded to group allocation; however, it was not practical to blind the attending anaesthetist to preoperative and intraoperative data, as this

		information was essential for the medical care of patients."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "A blinded investigator that was not directly involved in the anaesthetic management of the patients, collected all intra- and postoperative data."
Incomplete outcome data (attrition bias)	Low risk	Quote: "One-hundred and four patients were screened for study eligibility between October 2012 and December 2014 (Fig. 1). Fifty-four patients were excluded before randomization. The remaining 50 patients were equally randomized to the DEX group (n=25) or the P-R group (n=25). No participant was lost to follow-up; however, two patients in the DEX group were excluded from the analysis because of incorrect allocation in one, and conversion to a general anaesthetic by surgeon s request at the start of the procedure in another"
Selective reporting (reporting bias)	Unclear risk	Comment: Insufficient information to permit judgement of , Low risk or High risk , No protocol available

#### *Wang et al 2016*

<b>Methods</b>	Randomized controlled trial
<b>Participants</b>	71 participants (18 TCI-E, 16 MCI-E, 17 TCI-M, 20 MCI-M) scheduled for awake craniotomy for the treatment of epilepsy
<b>Interventions</b>	Asleep Awake Asleep approach: comparison between target controlled infusion (TCI) and Manual controlled infusion (MCI), subgroups eloquent (E) or motor area (M)
<b>Outcomes</b>	Times of awakening, BIS values and haemodynamic variables, Incidence of adverse events
<b>Notes</b>	Source of funding: Anaesthesiology departmental funding of Xuan Wu hospital

#### Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Insufficient information about the sequence, generation process to permit judgement of Low risk or High risk .
Allocation concealment (selection bias)	Unclear risk	Comment: the method of concealment is not described
Blinding of participants and personnel (performance bias)	High risk	Comment: No blinding
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Collection of the data was assigned to a single physician and was conducted in a blinded fashion" Comment: Blinding of outcome assessment ensured

Incomplete outcome data (attrition bias)	Low risk	Quote: "All patients remained awake and cooperative throughout the time of neurological testing" Comment: all patients remained in the study
Selective reporting (reporting bias)	High risk	Quote: "We did not discuss the amount of the medicine, although it may help us explore the results. In the fourth phase of this study, the dosage of muscle relaxants is not limited and a large number of muscle relaxants will impact on the need of propofol and remifentanyl dose." Comment: no protocol available

### Footnotes

### Characteristics of excluded studies

#### *Alimohamadi et al 2016*

Reason for exclusion	Lack of description of the anaesthetic technique.
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#### *Baran et al 2018*

Reason for exclusion	Mixed population (GA and AC in the same group), lack of description of anaesthetic technique,
----------------------	---

#### *Eseonu et al 2018*

Reason for exclusion	Same population of the included studies by the same author
----------------------	--

#### *Freyshlag et al 2017*

Reason for exclusion	Lack of description of the anaesthetic technique.
----------------------	---

#### *Gravesteijn et al 2017*

Reason for exclusion	Lack of description of the anaesthetic technique.
----------------------	---

#### *Leal et al 2018*

Reason for exclusion	Lack of description of the anaesthetic technique.
----------------------	---

#### *Lima et al 2017*

Reason for exclusion	Lack of description of the anaesthetic technique.
----------------------	---

#### *Ma et al 2016*

Reason for exclusion	Mixed population (craniotomies and endoscopic procedures in the same group)
----------------------	---

#### *Magill et al 2018*

<b>Reason for exclusion</b>	Lack of description of the anaesthetic technique.
-----------------------------	---

*Meziane et al 2017*

<b>Reason for exclusion</b>	Case Report.
-----------------------------	--------------

*Milos et al 2016*

<b>Reason for exclusion</b>	Article not in english.
-----------------------------	-------------------------

*Rech et al 2017*

<b>Reason for exclusion</b>	Lack of description of the anaesthetic technique.
-----------------------------	---

*Shahar et al 2018*

<b>Reason for exclusion</b>	Lack of description of the anaesthetic technique.
-----------------------------	---

*Sollmann et al 2018*

<b>Reason for exclusion</b>	Lack of description of the anaesthetic technique.
-----------------------------	---

*Trimble et al 2015*

<b>Reason for exclusion</b>	Lack of description of the anaesthetic technique.
-----------------------------	---

*Venkatraghavan et al 2016*

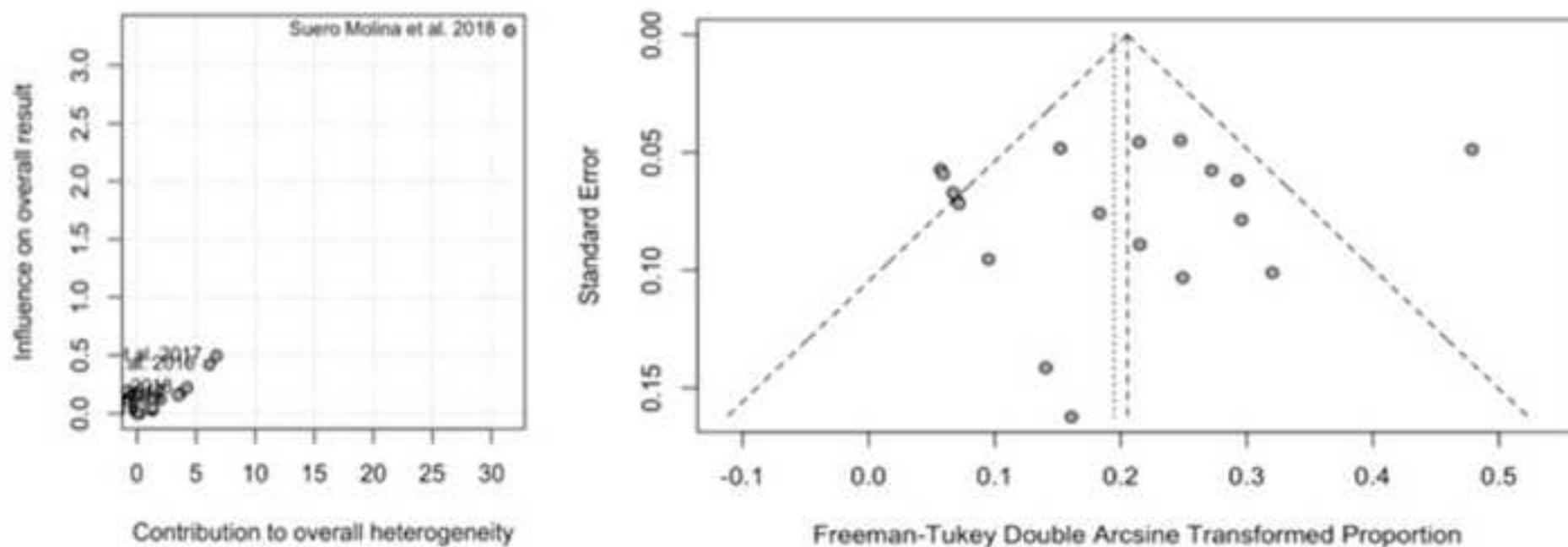
<b>Reason for exclusion</b>	Mixed population
-----------------------------	------------------

Figure S5. Certainty assessment per outcome measures.

Certainty assessment										Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients	Effect	Certainty	
							Awake-Asleep-Asleep	MAC	Relative (95% CI)	Absolute (95% CI)
Duration of Surgery										
3	observational studies	serious La	serious L2,Lo	Not serious	serious L3,Lo	none	167	158	-	MD 48.76 lower (63.55 lower to 35.97 lower)
Length of hospital stay										
3	observational studies	serious La	serious L2,Lo	Not serious	serious L3,Lo	none	167	158	-	MD 1.3 lower (2.69 lower to 0.1 higher)
Neuroblepharitis										
3	observational studies	serious La	serious L2,Lo	Not serious	serious L3,Lo	none	30/168 (6.0%)	10/259 (6.3%)	OR 0.86 (0.30 to 2.45)	8 fewer per 1,000 (from 43 fewer to 78 more)
Seizures										
3	observational studies	serious L2,Lo	serious L2,Lo	Not serious	serious L3,Lo	none	23/168 (13.7%)	10/259 (6.3%)	OR 2.38 (1.03 to 5.39)	75 more per 1,000 (from 3 more to 203 more)
AC failure										
3	observational studies	serious L2,Lo	serious L2,Lo	Not serious	serious #	none	6/168 (3.6%)	24/259 (15.1%)	OR 0.28 (0.11 to 0.71)	104 fewer per 1,000 (from 39 fewer to 132 fewer)

# AC Failure

Figure S6. Assessment of heterogeneity and publication bias. Baujat and Funnel plots for AC Failure.



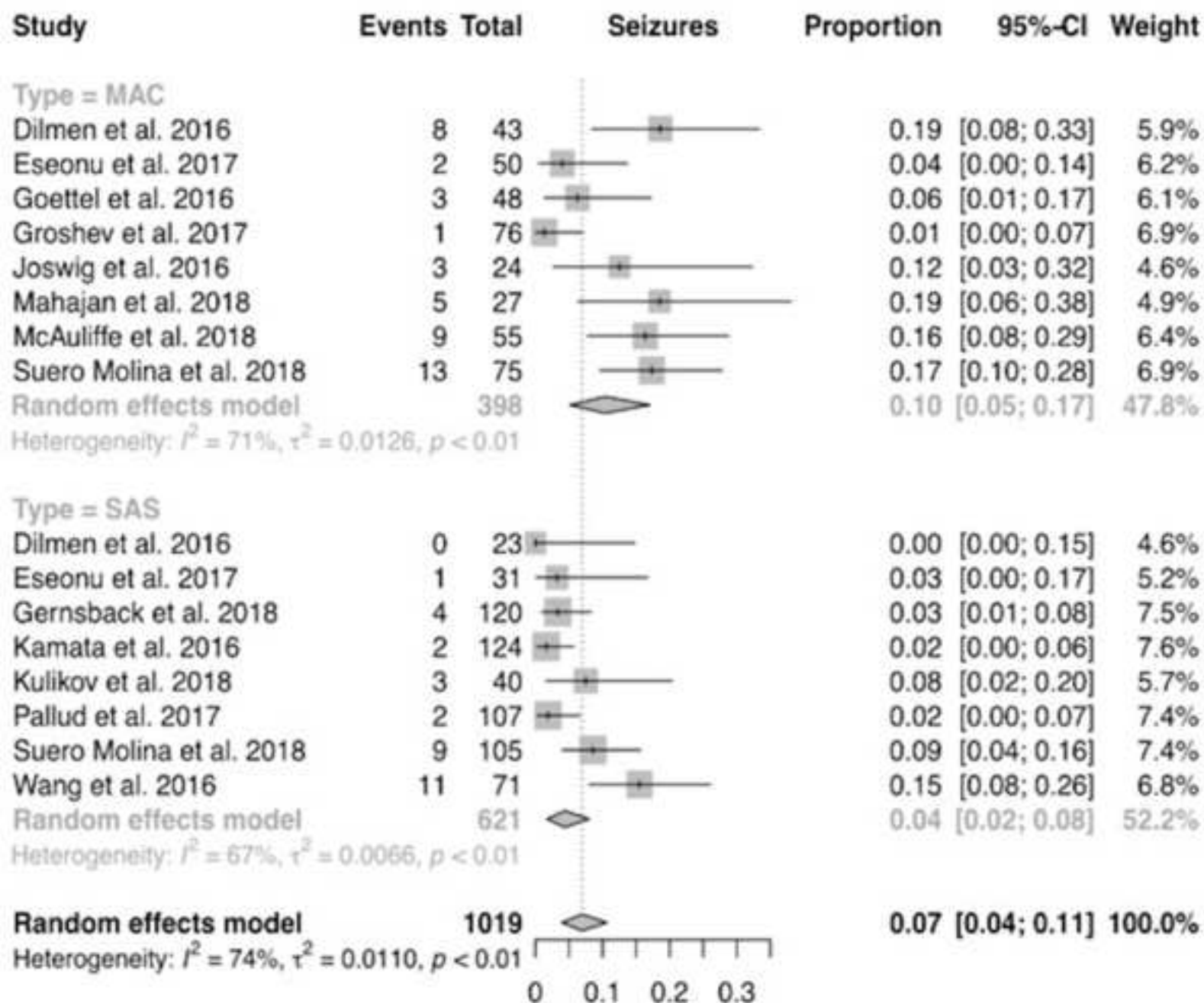
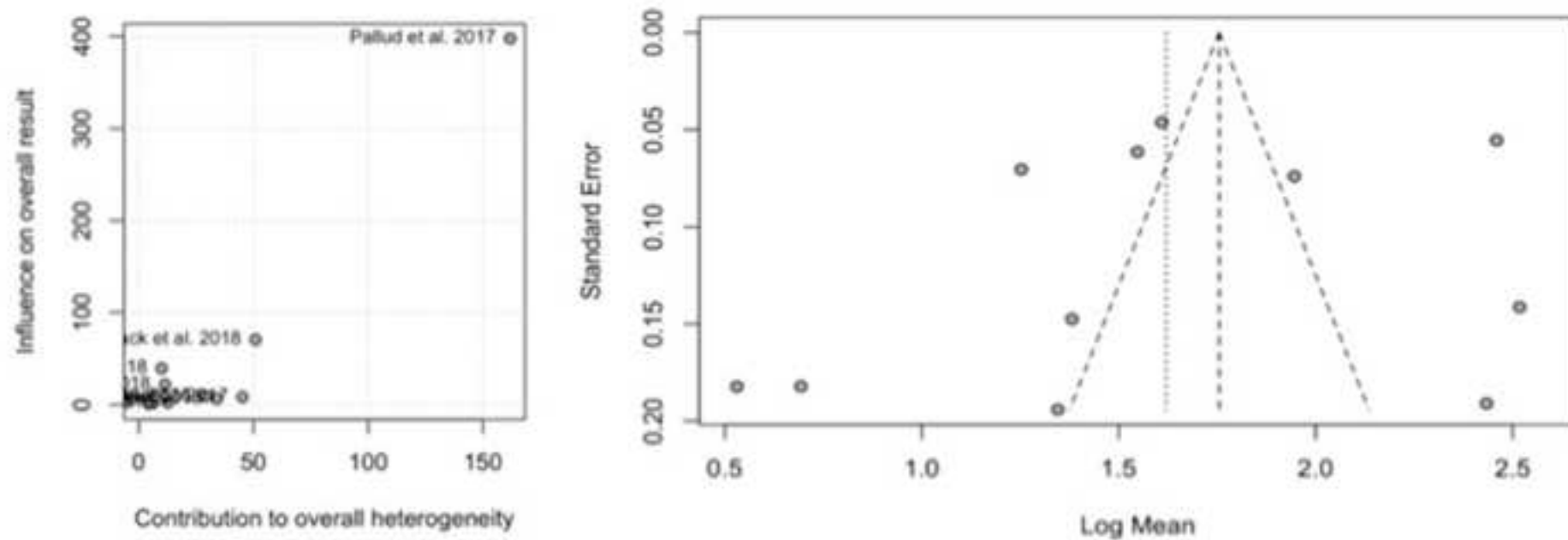


Figure S7. Pooled meta-analysis of MAC and SAS studies for Seizures. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.



# Seizures

Figure S8. Assessment of heterogeneity and publication bias. Bujat and Funnel plots for Seizures.



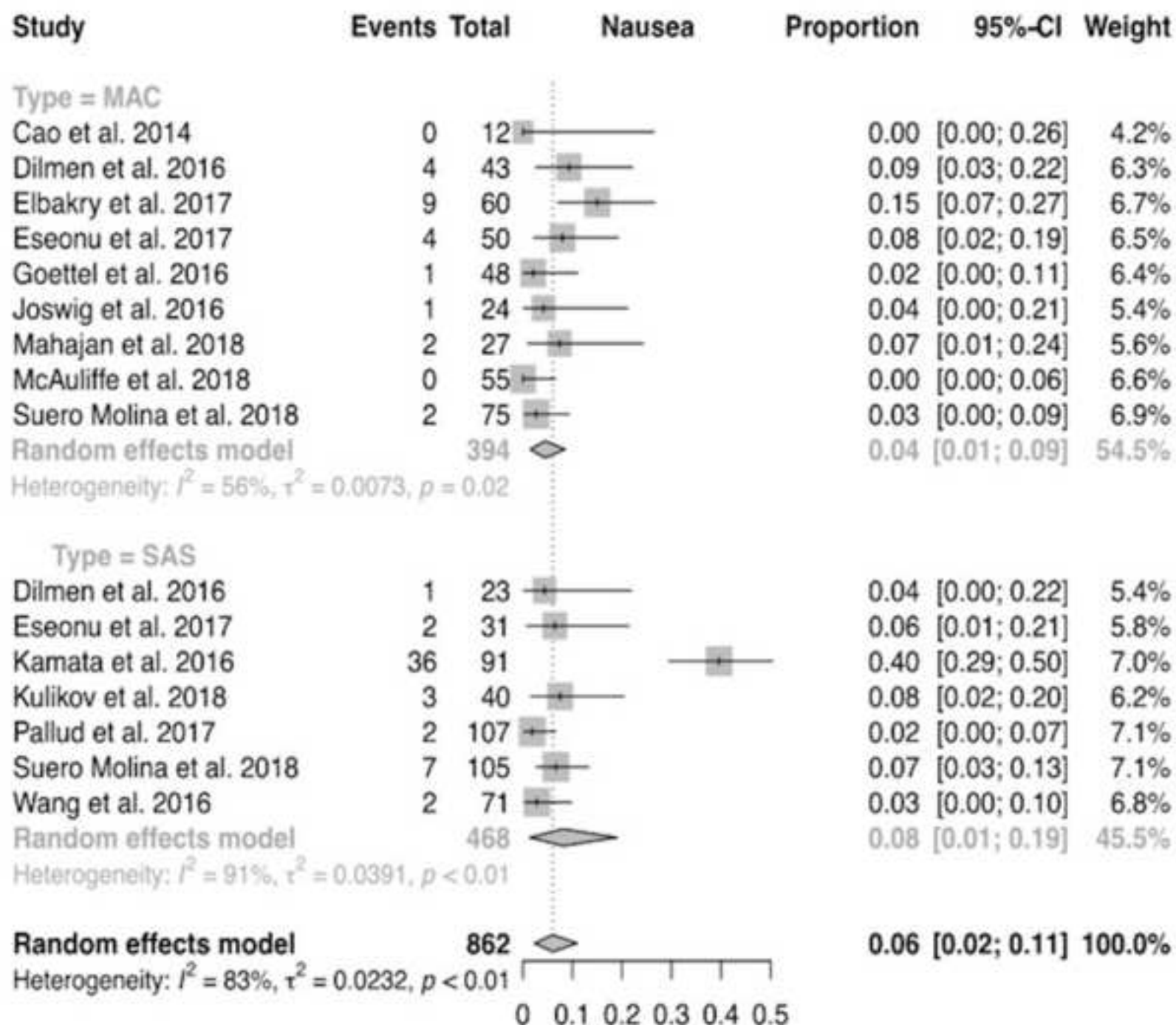
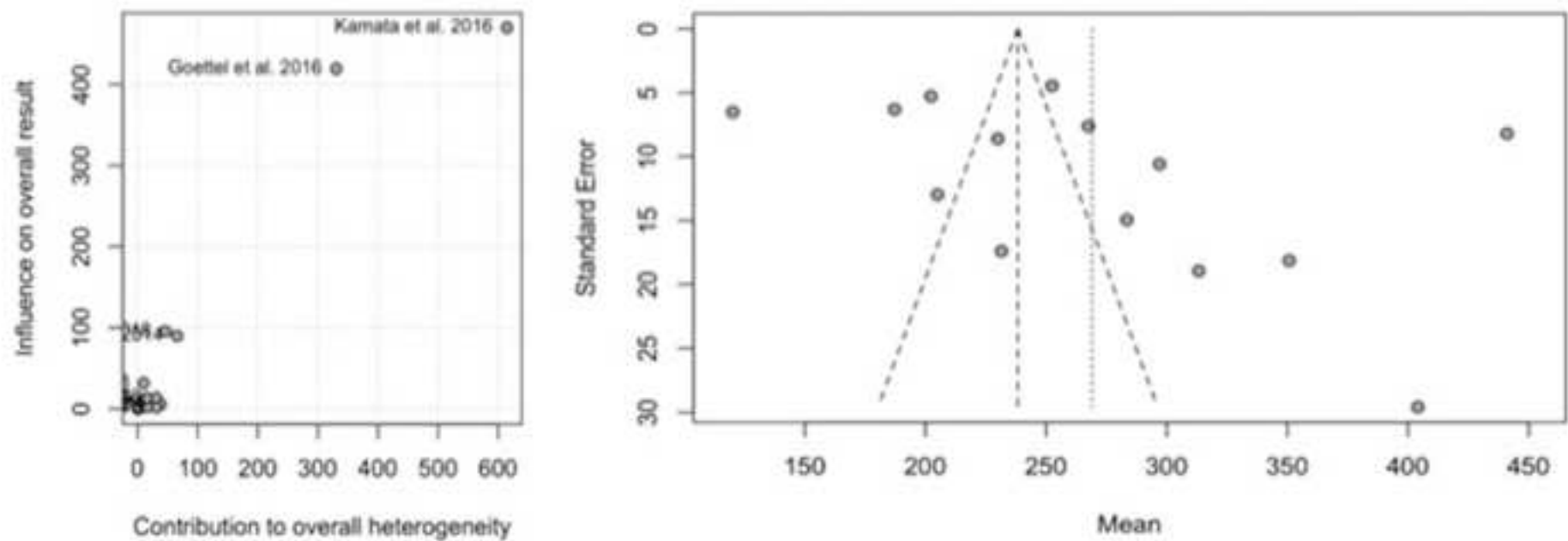


Figure S9. Pooled meta-analysis of MAC and SAS studies for Nausea. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

# Nausea

Figure S10. Assessment of heterogeneity and publication bias. Baujat and Funnel plots for Nausea.



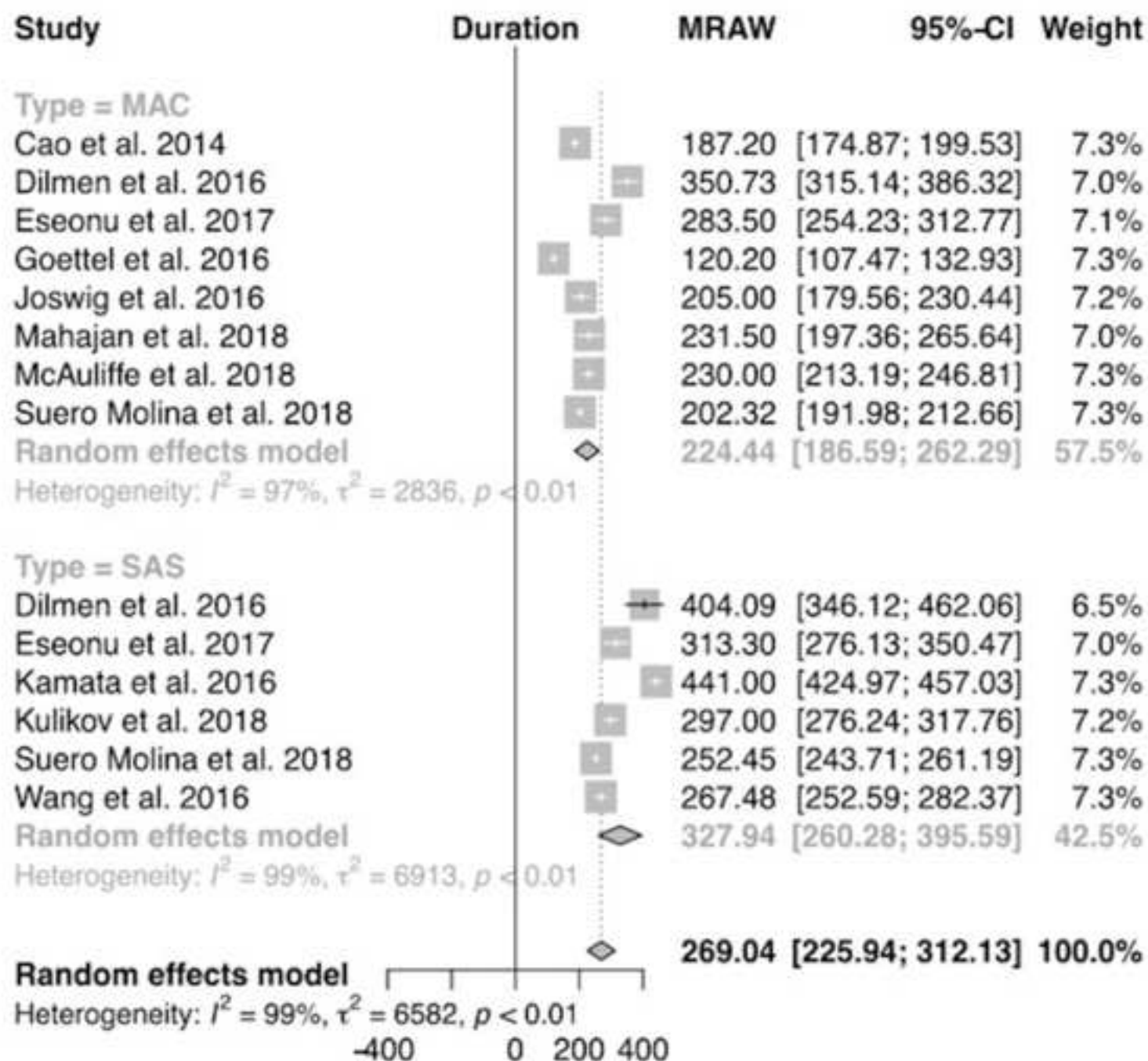
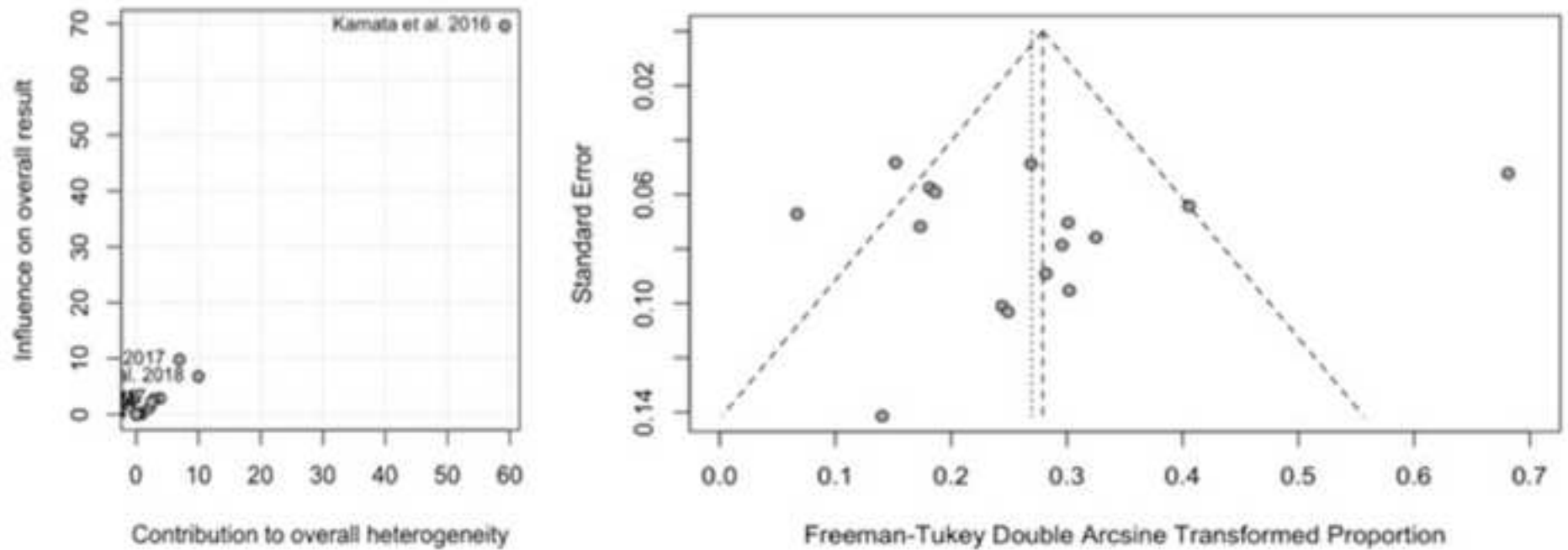


Figure S11. Pooled meta-analysis of MAC and SAS studies for Duration of the Surgical Procedure. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

## Duration of Surgery

Figure S12. Assessment of heterogeneity and publication bias. Baujat and Funnel plots for Duration of the Surgical Procedure.



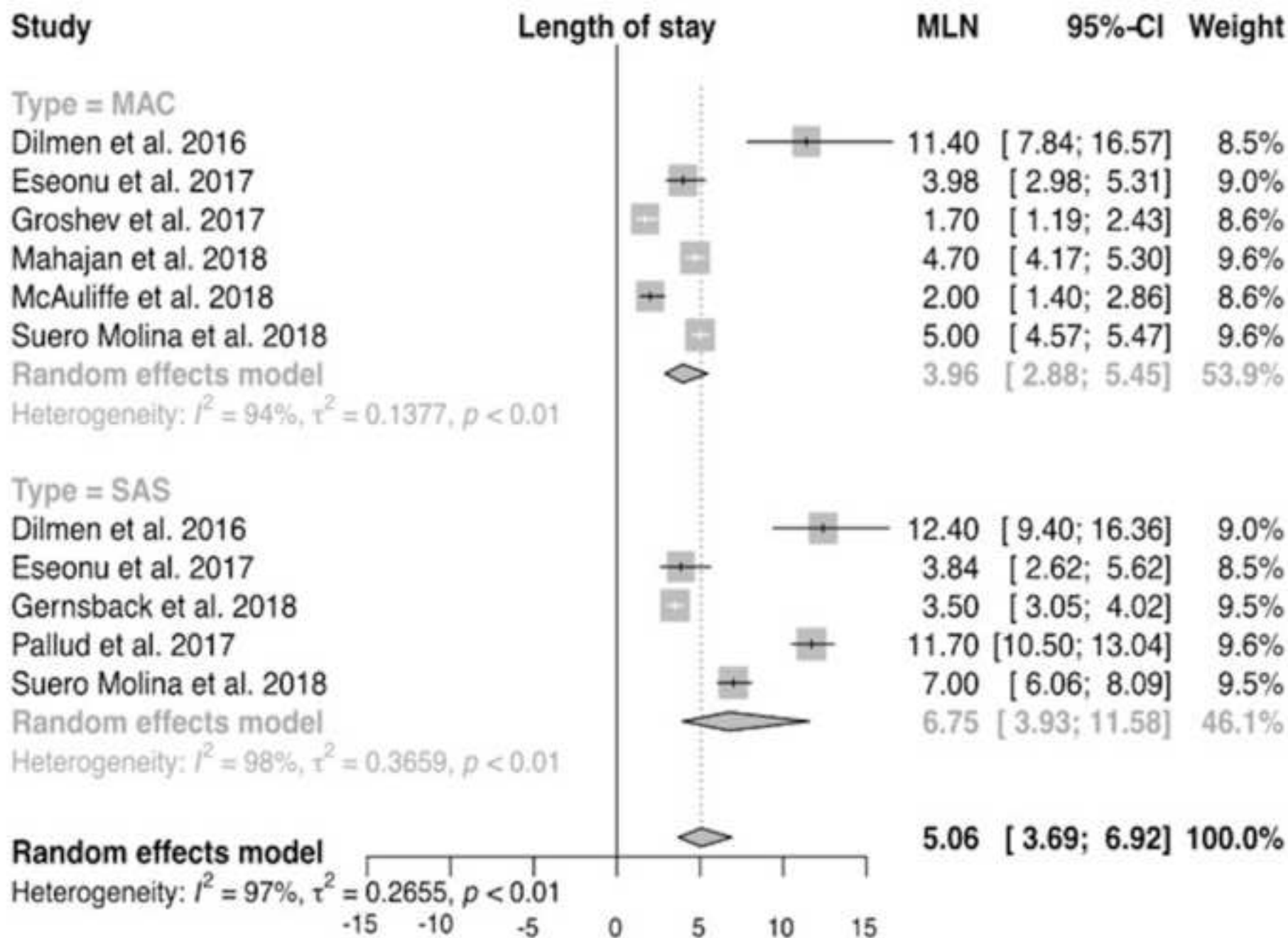
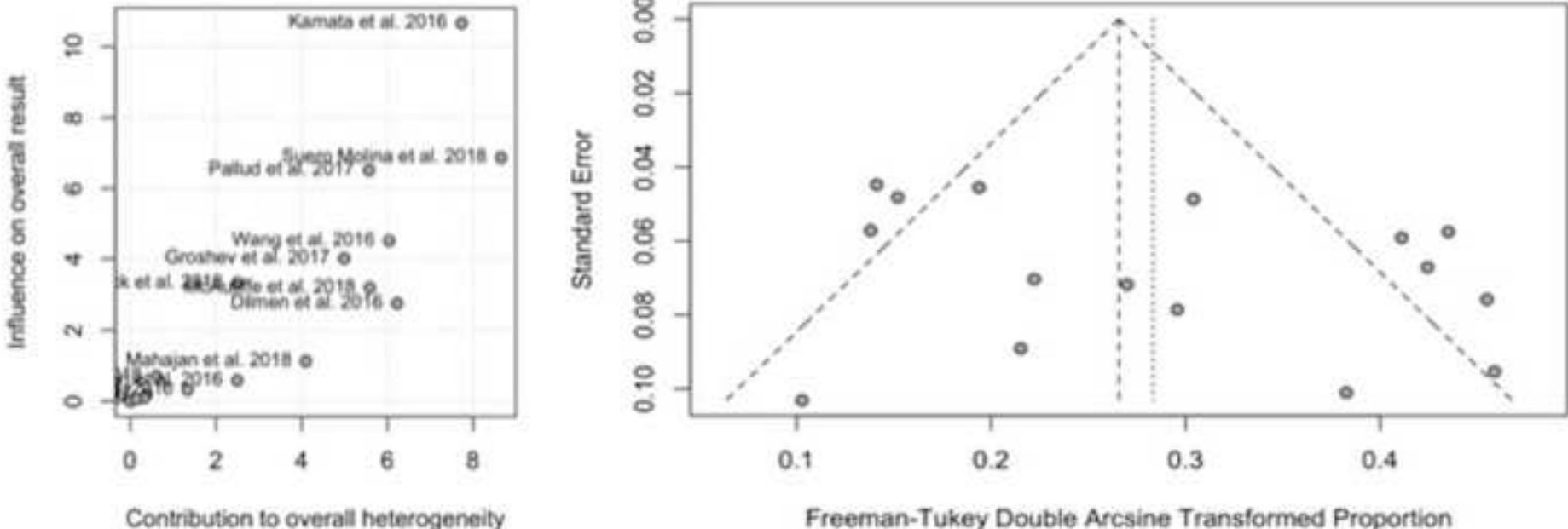


Figure S13. Pooled meta-analysis of MAC and SAS studies for Hospital Length of Stay. MAC, Monitored Anesthesia Care; SAS, Sleep-Awake-Sleep; AC, Awake Craniotomy.

## Length of Stay

Figure S14. Assessment of heterogeneity and publication bias. Baujat and Funnel plots for Hospital Length of Stay



Study	Conversion into GA	Intraoperative seizures/history of seizures in these Patients	Intraoperative hypoxia	Intraoperative hypertension (>20% deviation from baseline	Nausea and/or vomiting	Settings of stimulator for brain mapping
Cao SE et al (2014)	0	NA	NA	NA	0	NA
Dilmen OK et al (2016)	0	SAS 0/NA; MAC 8/NA	SAS 8 (1 severe < 90%, 7 moderate 90-95%); MAC 1 (moderate)	SAS 0; MAC 8 (need for antihypertensive medication)	SAS 1; MAC 4	NA
Elbakry A et al (2017)	PD group n=2 patients;PR group n=3 (patients were not included in the study)	NA	PD group n=0; PR group n=3	PD group n=2; PR group n=2	PD group n= 2; PR group n=4, vomiting PR group n=3	NA
Eseonu CI et al (2017)*	SAS 1; MAC 0	SAS 1/17; MAC 2/32	SAS 0; MAC 0	SAS 3; MAC 4	SAS 0; MAC 1	Ojemann stimulator (0.5 msec at 50Hz, 2mA to 6 mA)*
Eseonu CI et al (2017)*	NA	NA/13	NA	NA	2 (postoperative)	Ojemann stimulator (0.5 msec at 50Hz, 2mA to 6 mA)*
Eseonu CI et al (2017)*^	0	2/23	NA	NA	3 (postoperative)	Ojemann stimulator (0.5 msec at 50Hz, 2mA to 6 mA)*
Eseonu CI et al (2018)*	0	Positive mapping 5/11; Negative mapping 0/7	NA	NA	NA	Ojemann stimulator (0.5 msec at 50Hz, 2mA to 6 mA)*
Gernsback JE et al (2018)	NA	4/48	NA	NA	NA	Ojemann stimulator (2 mA to 6 mA)
Goettel N et al (2016)	1 (DEX group, excluded from stat analysis)	3/21 (tot); 0/10 (PR group); 3/11 (DEX group)	5 (PR group); 0 (DEX group)	2 (PR group); 1 (DEX group)	1 (PR group); 0 (DEX group) (intraop)/ 12 (PR group); 3 (DEX group) (postop use of antiemetics)	NA
Groshev A et al (2017)	0	1/29	NA	NA	NA	NA
Joswig H et al (2016)	NA	3/17	NA	NA	1 (intraoperative)	Ojemann stimulator (1 msec at 60Hz, 1.5 mA to 3.5 mA)



Kamata K et al (2016)	NA	2/ NA	NA	NA	Control vs Dexamethasone Nausea: 10/11 Vomiting: 11/4	NA
Kahn SA et al (2016)	0	1/8	NA	NA	NA	NA
Kulikov A et al (2018)	3	3/28	NA	20	3	NA
Mahajan C et al (2018)	0	5/ NA	0	NA	2	NA
McAuliffe N et al (2018)	0	9/35	0	0	0 (intraoperative)	Ojemann stimulator (0.5 msec at 60Hz, 2 mA to 8 mA)
Pallud J et al (2016)	NA	2/85	NA	NA	NA	Osiris Neurostimulator (1 msec at 60Hz, 1 mA to 6 mA)
Prontera A et al (2017)	0	NA / NA	0	0	NA	Ojemann stimulator (1 msec at 60Hz)
Shinoura N et al (2016)	NA	NA / NA	NA	NA	NA	Ojemann stimulator (1 msec at 60Hz, 3 mA to 5 mA)
Suero Molina E et al (2018)	SAS 2 (1 seizure, 1 anaesthetic complications); MAC 1 (patient preference)	SAS 9/ NA MAC 13/ NA	SAS 2; MAC 2	Hypertension time before induction SAS vs MAC (31.96 min vs 25.67 min) Less antihypertensive drugs used in the MAC group	SAS 7; MAC 2	Ojemann stimulator (50Hz, 1 mA to unspecified)
Wang et al (2016)	NA	TCI-E 1; MCI-E 3; TCI-M 3; MCI-M 4/ NA	TCI-E 4; MCI-E 4; TCI-M 0; MCI-M 0 (TCIM, MCIM on MV)	TCI-E 1; MCI-E 5; TCI-M 1; MCI-M 1	TCI-E 0; MCI-E 1; TCI-M 0; MCI-M 1	NA

**Appendix Table S15.** Perioperative outcomes not included in the quantitative analysis.

NA, Not Available; MAC, monitored anaesthesia care; SAS, asleep-awake-asleep protocol; TCI-E, Target Controlled Anaesthesia for Epileptogenic foci in Eloquent Areas; TCI-M, Target Controlled Anaesthesia for Epileptogenic foci in Motor Areas; MCI-E, Manually Controlled Anaesthesia for Epileptogenic foci in Eloquent Areas; MCI-M, Manually Controlled Anaesthesia for Epileptogenic foci in Motor Areas; DEX, Dexmedetomidine; PD, Propofol-Dexmedetomidine; PR, Propofol-Remifentanyl.

\* Four studies by Eseonu et al. partially reported on the same cohort.

\*^ Only the largest study by Eseonu et al. was included in the quantitative analysis.

Study	Pre-operative Neurological dysfunction	New neurological dysfunction (n)	Persistent neurological dysfunction >6 months if not otherwise stated (n)	Mortality (n)	Postoperative intracranial haematoma (n)	Tumor characteristics	Complete tumour resection (n)	Length of hospital stay in days (mean and SD)
Cao SE et al (2014)	NA	NA	NA	0	NA	NA	NA	NA
Dilmen OK et al (2016)	NA	SAS 1; MAC 2	SAS 0; MAC 1 (language deficit)	0	NA	NA	NA	SAS 12.4 ± 8.22; MAC 11.40 ± 14.10
Elbakry A et al (2017)	NA	NA	NA	0	NA	NA	NA	NA
Eseonu CI et al (2017)*	-	SAS 16; MAC 24	SAS 3; MAC 3	0	NA	-	NA	SAS 3.84; MAC 3.98
Eseonu CI et al (2017)*	-	11 (motor); 1 (sensory);0 (cognitive); 0 (visual)	3 (motor)	0	NA	-	NA	4.12
Eseonu CI et al (2017)*^	Motor Deficit:(20% MAC, 16.1% SAS). Sensory deficit (8% MAC, 3.2 % SAS) Dysarthria (6% MAC, 3.2% SAS) Cognitive deficit (12% MAC, 9.7% SAS) Visual deficit (4% MAC, 12.9% SAS)	19 (motor); 4 (language); 3 (cognitive); 2 (visual)	3 (motor); 4 (language)	0	NA	Tumour mean vol. (cm³) 31.4 MAC, 31.9 SAS; tumour types: glioblastoma (30% MAC, 45.2% SAS) Astrocytoma (36% MAC, 12.9% SAS) Oligodendroglioma (18% MAC, 19.3% SAS) Others (16% MAC, 22.6% SAS)	7	4.2

Eseonu CI et al (2018)*	-	Positive mapping 17 (motor), 1 (sensory), 3 (cognitive); Negative mapping 3 (motor), 0 (sensory), 1 (cognitive)	Positive mapping 3 (motor); Negative mapping 0	0	NA	-	Positive mapping NK; Negative mapping 20	Positive mapping 4 $\pm$ 2.6; Negative mapping 3.1 $\pm$ 1.5
Gernsback JE et al (2018)	65% (speech, motor and mental status combined)	NA	NA	0	NA	Glioblastoma 43.3%, high-grade glioma 12.5%, low-grade glioma 24.2%, metastasis 15.8%, others 4.2%.	NA	3.5 $\pm$ 2.7
Goettel N et al (2016)	NA	2 (PR group); 0 (DEX group)	NA	0	NA	NA	NA	NA
Groshev A et al (2017)	89% (not specified)	8 (motor); 1 (language)	3 (motor); 0 (language)	0	0	Metastasis 41%, glioblastoma 34%, glioma grade III 18%, glioma I-II 5%, meningioma 1%.	45	1.7
Joswig H et al (2016)	Motor 25%, Speech 12.5 %.	7	1	0	1	Glioblastoma 21%, oligodendroglioma 37.5%, metastasis 12.5%, others 29.1%.	8	NA
Kamata K et al (2016)	NA	NA	NA	NA	NA	WHO IV 4.4%, WHO III 49.4%, WHO II 44%, WHO I 2.2%.	NA	NA
Kahn SA et al (2016)	Motor 25%, sensorial 12.5 %.	2	NA	0	NA	Oligodendroglioma 43.5%, glioblastoma 37.5%, astrocytoma 6.5%	NA	4

						Metastasis 6.5%, others 6.5%.		
Kulikov A et al (2018)	Speech 35%,	NA	NA	0	NA	High grade glioma 45%, Low grade glioma 50%, Others 5%.	NA	NA
Mahajan C et al (2018)	NA	6	NA	0	NA	NA	NA	4.7 ± 1.5 days
McAuliffe N et al (2018)	NA	3	NA	0	1	High grade 45% low grade 53% others 2%.	32	2
Pallud J et al (2016)	Neurological 18.7% neuropsychological 91.6%.	32	NA	0	1	Tumour vol. flair, mean cm <sup>3</sup> 65.9. Grade IV 14%, Grade III 44% Grade II 49%.	49	11.7 ± 6.7
Prontera A et al (2017)	NA	NA	NA	0	NA	Grade IV 14%, Grade II 42.8%, Grade III 14.2%, Others 28.5%.	NA	NA
Shinoura N et al (2016)	Motor 83.6%	24	7 (1 month)	NA	NA	High grade glioma 23%, metastasis 49.2%, Low grade glioma 3.3%, Others 24.6 %.	NA	NA
Suero Molina E et al (2018)	NA	NA	NA	NA	NA	WHO II SAS 30.5%, MAC 28%; WHO III SAS 20%, MAC 17.3%; WHO IV SAS 49.5%, MAC 54.7%.	NA	SAS 7; MAC 5
Wang et al (2016)	NA	NA	NA	NA	NA	NA	NA	NA

**Appendix Table S16.** Neurosurgical characteristics and outcomes not included in the quantitative analysis.

NA, Not Available; MAC, monitored anaesthesia care; SAS, asleep-awake-asleep protocol; DEX, Dexmedetomidine; PR, Propofol-Remifentanyl.

\* Four studies by Eseonu et al. partially reported on the same cohort.

\*^ Only the largest study by Eseonu et al. was included in the quantitative analysis, for which we report the tumour characteristics and pre-op dysfunction.