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Isolated forearm technique: a meta-analysis to compare connected consciousness during different anaesthesia regimens

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Summary

Background: Anaesthesia should prevent patients from experiencing surgery, defined as connected consciousness. Isolated forearm technique (IFT) represents the gold standard for connected consciousness monitoring. We evaluated the efficacy of different anaesthesia regimens in preventing IFT responses.

Methods: We conducted a systematic review with meta-analysis of studies evaluating IFT in adults. Meta-analysis proportions of IFT-positives were compared for inhalational versus intravenous anaesthesia and anaesthesia brain monitor (ABM)-guided versus non-ABM-guided.

Results: Of 1131 patients in 22 studies, 393 (34.8%) had an IFT response during induction *or* maintenance. IFT positives were less frequent during induction (19.7% [95% CI, 17.5-22.1]) than during maintenance (31.2% [95% CI, 27.8-34.8]). Proportions of IFT positives during induction *and* maintenance were similar for inhalational (0.51 [95% CI, 0.38-0.65]) and intravenous (0.52 [95% CI, 0.26-0.77]) anaesthesia. Proportions of IFT positives during maintenance were lower with inhalational (0.18 [95% CI, 0.08-0.38]) than with intravenous (0.48 [95% CI, 0.24-0.73]) anaesthesia. Proportions of IFT positives during induction *and* maintenance were not significantly different for ABM-guided (0.64 [95% CI, 0.39-0.83]) and non-ABM-guided (0.48 [95% CI, 0.34-0.62]) anaesthesia. Proportions of IFT positives during maintenance were lower with non-ABM-guided (0.19 [95% CI, 0.09-0.37]) than with ABM-guided (0.57 [95% CI, 0.34-0.77]). Proportions of IFT positives decreased significantly with increasing age and premedication use. Of the 34 anaesthesia regimens, 16 were inadequate. Studies had low methodological quality (only seven randomized controlled trials) and significant heterogeneity.

Conclusions: Standard anaesthesia regimens may not prevent connected consciousness. More accurate ABM methodology, to reduce the likelihood of connected consciousness, is desirable.

Keywords: Intraoperative monitoring; Consciousness monitors; Intraoperative awareness.

Introduction

One of the most important objectives of anaesthesia is to prevent the patient from experiencing surgery, which has been defined as connected consciousness.[1] Various methods have been proposed to monitor connected consciousness. The isolated forearm technique (IFT) and bispectral index (BIS) monitoring are the two most important methods. IFT is a qualitative method: in response to verbal instructions, the patient either does or does not move the forearm that has been isolated from the systemic circulation. Isolation is accomplished using a cuffed upper arm tourniquet, which is inflated before the administration of neuromuscular blocking agents to a pressure higher than the systolic blood pressure. Movement of the isolated forearm in response to instructions is considered a positive IFT test, which can be interpreted as a sign of connected consciousness.[1] IFT has been recognized as the gold standard for consciousness monitoring in the presence of neuromuscular blocking agents.[2]

BIS monitoring is a quantitative method: it is based on bispectral processing of spontaneous cortical activity of the monolateral frontal cortex, which determines the harmonic and phase relations among the various electroencephalography (EEG) frequencies.[3 4] BIS values between 40 and 60 are generally recommended as adequate targets for guiding the administration of hypnotics during general anaesthesia.[5 6] However, some patients have been reported to exhibit a positive IFT response during surgery with BIS values in this range, thereby suggesting that connected consciousness might not be avoided at these levels.[7-10] Further increasing the uncertainty about the role of processed EEG anaesthesia brain monitors (ABMs) in preventing connected consciousness, a recent study showed that BIS can fall below 50 in awake volunteers after neuromuscular blockade.[11] All of these data underline the fact that the processes involved in the production of anaesthesia are still far from being well understood and that ABM-guided anaesthesia cannot completely eliminate the risk of insufficient anaesthesia: a patient believed to be deeply anaesthetized in the operating room may still be able to hear and respond to voices of operating room personnel, indicating the presence of connected consciousness.

The magnitude of the problem of connected consciousness is not well established. To quantify the incidence of connected consciousness and related explicit recall in patients undergoing anaesthesia, we conducted a systematic review, with meta-analysis, of adult-only studies in which IFT was used. We determined the overall incidence of connected consciousness (defined by a positive IFT test) and explicit recall and performed subgroup analyses to assess the effects of the type of anaesthesia (intravenous or inhalational) and the use or non-use of ABM during induction and surgery. We also performed regression meta-analysis to identify factors associated with a positive IFT test or explicit recall.

Materials and methods

1. Search strategy

We performed a systematic review with meta-analysis of previously published studies in which the level of consciousness during general anaesthesia was monitored with IFT. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, www.prisma-statement.org) when designing the study and preparing this report.

We conducted a comprehensive search of the Medline, EMBASE and Google Scholar databases using the following Medical Subject Headings (MeSH) terms: anaesthesia, brain, consciousness monitors, awareness, mental recall, and surgery. Using the "AND" function, the MeSH Terms were combined with each other and with the following additional terms: isolated forearm technique, IFT, bispectral index, BIS, Narcotrend, anaesthesia brain monitor, and ABM. The search period included articles published between 1977[12] and June 2017. No language restrictions were applied for the searches, but only those studies written in English language were selected for inclusion in this systematic review. The date of the last search was June 30, 2017.

Two authors (FL, PZ) independently identified the titles and abstracts of potentially eligible studies. The full-text versions of these studies were then reviewed by FL and PZ to select the studies included in this systematic review. Any disagreements at either the title and abstract screening or full-text review stages were resolved by consensus with input from a third author (MC).

2. Eligibility and inclusion

Studies were included if they involved patients only ≥18 years old, evaluated the use of the IFT to monitor consciousness during anaesthesia, and were controlled or observational trials. Furthermore, studies were excluded if they involved paediatric patients, did not clearly specify the anaesthesia regimen or number of patients who were considered IFT positives (defined in the "End-point" section), or involved the use of the IFT solely to monitor emergence from anaesthesia. Review articles and case reports were excluded. If the exact timing of IFT responses was not specified, we classified them as occurring during the maintenance phase.

3. End-points

We considered four main end-points: the number of IFT positives at any time during general anaesthesia (from induction to the end of surgery); the number of IFT positives during the induction phase of anaesthesia; the number of IFT positives during the maintenance phase of anaesthesia (from 10 minutes after induction to the end of surgery); and the number of patients reporting explicit recall of surgery in the postoperative period. A patient was considered IFT-positive if verified movement occurred in response to direct verbal instructions given by study personnel, or if the patient initiated spontaneous, purposeful movement indicating a desire to communicate. A patient was considered IFT negative if there was no movement or if only random, spontaneous, or reflex movements occurred, which were not associated with any stimulus.

4. Data extraction

Data regarding the baseline characteristics (age and weight) of the study groups, anaesthetic drug types and dosages, use of premedication, number of patients with an IFT-positive response, phase of anaesthesia during which a positive response occurred, ABM values at time of the IFT-positive response, and the number of patients with explicit recall were extracted from all included studies.

We also rated the depth of anaesthesia used in each study. To do this, two anaesthesiologist authors (PZ, MC), who were blinded to the IFT results, independently categorized the anaesthesia regimen of each study (based on drugs and dosage) as "light" or "adequate". Any disagreements were resolved by consensus with input from a third anaesthesiologist author (CO), who was likewise unaware of the IFT results.

5. Assessment of risk of bias

The risk of bias of the included studies was assessed using the Cochrane risk of bias tool.[13]

6. Statistical analysis

To compare anaesthesia techniques, the patients were assigned to groups according to their anaesthesia regimen: inhalational anaesthesia for maintenance phase, intravenous anaesthesia for maintenance phase, ABM-guided anaesthesia, and non-ABM-guided anaesthesia.

Meta-analyses of single proportions were performed within a frequentist framework, using both random and fixed effects models. The Mantel-Haenszel method was used to calculate the fixed effects estimate. A continuity correction of 0.5 was added to the frequencies of every study, and logit transformation was used to calculate the overall proportions. Confidence intervals (CIs) for the individual studies were computed using the Clopper-Pearson method. The random effects model was computed with inverse-variance weighting using the DerSimonian-Laird method to account for heterogeneity. Heterogeneity across studies was tested using the Cochran's Q statistic and the I^2 statistic. A threshold of $p < 0.1$ was used to decide whether heterogeneity was present. I^2 was considered substantial when it was > 50%. To explore the observed heterogeneity, we performed subgroup and meta-regression (univariable and multivariable) analyses. During subgroup analysis, we compared the proportion of IFT positives with non-ABM-guided versus ABM-guided anaesthesia among patients receiving just intravenous anaesthesia. During meta-regression, we examined the effects of depth of anaesthesia (light or adequate), premedication (yes or no), use of inhalational anaesthetics during induction, patient age, and patient weight on the presence of an IFT-positive response or explicit recall. We also conducted sensitivity analysis (using random effects models) of only randomized controlled trials (RCTs). Computations were performed using the R (version 3.3.1 for Windows) package meta.

Results

Of the 1233 potentially relevant studies initially identified in the literature, 1211 were excluded because they did not meet the inclusion criteria, were duplicates, or contained incomplete method or outcome data. Therefore, 22 studies involving 1131 patients were eligible for meta-analysis.[7-10 14-31] However, seven studies[14-18 26 28] evaluated two or more different anaesthesia regimens, so each regimen was considered separately, for a total of 34 different regimens evaluated during the meta-analyses.

The PRISMA flow diagram of our study selection process is presented in Figure 1. The characteristics of the included studies are reported in Table 1. The risk of bias summary of the included studies is shown in Figure 2. As shown, the overall quality was low, as many trials exhibited a high risk of bias. Only 7 studies of 22 were RCTs.[14-18 26 28]

Absolute number of IFT positives and explicit recall

Of 1131 patients, 393 (34.8%; 95% CI, 32.0-37.6) had a positive IFT response at any time during the induction *or* maintenance phase. A total of 223 patients (19.7%; 95% CI, 17.5-22.1) had a positive IFT response during induction. In trials that considered both the induction *and* maintenance phases,[7-10 14-24] 208 of the 666 patients (31.2%; 95% CI, 27.8-34.8) had a positive IFT response during maintenance of anaesthesia.

Explicit recall was assessed in 485 patients; of these, 30 (6.2%; 95% CI, 4.4-8.7) had explicit recall.

IFT positives during induction phase

The 223 patients with a positive IFT response during the induction phase had a mean age and weight of 38.7 (95% CI, 26.8-50.6) years and 72.9 (95% CI, 68.8-77.0) kg. In two studies[21 26] (including five anaesthesia regimens), anaesthesia was induced with intravenous and inhalational drugs, whereas in the other 20 included studies, only intravenous agents were used for induction. Seven studies[7-10 25 29 31] used ABM-guided anaesthesia.

Comparing the meta-analysis proportions of IFT-positive patients during the induction phase, there were no significant differences between anaesthesia techniques: intravenous versus intravenous and inhalational drugs, usage versus non-usage of premedication, and usage versus non-usage of ABM. A positive IFT response during induction was more frequent in heavier patients than in normal-weight patients, although the difference did not reach statistical significance (p=0.0682).

Inhalational versus intravenous anaesthesia during induction and maintenance phases

We compared a total of 15 inhalational anaesthesia regimens [9 14-22] to 6 intravenous regimens.[7 8 10 16 23 24] All of these evaluated IFT responses in both the induction and maintenance phases. Target-controlled infusion (TCI) anaesthesia was used in 3 of the 6 intravenous regimens.[7 8 10] Inhalational anaesthesia was received by 474 patients; their mean age and weight were 30.9 (95% CI, 21.9-39.9) years and 71.1 (95% CI, 64.9-77.3) kg. Intravenous anaesthesia was received by 192 patients; their mean age and weight were 43.7 (95% CI, 36.3-51.1) years and 70.4 (95% CI, 59.2-81.6) kg.

Of the 474 patients who received inhalational anaesthesia, 224 (47.3%; 95% CI, 42.8-51.6) had a positive IFT response at any time during anaesthesia, and among the 192 who received intravenous anaesthesia, 97 (50.5%; 95% CI, 43.5-57.5) had a positive IFT response at any time. A positive IFT response during maintenance occurred in 121 of the 474 patients (25.5%; 95% CI, 21.8-29.6) who received inhalational anaesthesia and 87 of the 192 patients (45.3%; 95% CI, 38.4-52.3) who received intravenous anaesthesia. Furthermore, explicit recall was reported by 9 of the 193 patients (4.7%; 95% CI, 2.4-8.6) who received inhalational anaesthesia and 18 of the 192 patients (9.4%; 95% CI, 6-14.3) who received intravenous anaesthesia.

Comparing the meta-analysis proportions of IFT-positive patients at any time, there were no significant differences between anaesthesia techniques: inhalational versus intravenous anaesthesia, 0.51 (95% CI, 0.38-0.65, I^2 = 81.9%, $p < 0.0001$) versus 0.52 (95% CI, 0.26-0.77, I^2 = 89.2%, $p < 0.0001$), respectively. IFT positives during the maintenance phase were less frequent during inhalational anaesthesia than during intravenous anaesthesia: 0.18 (95% CI, 0.08-0.38, I^2 = 87.8%, p <

0.0001) versus 0.48 (95% CI, 0.24-0.73, I^2 = 88%, p < 0.0001), respectively. Among the seven studies that evaluated explicit recall, the incidence of explicit recall was lower for inhalational anaesthesia than for intravenous anaesthesia: 0.08 (95% CI, 0.05-0.14, I^2 = 0%, p = 0.4253) versus 0.12 (95% CI, 0.06-0.24, I^2 = 53.4%, p = 0.0568).

High heterogeneity was found between the inhalational and intravenous anaesthesia groups of regimens. Detailed results of comparisons between inhalational and intravenous anaesthesia, regarding the proportions of patients with an IFT-positive response at any time and during anaesthesia maintenance, as well as the rates of explicit recall, are reported in Figure 3 (which includes the results of both the fixed and random effects models and the heterogeneity analyses).

ABM-guided versus non-ABM-guided anaesthesia during induction and maintenance phases

We analysed 4 ABM-guided anaesthesia[7-10] and 17 non-ABM-guided anaesthesia regimens.[14-24] These regimens evaluated IFT responses in both the induction and maintenance phases. A total of 124 patients received ABM-guided anaesthesia; their mean age and weight were 67.3 (95% CI, 60.2-74.4) years and 79.7 (95% CI, 74.2-85.2) kg. A total of 542 patients received non-ABM-guided anaesthesia; their mean age and weight were 33.6 (95% CI, 25.0-42.2) years and 78.7 (95% CI, 70.9-86.6) kg.

Of the 124 patients who received ABM-guided anaesthesia, 76 (61.2%; 95% CI, 52.5-69.4) had a positive IFT response at any time during anaesthesia, and among the 542 who received non-ABM-guided anaesthesia, 269 (49.6%; 95% CI, 45.4-53.8) had a positive IFT response at any time. A positive IFT response during the maintenance phase of anaesthesia occurred in 66 of the 124 patients (53.2%; 95% CI, 44.4-61.7) who received ABM-guided anaesthesia and 142 of the 542 patients (26.2%; 95% CI, 22.6-30) who received non-ABM-guided anaesthesia. Furthermore, explicit recall was reported by 15 of the 124 patients (12.1%; 95% CI, 7.4-19) who received ABM-guided anaesthesia and 12 of the 261 patients (4.6%; 95% CI, 2.6-7.8) who received non-ABM-guided anaesthesia.

Comparing the meta-analysis proportions of patients with a positive IFT response at any time, there were no significant differences between anaesthesia techniques. The proportion was 0.64 (95% CI, 0.39-0.83, I^2 = 80.6%, $p < 0.0001$) for ABM-guided anaesthesia and 0.48 (95% CI, 0.34-0.62, I^2 = 84.9%, $p < 0.0001$) for non-ABM-guided anaesthesia. IFT positives during the maintenance phase were less frequent during non-ABM-guided anaesthesia than during ABM-guided anaesthesia: 0.19 (95% CI, 0.09-0.37, I^2 = 88.9%, $p < 0.0001$) versus 0.57 (95% CI, 0.34-0.77, I^2 = 77%, $p < 0.005$), respectively. Among the four trials that evaluated explicit recall, the incidence of explicit recall was lower for non-ABM-guided anaesthesia than for ABM-guided anaesthesia: 0.08 (95% CI, 0.05-0.13, I^2 = 0%, $p < 0.05$) versus 0.16 (95% CI, 0.06-0.37, I^2 = 65.8%, $p < 0.05$).

High heterogeneity was found among both the ABM-guided and non-ABM-guided groups of regimens. Detailed results of the comparisons between ABM-guided anaesthesia and non-ABM-guided anaesthesia groups, with respect to the proportions of patients with an IFT-positive response at any time and during anaesthesia maintenance, as well as the rates of explicit recall, are reported in Figure 4 (which includes the results of both the fixed and random effects models and heterogeneity analyses).

To explore the high heterogeneity, an additional subgroup analysis of the intravenous anaesthesia regimens was performed, subdividing the regimens based on whether ABM was or was not used. Non-ABM-guided intravenous anaesthesia appeared to be associated with fewer IFT positives at any time during anaesthesia (32 of 102 patients, meta-analysis proportion = 0.26 [95% CI, 0.26-0.77], I^2 = 89.2%, $p < 0.0001$) than ABM-guided intravenous anaesthesia (65 of 90 patients, meta-analysis proportion = 0.71 [95% CI, 0.55-0.84], I^2 = 36.8%, $p < 0.05$). Non-ABM-guided intravenous anaesthesia was also associated with fewer IFT positives during maintenance of anaesthesia (32 of 102 patients, meta-analysis proportion = 0.26 [95% CI, 0.04-0.74], I^2 = 92.9%, $p < 0.0001$) than ABM-guided intravenous anaesthesia (55 of 90 patients, meta-analysis proportion = 0.68 [95% CI, 0.39-0.88], I^2 = 74.6%, $p < 0.05$). High heterogeneity was also observed among these studies, and this analysis did not reach significance (Figure 5).

Sensitivity analysis of randomized controlled trials

A sensitivity analysis using random effects models considering just RCTs[14-18 26 28] has been performed, where pooled estimates are calculated omitting one study at a time. This analysis did not reveal any statistically significant differences, either among proportions or heterogeneity.

Meta-regression analysis

Our meta-regression analysis revealed that the proportion of patients with a positive IFT response during the maintenance phase of anaesthesia was lower with increasing age and the use of premedication ($p = 0.0123$). Sixteen of the 34 anaesthesia regimens appeared to be conducted using light anaesthesia (Table 1). There was a trend toward light anaesthesia increasing the proportion of patients with a positive IFT response, but the association did not reach statistical significance.

Discussion

Our results suggest that there were no differences among the four different anaesthesia regimens in the meta-analysis proportion of patients who were IFT-positive at any time during anaesthesia. Anaesthesia induction was associated with fewer IFT positives (19.7%, 95% CI, 17.5-22.1) than the maintenance phase of anaesthesia (31.2%; 95% CI, 27.8-34.8). Potential differences in IFT responses among the different anaesthesia regimens were less during the induction of anaesthesia. Only one study did not report any patient with a positive IFT response.[21] In that study, a combined intravenous–inhalational anaesthesia technique was used for induction, followed by non-ABM-guided inhalational anaesthesia. Adequate anaesthesia for induction can be useful to avoid connected consciousness during the first 10 minutes after induction. Reducing the likelihood of a positive IFT response after intubation by early administration of a volatile anaesthetic drug, while waiting for a neuromuscular blocking agent to take effect, has also been confirmed by a recent prospective study.[31]

By contrast, we found important differences among anaesthesia regimens in preventing an IFT-positive response during the maintenance phase of anaesthesia (from 10 minutes after induction to the end of surgery). Inhalational anaesthesia was associated with a lower frequency of IFT positives than intravenous anaesthesia. Connected consciousness was likewise more common with ABM-guided anaesthesia than with non-ABM-guided anaesthesia during maintenance. BIS values were equal to or greater than 60 at the time of an IFT-positive response: 64±3,[7] 60 (interquartile range [IQR], 50-67),[9] and 61 (IQR, 52-67).[10] These values are at the upper limit of BIS values recommended in the literature[5] [6]. In two ABM-guided anaesthesia studies (with BIS target 55-60), [9] [10] the concentrations of isoflurane (0.3 [0.2 to 0.9] minimum alveolar concentration [MAC]) and propofol TCI (2.0 mcg kg^{-1} min^{-1}) adopted for maintenance seem to be in the lower range of those used in clinical practice.

Other trials, in which ABM-guided anaesthesia appeared to increase the incidence of awareness,[32 33] suggested that ABM-guided anaesthesia, particularly for intravenous anaesthesia, might also be associated with an increased risk of IFT positives. The only non-ABM-guided anaesthesia study with a high proportion of IFT positives (0.72; 95% CI, 0.53-0.86]) involved the use of light anaesthesia with midazolam and alfentanil, which the authors themselves defined as "general amnesia" rather than "general anaesthesia".[23]

The low reliability of BIS has also been recently demonstrated by Schuller et al.,[11] who enrolled awake subjects to monitor the BIS response to neuromuscular blocking agents in the absence of hypnotics. The BIS monitor reported values below 60 after neuromuscular blockade, with transient decreases to values of 44, thereby showing that patients can be awake at low BIS values.

Therefore, MAC-guided inhalational anaesthesia seems to be more effective than ABM-guided inhalational anaesthesia, as well as ABM-guided intravenous anaesthesia, in preventing IFT-positive responses and accidental awareness during surgery. The most likely explanations for the relatively poor results with ABMs include the use of inadequate types of ABM or the use of target ranges of BIS values that are inappropriate for achieving abolition of connected consciousness. Thus, avoiding connected consciousness may require lowering target BIS values.

Even if our subgroup analysis did not reveal any statistical difference, the meta-analysis proportion of IFT responses of Non-ABM-guided intravenous anaesthesia is lower (32 of 102 patients, meta-analysis proportion = 0.26 [95% CI, 0.26-0.77], I^2 = 89.2%, $p < 0.0001$) than ABM-guided intravenous anaesthesia (65 of 90 patients, meta-analysis proportion = 0.71 [95% CI, 0.55-0.84], I^2 = 36.8%, $p < 0.05$). Non-ABM-guided intravenous anaesthesia was also associated with fewer IFT positives during maintenance of anaesthesia (32 of 102 patients, meta-analysis proportion = 0.26 [95% CI, 0.04-0.74], I^2 = 92.9%, $p < 0.0001$) than ABM-guided intravenous anaesthesia (55 of 90 patients, meta-analysis proportion = 0.68 [95% CI, 0.39-0.88], I^2 = 74.6%, $p < 0.05$) (Figure 5).

Therefore, if meta-analysis proportion of IFT responses during inhalational anaesthesia maintenance (0,18 [95% CI, 0.08-0.38] is compared to IFT responses during ABM intravenous anaesthesia (0,68 [95% CI, 0.39-0.88]) IFT responses increase during this last anaesthesia regimen, confirming that ABM anaesthesia increases the risk of connected consciousness, also during intravenous anaesthesia.

However, given the small number of studies involved, more trials have to be conducted to define the exact role of ABM monitoring during intravenous anaesthesia.

Our meta-regression analysis found that the proportion of patients with an IFT-positive response decreased in the elderly and in patients who were premedicated. These results are consistent with those previously reported in the literature.[31]

The influence of level of anaesthesia on outcome of patients undergoing general anaesthesia continues to be debated in the literature. A deep hypnotic level has been independently associated with postoperative mortality.[34-36] Nevertheless, BIS values < 45 alone, without hypotension (and resultant potential cerebral hypoperfusion), have been associated with a (nonsignificant) reduction in mortality.[37] Inadequate anaesthesia may increase the risk of connected consciousness and, particularly, of implicit memory that may lead to adverse psychiatric sequelae, including symptoms of post-traumatic stress disorder.[38-42]

Intraoperative neurophysiological monitoring (i.e., electroencephalography and somatosensory evoked potentials) has been successfully utilized to detect and monitor painful stimulation during surgery;[43] this can facilitate achieving optimal brain suppression, sufficient to abolish pain and connected consciousness without producing cerebral hypoperfusion. A recent study conducted comparing IFT responsiveness and frontal EEG patterns concluded that the alpha-delta dominant frontal EEG signature (seen in slow-wave sleep) is not sufficient to ensure unconsciousness during general anaesthesia[44]; further studies should investigate if connected consciousness during anaesthesia requires frontal cortical activity, and which EEG pattern and which brain regions (frontal, temporal, parietal) have to be monitor to be achieve the abolition of IFT responses.

This meta-analysis has some limitations. First, although the technique of detecting the IFT response (based on the method described by Tunstall)[12] was the same for all studies, we found a high degree of heterogeneity among studies with regard to the conduct of anaesthesia, especially with respect to the types and doses of drugs used; however, this heterogeneity may reflect the diversity seen in current anaesthetic practice. In our meta-regression analysis, light anaesthesia did not significantly increase the proportion of patients with positive responses among patients receiving intravenous anaesthesia, inhalational anaesthesia, ABM-guided anaesthesia, or non-ABM-guided anaesthesia. Instead, our results indicate that use of premedication and patient age were important factors associated with the occurrence of a positive IFT response, which may have contributed to the heterogeneous results among studies. An important limitation is that only 7 of the 22 included studies were RCTs,[14-18 26 28] thereby increasing the risk of bias. However, sensitivity analysis of these studies did not reveal any statistically differences, either among proportions or heterogeneity. The overall quality of the included studies was low; in particular subgroup analyses have low statistical significance due to the high heterogeneity and small number of the studies involved. Another limitation was related to the IFT technique itself: a movement response may not be detected in patients who are unable to squeeze the researcher's hand despite being able to hear the instructions to do so. Accordingly, false negatives may occur when the nondominant forearm is isolated or when severe weakness of the forearm is present. Thus, the method of detecting the IFT response must be standardized. A different monitoring technique, such as bilateral electromyography, may be considered, which would also have the advantage of not requiring a cuffed tourniquet.

Conclusions

The processes involved in the production of anaesthesia and how they apply to clinical process are still far from being well understood. Compared to non-ABM-guided anaesthesia, ABM-guided anaesthesia seems less likely to prevent connected consciousness during the maintenance phase of anaesthesia, particularly when intravenous anaesthesia is used. Young age and lack of premedication increase the likelihood of a positive IFT response during the maintenance phase of anaesthesia. This suggests the need for increased attention during the daily conduct of anaesthesia, particularly in adults who are younger or not premedicated. Of note, the included studies were of generally poor methodological quality, with high heterogeneity, and only seven studies were RCTs. Future research should focus on determining a more accurate method of monitoring both a patient's baseline brain reserve (before anaesthesia) and the intraoperative level of consciousness that provides each patient with the best anaesthesia regimen and outcomes.

Authors' contributions

FL and PZ conceived of the study; acquired, collected, and analysed data; and drafted and revised the final manuscript. PT collected and analysed data, performed the statistical analysis, critically revised the final manuscript. CO and MC participated in conceiving the study, analysed data, participated in the discussion of the results, and critically revised the final manuscript. All authors read and approved the version to be published, and gave agreement 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.

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Declaration of interests

The authors declare that they have no competing interests.

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Captions of figures

Figure 1: PRISMA flow diagram of the study selection process

Figure 2. Risk of bias summary of included studies

Green circle, low risk; yellow circle, medium risk; red circle, high risk; (/), unable to determine.

Figure 3. Forest plots of the meta-analysis of single proportions of patients with an IFT-positive response, comparing inhalational versus intravenous anaesthesia.

INA, sudies evaluating IFT responses during induction and mainthenance with inhalational anaesthesia;

IVA, sudies evaluating IFT responses during induction and mainthenance with intravenous anaesthesia;

INA > 10 min, sudies evaluating IFT responses during mainthenance with inhalational anaesthesia;

IVA > 10 min, sudies evaluating IFT responses during mainthenance with intravenous anaesthesia;

INA MEM, sudies evaluating explicit recall after mainthenance with inhalational anaesthesia;

IVA MEM, sudies evaluating explicit recall after mainthenance with intravenous anaesthesia.

Figure 4. Forest plots of the meta-analysis of single proportions of patients with an IFT-positive response, comparing non-ABM-guided versus ABM-guided anaesthesia.

NA, sudies evaluating IFT responses during induction and mainthenance with Non-ABM-guided anaesthesia;

A, sudies evaluating IFT responses during induction and mainthenance with ABM-guided anaesthesia;

NA > 10 min, sudies evaluating IFT responses during mainthenance with Non-ABM-guided anaesthesia;

A > 10 min, sudies evaluating IFT responses during mainthenance with ABM-guided anaesthesia;

NA MEM, sudies evaluating explicit recall after mainthenance with Non-ABM-guided anaesthesia;

A MEM, sudies evaluating explicit recall after mainthenance with ABM-guided anaesthesia.

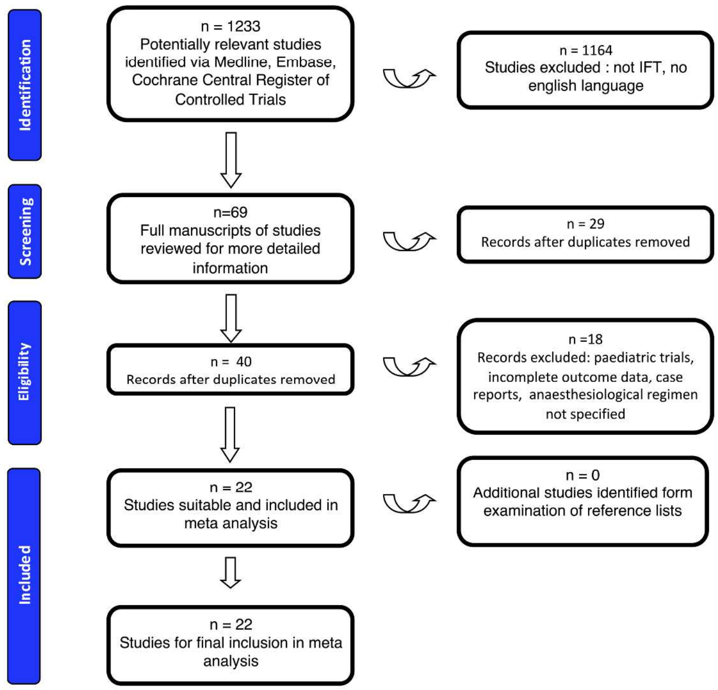
Figure 5. Forest plots of the meta-analysis of single proportions of patients undergoing intravenous anaesthesia with an IFT-positive response, comparing non-ABM-guided versus ABM-guided anaesthesia.

Study	Type of surgery	ANA regimen	Premedication	Light ANA	ABM-guided-ANA Type (target value)	Patients (N)	Total IFT^{+}(N)	IFT^{+} at maintenance (N)	Explicit recall (N)
Tunstall 79	CS	Induction: IV Maintenance: IA	No	Yes	No	16	12	1	nd
Tunstall 79	CS	Induction: IV Maintenance: IA	No	No	No	16	11	0	nd
Russell 85	MGS	Induction: IV Maintenance: IA	Yes	No	No	25	18	18	nd
Schultetus 86	CS	Induction: IV Maintenance: IA	No	Yes	No	12	1	0	0
Schultetus 86	CS	Induction: IV Maintenance: IA	No	No	No	13	7	0	1
Schultetus 86	CS	Induction: IV Maintenance: IA	No	Yes	No	11	4	0	2
Russell 86	MGS	Induction: IV Maintenance: IA	Yes	No	No	25	11	11	1
Russell 86	MGS	Induction: IV Maintenance: IV	Yes	Yes	No	30	2	2	0
Baraka 89	CS	Induction: IV + IA	No	No	No	10	6	nd	1
Baraka 89	CS	Induction: IV + IA	No	No	No	10	8	nd	1
Baraka 89	CS	Induction: IV + IA	No	Yes	No	10	1	nd	0
Baraka 89	CS	Induction: IV + IA	No	Yes	No	10	3	nd	0
Baraka 89	CS	Induction: IV	No	Yes	No	10	0	nd	0
Baraka 90	CS	Induction: IV	No	Yes	No	13	0	nd	nd
Tunstall 89	CS	Induction: IV Maintenance: IA	No	No	No	63	31	31	nd
Tunstall 89	CS	Induction: IV Maintenance: IA	No	No	No	50	47	47	nd
King 93	CS	Induction: IV Maintenance: IA	No	Yes	No	30	29	0	0
Russell 93	MGS	Induction: IV Maintenance: EA	Yes	Yes	No	32	23	23	3
Gaitini 95	CS	Induction: IV Maintenance: IA	No	No	No	25	13	nd	nd
Gaitini 95	CS	Induction: IV Maintenance: IA	No	Yes	No	25	5	nd	nd
Russell 97	MGS	Induction: IV+IA Maintenance: IA	Yes	No	No	68	0	0	5
Pierre 00	GS	Induction: IV	Yes	Yes	No	10	8	nd	1
Pierre 00	GS	Induction: IV	Yes	Yes	No	10	7	nd	0
Pierre 00	GS	Induction: IV	Yes	Yes	No	10	2	nd	0
Russell 01	MGS	Induction: IV Maintenance: IV	Yes	Yes	No	40	7	7	0
Schneider 02	GS	Induction: IV	Yes	No	Yes BIS (50-60)	20	8	nd	0
Slavov 02	GS	Induction: IV	No	No	No	41	10	nd	nd
Kressens 03	GS	Induction: IV Maintenance: IV	No	Yes	Yes BIS (60-70)	56	37	27	9

Russell 06	MGS	Induction: IV Maintenance: IV	No	No	Yes Narcotrend (C0)	12	12	12	4
Kocaman 07	MGS	Induction: IV	Yes	No	Yes BIS (40-60)	51	7	nd	nd
Russell 13	MGS	Induction: IV Maintenance: IA	No	No	Yes BIS (55-60)	34	11	11	0
Russell 13	MGS	Induction: IV Maintenance: IV	No	No	Yes BIS (55-60)	22	16	16	2
Zand 14	CS	Induction: IV Maintenance: IA	No	No	No	61	24	2	nd
Sanders 17	GS	Induction: IV	Yes/No	No	Yes/No If used: BIS (40-60)	260	12	nd	nd

Table 1: Included studies and related anaesthetic regimens

ABM = anaesthesia brain monitor, ANA = anaesthesia, BIS = bispectral index, CS = Caesarean section, GS = general surgery, IA = inhalational anaesthesia, IFT = isolated forearm test, IV = intravenous anaesthesia, MGS = major gynaecological surgery, N = number, nd = not determined



PRISMA flow diagram of the study selection process

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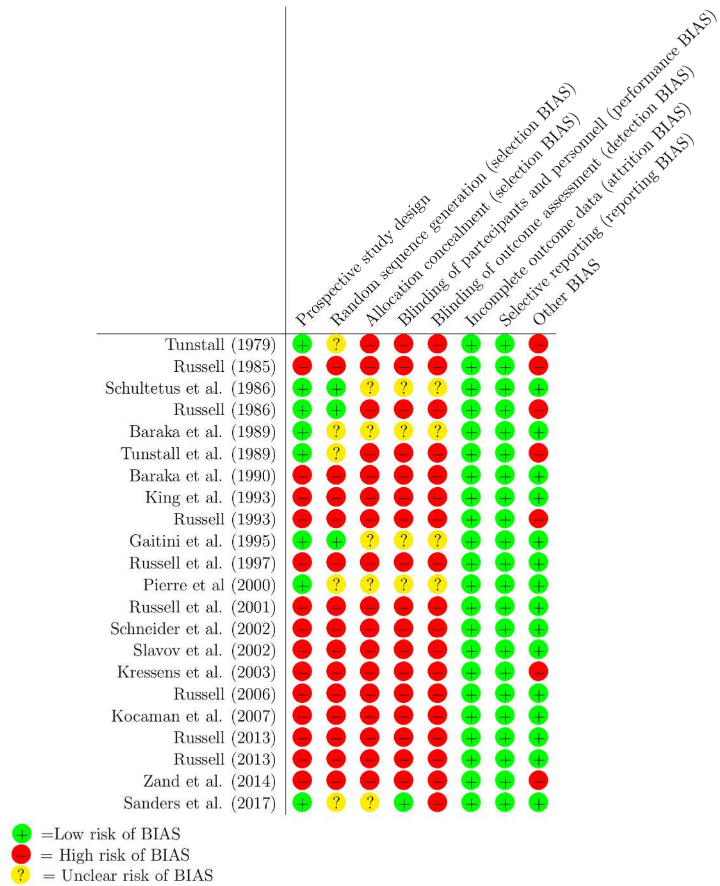

Risk of bias summary of included studies. ‼ ┼ Green circle, low risk; yellow circle, medium risk; red circle, high risk; (/), unable to determine.‼ ┼

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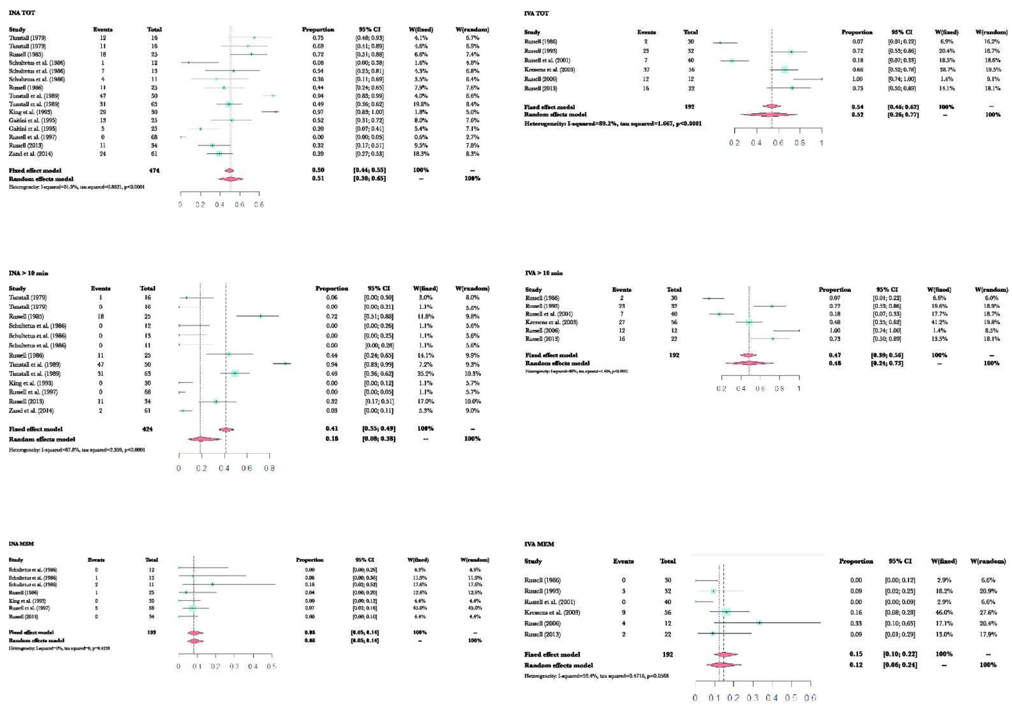

Forest plots of the meta-analysis of single proportions of patients with an IFT-positive response, comparing inhalational versus intravenous anaesthesia.
INA, sudies evaluating IFT responses during induction and mainthenance with inhalational anaesthesia;
IVA, sudies evaluating IFT responses during induction and mainthenance with intravenous anaesthesia;
INA > 10 min, sudies evaluating IFT responses during mainthenance with inhalational anaesthesia;
IVA > 10 min, sudies evaluating IFT responses during mainthenance with intravenous anaesthesia;
INA MEM, sudies evaluating explicit recall after mainthenance with inhalational anaesthesia;
IVA MEM, sudies evaluating explicit recall after mainthenance with intravenous anaesthesia.

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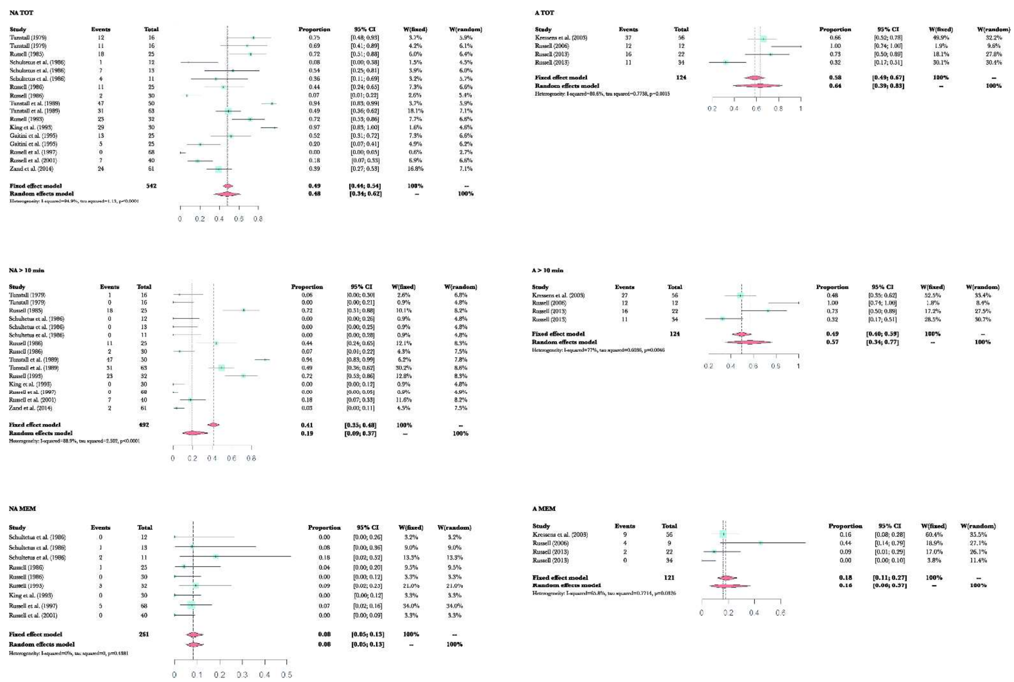

Forest plots of the meta-analysis of single proportions of patients with an IFT-positive response, comparing non-Anaesthesia Brain Monitor (ABM)-guided versus ABM-guided anaesthesia. NA, sudies evaluating IFT responses during induction and mainthenance with Non-ABM-guided anaesthesia;
A, sudies evaluating IFT responses during induction and mainthenance with ABM-guided anaesthesia;
NA > 10 min, sudies evaluating IFT responses during mainthenance with Non-ABM-guided anaesthesia;
A > 10 min, sudies evaluating IFT responses during mainthenance with ABM-guided anaesthesia;
NA MEM, sudies evaluating explicit recall after mainthenance with Non-ABM-guided anaesthesia;
A MEM, sudies evaluating explicit recall after mainthenance with ABM-guided anaesthesia.

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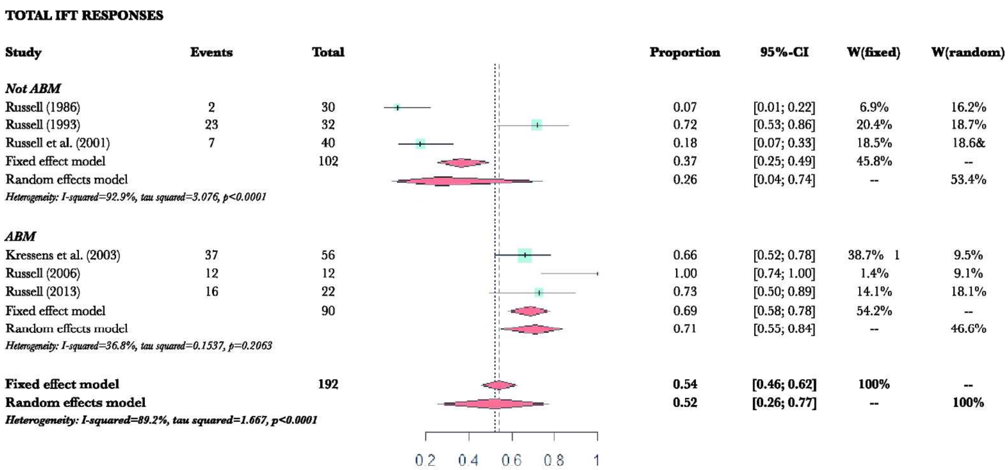

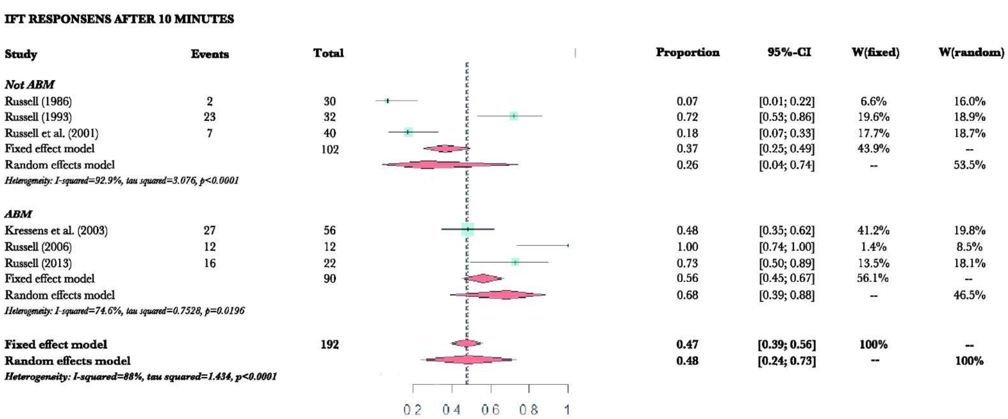

Forest plots of the meta-analysis of single proportions of patients undergoing intravenous anaesthesia with an IFT-positive response, comparing non-Anaeshtesia Brain Monitor (ABM)-guided versus ABM-guided anaesthesia.

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