BJA

British Journal of Anaesthesia, 121 (1): 198–209 (2018)

doi: 10.1016/j.bja.2018.02.019
Advance Access Publication Date: 27 March 2018
Review Article

REVIEW ARTICLES

Isolated forearm technique: a meta-analysis of connected consciousness during different general anaesthesia regimens

F. Linassi[1,*], P. Zanatta[2], P. Tellaroli[3], C. Ori[1] and M. Carron[1]

[1]Department of Medicine, Anaesthesiology and Intensive Care, University of Padova, Padova, Italy, [2]Department of Anaesthesia and Intensive Care, Integrated University Hospital of Verona, Verona, Italy and [3]Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy

*Corresponding author. E-mail: federico.linassi@studenti.unipd.it

This article is accompanied by an editorial: Can use of frontal EEG monitoring increase intraoperative connected consciousness? by Sanders et al., *Br J Anesth* 2018:121:191–193, doi: 10.1016/j.bja.2018.03.019.

Abstract

Background: General anaesthesia should prevent patients from experiencing surgery, defined as connected consciousness. The isolated forearm technique (IFT) is the current 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. Proportions of IFT-positive patients 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-positive patients 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-positive patients 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, but 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-positive patients 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 but 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-positive patients decreased significantly with increasing age and premedication use. Of the 34 anaesthesia regimens, 16 were inadequate. Studies had low methodological quality (only seven randomised controlled trials) and significant heterogeneity.

Conclusions: Standard general anaesthesia regimens might not prevent connected consciousness. More accurate anaesthesia brain monitor methodology to reduce the likelihood of connected consciousness is desirable.

Keywords: consciousness monitors; surgical equipment; intraoperative awareness; intraoperative complications; intraoperative monitoring; surgical procedures

Editorial decision: February 19, 2018; **Accepted:** February 19, 2018

Editor's key points

- A systematic review and meta-analysis was performed of studies using the isolated forearm technique (IFT) to monitor connected consciousness during general anaesthesia.
- Although the studies had low methodological quality and significant heterogeneity, potentially important differences in anaesthesia techniques associated with positive IFT responses were observed.
- Anaesthesia brain monitor-guided anaesthesia appears less likely to prevent connected consciousness during maintenance of anaesthesia, particularly when intravenous anaesthesia is used.
- Young age and lack of premedication increased the likelihood of a positive IFT response during maintenance of anaesthesia.

One of the most important objectives of general 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 arterial 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 is recognised as the current gold standard for consciousness monitoring in the presence of neuromuscular blocking agents.[2]

BIS monitoring is a quantitative method based on the bispectral processing of the spontaneous cortical activity of the monolateral frontal cortex, which determines the harmonic and phase relations amongst various 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 block.[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 anaesthetised 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 general 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 (i.v. or inhalation) and the use or non-use of ABM during the induction of anaesthesia and surgery. We also performed a regression meta-analysis to identify the factors associated with a positive IFT test or explicit recall.

Methods

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) 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 2017. No language restrictions were applied for the searches, but only those studies written in English were selected for inclusion in this systematic review. The date of the last search was June 30, 2017.

Two authors (F.L. and P.Z.) independently identified titles and abstracts of potentially eligible studies. The full-text versions of these studies were then reviewed by F.L. and P.Z. 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 (M.C.).

Eligibility and inclusion

Studies were included if they involved patients only ≥18 yr 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 positive (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.

End-points

We considered four main end-points: the number of IFT-positive patients ('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 min 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 the 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, and reflex movements occurred that were not associated with any stimulus.

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 (P.Z. and M.C.), who were blinded to the IFT results, independently categorised 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 (C.O.), who was likewise unaware of the IFT results.

Assessment of risk of bias

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

Statistical analysis

To compare the anaesthesia techniques, the patients were assigned to groups according to their anaesthesia regimen: inhalation anaesthesia for maintenance phase, i.v. 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-effect models. The Mantel–Haenszel method was used to calculate the fixed-effect 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-effect model was computed with inverse-variance weighting using the DerSimonian–Laird method to account for heterogeneity. The heterogeneity across studies was tested using 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 the subgroup analysis, we compared the proportion of IFT positives with non-ABM-guided *vs* ABM-guided anaesthesia amongst patients receiving just i.v. anaesthesia. During meta-regression, we examined the effects of depth of anaesthesia (light or adequate), premedication (yes or no), use of inhalation anaesthetics during induction, patient age, and patient weight on the presence of an IFT-positive response or explicit recall.

We also conducted a sensitivity analysis (using random-effect models) of only randomised controlled trials (RCTs). Computations were performed using the R (version 3.3.1 for Windows) package meta (Schwarzer G., Institute of Medical Biometry and Medical Informatics, University Medical Center, Freiburg, Germany).

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 Fig. 1. The characteristics of the included studies are reported in Table 1. The risk-of-bias summary of the included studies is shown in Fig. 2. As shown, the overall quality was low, as many trials exhibited a high risk of bias. Only seven 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 the 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) yr and 72.9 (95% CI: 68.8–77.0) kg. In two studies[21,26] (including five anaesthesia regimens), anaesthesia was induced with i.v. and inhalation drugs, whereas in the other 20 included studies, only i.v. 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: i.v. *vs* i.v. and inhalation drugs, usage *vs* non-usage of premedication, and usage *vs* 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 ($P = 0.0682$).

Inhalation *vs* i.v. anaesthesia during the induction and maintenance phases

We compared a total of 15 inhalation anaesthesia regimens[9,14–22] to six i.v. 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

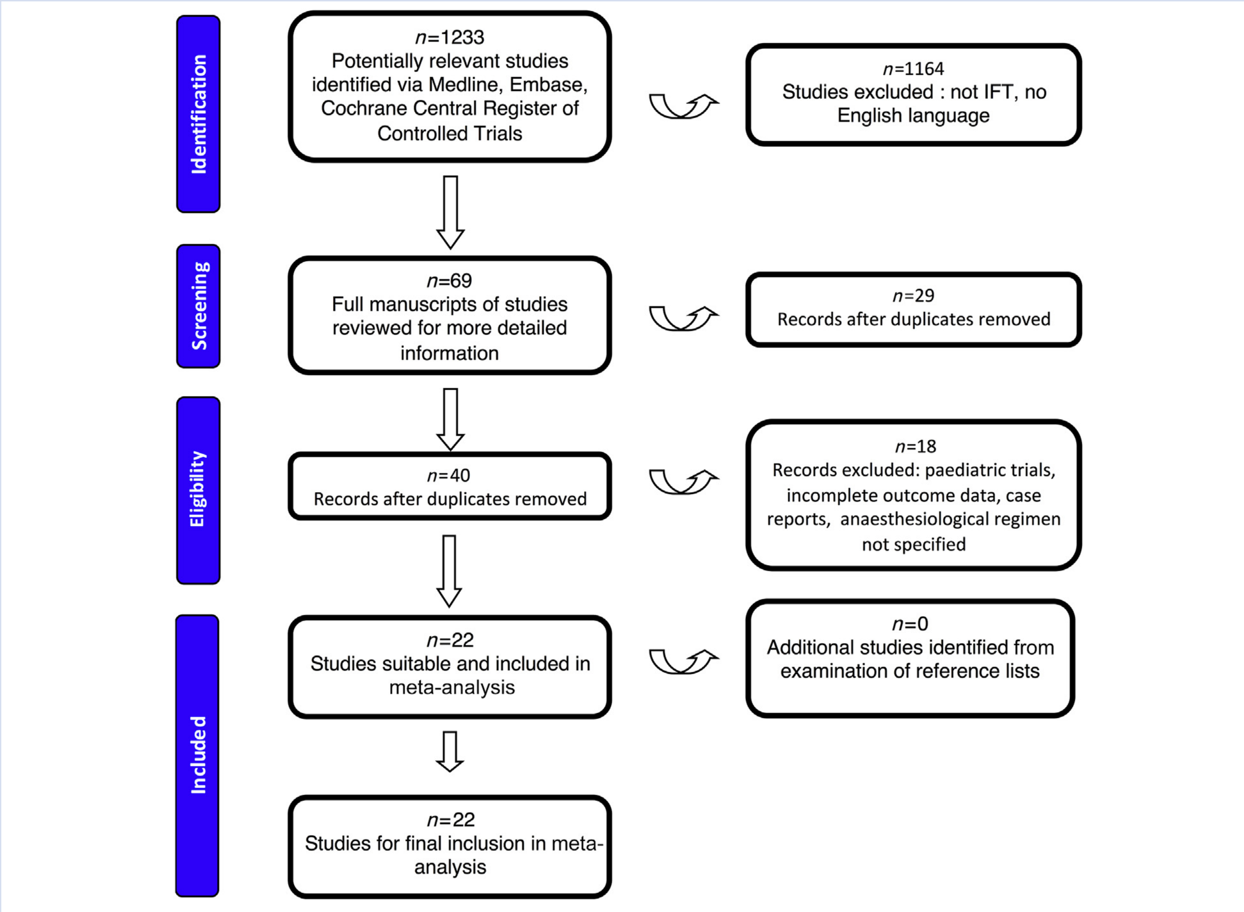

Fig 1. PRISMA flow diagram of the study selection process. IFT, isolated forearm technique; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

in three of the six i.v. regimens.[7,8,10] Inhalation anaesthesia was received by 474 patients; their mean age and weight were 30.9 (95% CI: 21.9–39.9) yr and 71.1 (95% CI: 64.9–77.3) kg. I.V. anaesthesia was received by 192 patients; their mean age and weight were 43.7 (95% CI: 36.3–51.1) yr and 70.4 (95% CI: 59.2–81.6) kg.

Of the 474 patients who received inhalation anaesthesia, 224 (47.3%; 95% CI: 42.8–51.6) had a positive IFT response at any time during anaesthesia, and amongst the 192 who received i.v. 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 inhalation anaesthesia and 87 of the 192 patients (45.3%; 95% CI: 38.4–52.3) who received i.v. anaesthesia. Furthermore, explicit recall was reported by nine of the 193 patients (4.7%; 95% CI: 2.4–8.6) who received inhalation anaesthesia and 18 of the 192 patients (9.4%; 95% CI: 6–14.3) who received i.v. anaesthesia.

Comparing the meta-analysis proportions of IFT-positive patients at any time, there were no significant differences between anaesthesia techniques: inhalation *vs* i.v. anaesthesia, 0.51 (95% CI: 0.38–0.65; $I^2 = 81.9\%$; $P < 0.0001$) *vs* 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 inhalation anaesthesia than during i.v. anaesthesia: 0.18 (95% CI: 0.08–0.38; $I^2 = 87.8\%$; $P < 0.0001$) *vs* 0.48 (95% CI: 0.24–0.73; $I^2 = 88\%$; $P < 0.0001$), respectively. Amongst the seven studies that evaluated explicit recall, the incidence of explicit recall was lower for inhalation anaesthesia than for i.v. anaesthesia: 0.08 (95% CI: 0.05–0.14; $I^2 = 0\%$; $P = 0.4253$) *vs* 0.12 (95% CI: 0.06–0.24; $I^2 = 53.4\%$; $P = 0.0568$).

High heterogeneity was found between the inhalation and i.v. anaesthesia groups of regimens. The detailed results of comparisons between inhalation and i.v. anaesthesia, regarding the proportions of patients with an IFT-positive response at any time and during anaesthesia maintenance, and the rates of explicit recall are reported in Fig. 3 (which includes the results of both the fixed- and random-effect models, and the heterogeneity analyses).

ABM-guided *vs* non-ABM-guided anaesthesia during the induction and maintenance phases

We analysed four ABM-guided anaesthesia[7–10] and 17 non-ABM-guided anaesthesia regimens.[14–24] These regimens

Table 1 Included studies and related anaesthetic regimens. ABM, anaesthesia brain monitor; ANA, anaesthesia; BIS, bispectral index; CS, Caesarean section; GS, general surgery; IA, inhalation anaesthesia; i.v., intravenous anaesthesia; IFT, isolated forearm technique; MGS, major gynaecological surgery; nd, not determined

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[14] (1979)	CS	Induction: i.v. Maintenance: IA	No	Yes	No	16	12	1	nd
Tunstall[14] (1979)	CS	Induction: i.v. Maintenance: IA	No	No	No	16	11	0	nd
Russell[19] (1985)	MGS	Induction: i.v. Maintenance: IA	Yes	No	No	25	18	18	nd
Schultetus and colleagues[15] (1986)	CS	Induction: i.v. Maintenance: IA	No	Yes	No	12	1	0	0
Schultetus and colleagues[15] (1986)	CS	Induction: i.v. Maintenance: IA	No	No	No	13	7	0	1
Schultetus and colleagues[15] (1986)	CS	Induction: i.v. Maintenance: IA	No	Yes	No	11	4	0	2
Russell[16] (1986)	MGS	Induction: i.v. Maintenance: IA	Yes	No	No	25	11	11	1
Russell[16] (1986)	MGS	Induction: i.v. Maintenance: i.v.	Yes	Yes	No	30	2	2	0
Baraka and colleagues[26] (1989)	CS	Induction: i.v.+IA	No	No	No	10	6	nd	1
Baraka and colleagues[26] (1989)	CS	Induction: i.v.+IA	No	No	No	10	8	nd	1
Baraka and colleagues[26] (1989)	CS	Induction: i.v.+IA	No	Yes	No	10	1	nd	0
Baraka and colleagues[26] (1989)	CS	Induction: i.v.+IA	No	Yes	No	10	3	nd	0
Baraka and colleagues[26] (1989)	CS	Induction: i.v.	No	Yes	No	10	0	nd	0
Baraka and colleagues[27] (1990)	CS	Induction: i.v.	No	Yes	No	13	0	nd	nd
Tunstall and Sheikh[17] (1989)	CS	Induction: i.v. Maintenance: IA	No	No	No	63	31	31	nd
Tunstall and Sheikh[17] (1989)	CS	Induction: i.v. Maintenance: IA	No	No	No	50	47	47	nd
King and colleagues[20] (1993)	CS	Induction: i.v. Maintenance: IA	No	Yes	No	30	29	0	0
Russell[23] (1993)	MGS	Induction: i.v. Maintenance: i.v.	Yes	Yes	No	32	23	23	3
Gaitini and colleagues[18] (1995)	CS	Induction: i.v. Maintenance: IA	No	No	No	25	13	nd	nd
Gaitini and colleagues[18] (1995)	CS	Induction: i.v. Maintenance: IA	No	Yes	No	25	5	nd	nd
Russell and Wang[21] (1997)	MGS	Induction: i.v.+IA Maintenance: IA	Yes	No	No	68	0	0	5
St Pierre and colleagues[28] (2000)	GS	Induction: i.v.	Yes	Yes	No	10	8	nd	1
St Pierre and colleagues[28] (2000)	GS	Induction: i.v.	Yes	Yes	No	10	7	nd	0
St Pierre and colleagues[28] (2000)	GS	Induction: i.v.	Yes	Yes	No	10	2	nd	0
Russell and Wang[24] (2001)	MGS	Induction: i.v. Maintenance: i.v.	Yes	Yes	No	40	7	7	0
Schneider and colleagues[29] (2002)	GS	Induction: i.v.	Yes	No	Yes BIS (50–60)	20	8	nd	0
Slavov and colleagues[30] (2002)	GS	Induction: i.v.	No	No	No	41	10	nd	nd
Kressens (2003)	GS	Induction: i.v. Maintenance: i.v.	No	Yes	Yes BIS (60–70)	56	37	27	9
Russell[8] (2006)	MGS	Induction: i.v. Maintenance: i.v.	No	No	Yes Narcotrend (C0)	12	12	12	4
Kocaman and colleagues[25] (2007)	MGS	Induction: i.v.	Yes	No	Yes BIS (40–60)	51	7	nd	nd

Continued

Table 1 Continued

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)
Russell[9] (2013)	MGS	Induction: i.v. Maintenance: IA	No	No	Yes BIS (55–60)	34	11	11	0
Russell[10] (2013)	MGS	Induction: i.v. Maintenance: i.v.	No	No	Yes BIS (55–60)	22	16	16	2
Zand and colleagues[22] (2014)	CS	Induction: i.v. Maintenance: IA	No	No	No	61	24	2	nd
Sanders and colleagues[31] (2017)	GS	Induction: i.v.	Yes/no	No	Yes/no If used: BIS (40–60)	260	12	nd	nd

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) yr 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) yr 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 amongst 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.

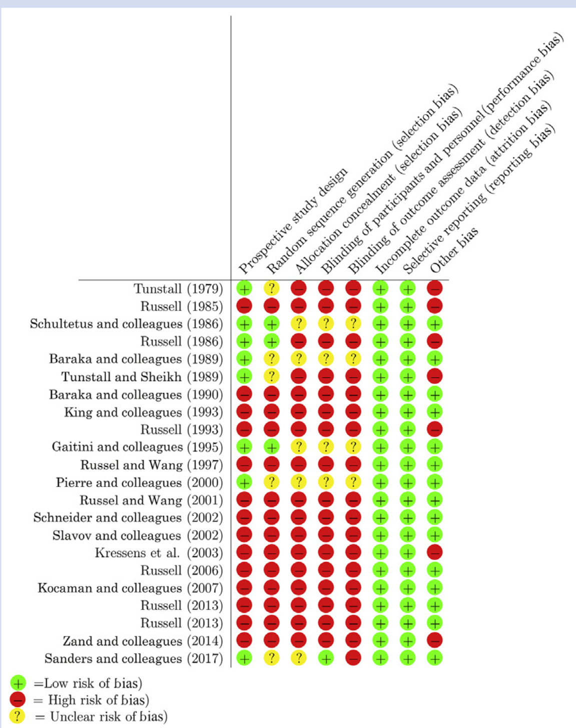

Fig 2. Risk-of-bias summary of included studies. Green circle, low risk; yellow circle, medium risk; red circle, high risk; (/), unable to determine.

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%; $P < 0.0001$) *vs* 0.57 (95% CI: 0.34–0.77; I^2 = 77%; $P < 0.005$), respectively. Amongst 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%; $P < 0.05$) *vs* 0.16 (95% CI: 0.06–0.37; I^2 = 65.8%; $P < 0.05$).

High heterogeneity was found amongst both the ABM-guided and non-ABM-guided groups of regimens. The 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, and the rates of explicit recall are reported in Fig. 4 (which includes the results of both the fixed- and random-effect models, and heterogeneity analyses).

To explore the high heterogeneity, an additional subgroup analysis of the i.v. anaesthesia regimens was performed, subdividing the regimens based on whether ABM was or was not used. Non-ABM-guided i.v. 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 i.v. 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 i.v. 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 i.v.

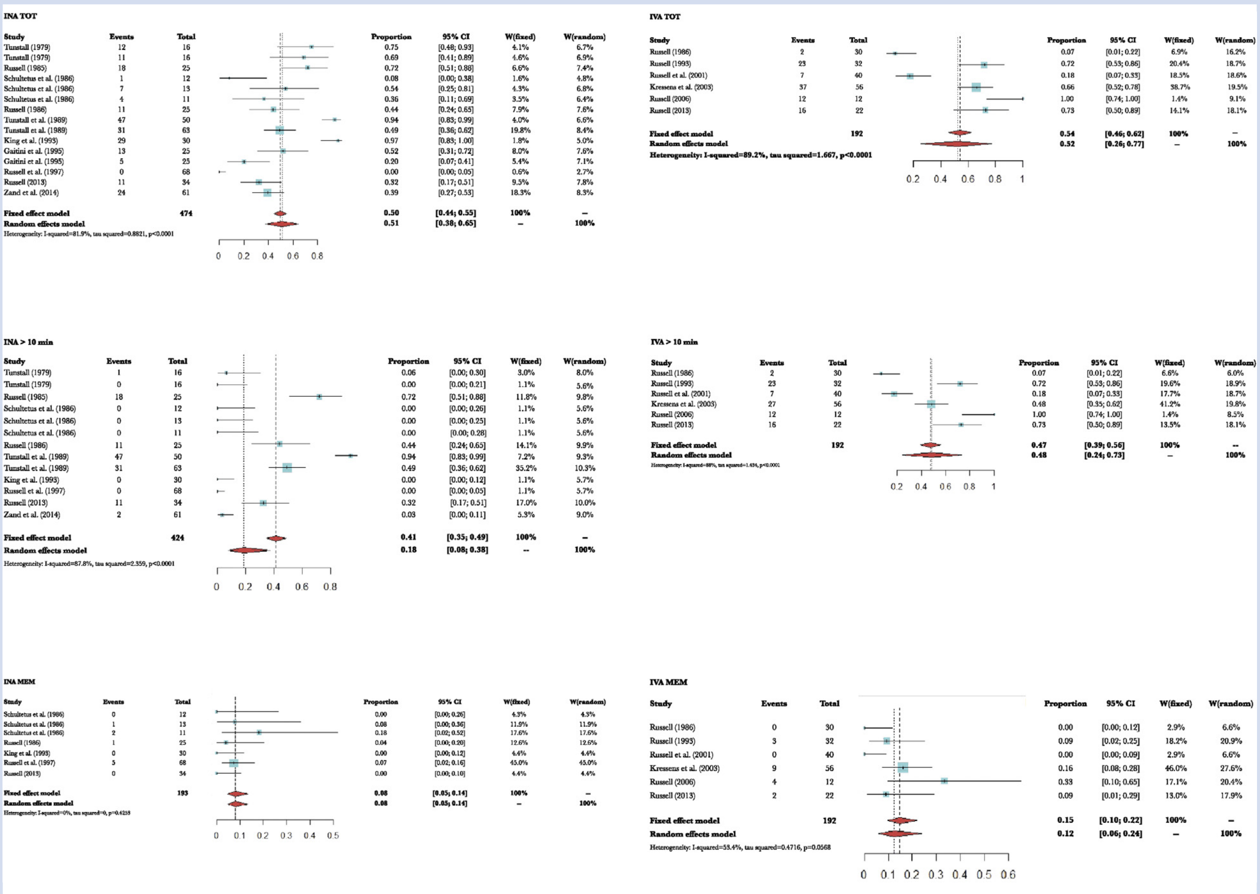

Fig 3. Forest plots of the meta-analysis of single proportions of patients with an IFT-positive response, comparing inhalation *vs* i.v. anaesthesia. CI, confidence interval; IFT, isolated forearm technique; INA, studies evaluating IFT responses during induction and maintenance with inhalation anaesthesia; INA MEM, studies evaluating explicit recall after maintenance with inhalation anaesthesia; INA >10 min, studies evaluating IFT responses during maintenance with inhalation anaesthesia; IVA, studies evaluating IFT responses during induction and maintenance with i.v. anaesthesia; IVA MEM, studies evaluating explicit recall after maintenance with i.v. anaesthesia; IVA >10 min, studies evaluating IFT responses during maintenance with i.v. anaesthesia.

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 amongst these studies, and this analysis did not reach significance (Fig. 5).

Sensitivity analysis of RCTs

A sensitivity analysis using random-effect models considering just RCTs[14–18,26,28] was performed, where pooled estimates are calculated omitting one study at a time. This analysis did not reveal any statistically significant differences, either amongst 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 thirty-four anaesthesia regimens appeared to be conducted using light anaesthesia (Table 1). There was a trend towards light anaesthesia increasing the proportion of patients with a positive IFT response, but the association did not reach statistical significance.

Discussion

Our meta-analysis results suggest that there were no differences amongst the four different anaesthesia regimens in the 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 amongst 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 i.v.–inhalation anaesthesia technique was used for induction, followed by non-ABM-guided inhalation anaesthesia.

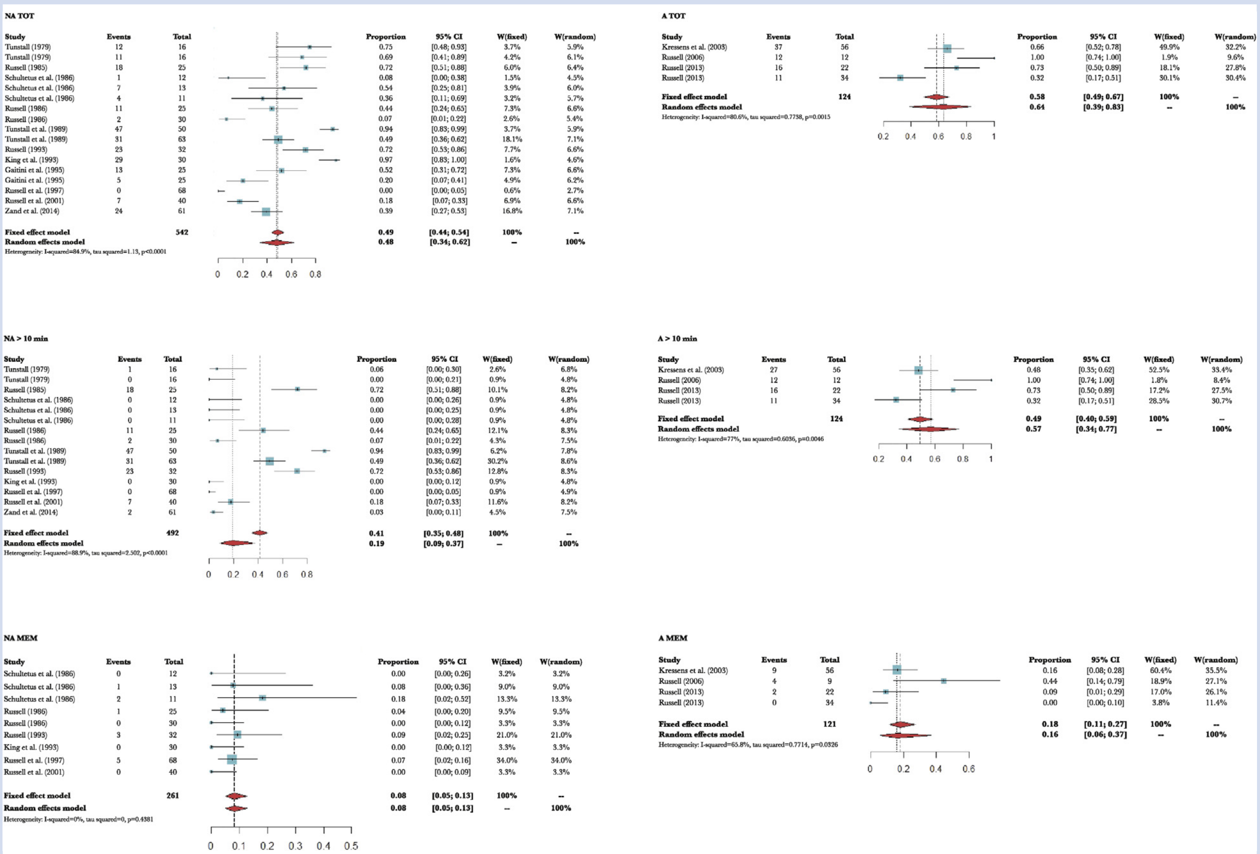

Fig 4. Forest plots of the meta-analysis of single proportions of patients with an IFT-positive response, comparing non-ABM-guided *vs* ABM-guided anaesthesia. A, studies evaluating IFT responses during induction and maintenance with ABM-guided anaesthesia; ABM, anaesthesia brain monitor; A MEM, studies evaluating explicit recall after maintenance with ABM-guided anaesthesia; A >10 min, studies evaluating IFT responses during maintenance with ABM-guided anaesthesia; CI, confidence interval; IFT, isolated forearm technique; NA, studies evaluating IFT responses during induction and maintenance with non-ABM-guided anaesthesia; NA MEM, studies evaluating explicit recall after maintenance with non-ABM-guided anaesthesia; NA >10 min, studies evaluating IFT responses during maintenance with non-ABM-guided anaesthesia.

Adequate anaesthesia for induction can be useful to avoid connected consciousness during the first 10 min after induction. Reducing the likelihood of a positive IFT response after intubation by early administration of a volatile anaesthetic drug, whilst waiting for a neuromuscular blocking agent to take effect, has also been confirmed by a recent prospective study.[31]

In contrast, we found important differences amongst anaesthesia regimens in preventing an IFT-positive response during the maintenance phase of anaesthesia (from 10 min after induction to the end of surgery). Inhalation anaesthesia was associated with a lower frequency of IFT positives than i.v. 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 [standard deviation (SD): 3],[7] 60 [inter-quartile range (IQR): 50–67],[9] and 61 (IQR: 52–67).[10] These values are at the upper limit of the 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 (0.2–0.9) minimum alveolar concentration (MAC)] and propofol TCI (2.0 μg kg^{-1} min^{-1}) adopted for maintenance are 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 i.v. 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 and colleagues,[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 block, with transient decreases to values of 44, thereby showing that patients can be awake at low BIS values.

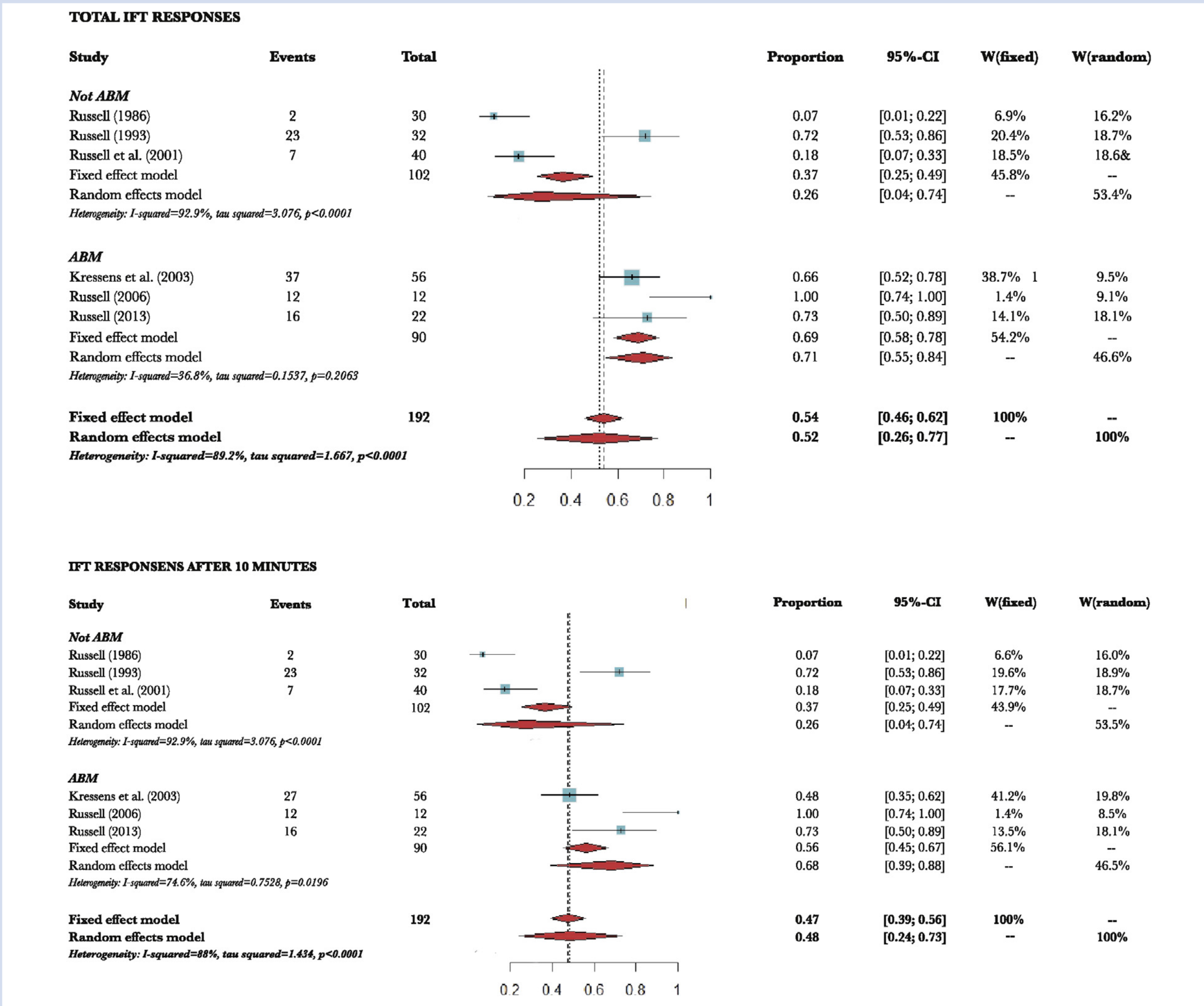

Fig 5. Forest plots of the meta-analysis of single proportions of patients undergoing i.v. anaesthesia with an IFT-positive response, comparing non-ABM-guided *vs* ABM-guided anaesthesia. ABM, anaesthesia brain monitor; CI, confidence interval; IFT, isolated forearm technique.

Therefore, MAC-guided inhalation anaesthesia seems to be more effective than ABM-guided inhalation anaesthesia and ABM-guided i.v. 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 and 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 or more effective ABM approaches.

Even if our subgroup analysis did not reveal any statistical difference, the proportion of IFT responses for non-ABM-guided i.v. anaesthesia was lower [32 of 102 patients; meta-analysis proportion =0.26 (95% CI: 0.26–0.77); I^2 = 89.2%; $P < 0.0001$] than for ABM-guided i.v. 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 i.v. 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 i.v. anaesthesia [55 of 90 patients; meta-analysis proportion =0.68 (95% CI: 0.39–0.88); I^2 = 74.6%; $P < 0.05$] (Fig. 5). Therefore, if the meta-analysis proportion of IFT responses during inhalation anaesthesia maintenance [0.18 (95% CI: 0.08–0.38)] is compared with IFT responses during ABM-guided i.v. anaesthesia [0.68 (95% CI: 0.39–0.88)], the IFT responses increase during this last anaesthesia regimen, confirming that ABM-guided anaesthesia also increases the risk of connected consciousness during i.v. anaesthesia. However, given the small number of studies involved, more trials must be conducted to define the exact role of anaesthesia brain monitoring during i.v. 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.[31]

The influence of level of anaesthesia on outcome of patients undergoing general anaesthesia continues to be debated. 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] An inadequate anaesthesia might increase the risk of connected consciousness and, particularly, of implicit memory with adverse psychiatric sequelae, including symptoms of post-traumatic stress disorder.[38–42]

Intraoperative neurophysiological monitoring (i.e. EEG and somatosensory evoked potentials) has been successfully utilised to detect and monitor painful stimulation during surgery[43]; this can facilitate 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, and parietal) need to be monitored to abolish 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 amongst studies with regard to the conduct of anaesthesia, especially with respect to the types and doses of drugs used. However, this heterogeneity could 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 IFT responses amongst patients receiving i.v. anaesthesia, inhalation anaesthesia, ABM-guided anaesthesia, or non-ABM-guided anaesthesia. Instead, our results indicate that the use of premedication and patient age were important factors associated with the occurrence of a positive IFT response, which might have contributed to the heterogeneous results amongst studies. An important limitation is that only seven of the 22 included studies were RCTs,[14–18,26,28] thereby increasing the risk of bias. However, the sensitivity analysis of these studies did not reveal any statistical differences, either amongst proportions or heterogeneity. The overall quality of the included studies was low; in particular, the subgroup analyses have low statistical significance because of the high heterogeneity and small number of studies involved. Another limitation was related to the IFT technique itself: a movement response might not be detected in patients unable to squeeze the researcher's hand despite being able to hear the instructions to do so. Accordingly, false negatives can 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 standardised. A different monitoring technique, such as bilateral electromyography, might be considered, which would also have the advantage of not requiring a cuffed tourniquet.

The processes involved in general anaesthesia and how they apply to clinical process are still far from being well understood. Compared with non-ABM-guided anaesthesia, ABM-guided anaesthesia seems less likely to prevent connected consciousness during the maintenance phase of anaesthesia, particularly when i.v. 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

Study concept: F.L., P.Z., C.O., M.C.
Data collection: F.L., P.Z., P.T.
Data analysis: all authors.
Statistical analysis: P.T.
Discussion of results: C.O., M.C.
Manuscript drafting and final manuscript revision: F.L., P.Z.
Critical revision of final manuscript: P.T., C.O., M.C.
Final version approval and agreed to be accountable for all aspects of the work: all authors.

Acknowledgements

The authors would like to thank S. Mocellin of the Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy for his contribution in reviewing the manuscript, and M. Girolimetto for her contribution in editing the figures.

References

1. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness ≠ unconsciousness. *Anesthesiology* 2012; **116**: 946–59
2. Jessop J, Jones JG. Conscious awareness during anesthesia—what are we attempting to monitor? *Br J Anaesth* 1991; **66**: 635–7
3. Kleiner B, Huber PJ, Dumermuth G. Analysis of the interrelations between frequency of the EEG by means of the bispectrum. *Electroencephalogr Clin Neurophysiol* 1969; **27**: 693–4
4. Barnett TP, Johnson LC, Naitoh P, Hicks N, Nute C. Bispectrum analysis of electroencephalogram signals during waking and sleeping. *Science* 1971; **172**: 401–2
5. Sebel PS, Lang E, Rampil IJ, et al. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg* 1997; **4**: 891–9
6. Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth Analg* 1997; **1**: 185–9

7. Kressens C, Klein J, Bonke B. Awareness: monitoring versus remembering what happened. *Anesthesiology* 2003; **99**: 570–5
8. Russell IF. The Narcotrend 'depth of anaesthesia' monitor cannot reliably detect consciousness during general anaesthesia: an investigation using the isolated forearm technique. *Br J Anaesth* 2006; **96**: 346–52
9. Russell IF. The ability of bispectral index to detect intra-operative wakefulness during isoflurane/air anaesthesia, compared with the isolated forearm technique. *Anaesthesia* 2013; **68**: 1010–20
10. Russell IF. The ability of bispectral index to detect intra-operative wakefulness during total intravenous anaesthesia compared with the isolated forearm technique. *Anaesthesia* 2013; **68**: 502–11
11. Schuller PJ, Newell S, Strickland PA, Barry JJ. Response of bispectral index to neuromuscular block in awake volunteers. *Br J Anaesth* 2015; **115**: i95–103
12. Tunstall ME. Detecting wakefulness during general anaesthesia for caesarean section. *Br Med J* 1977; **1**: 1321
13. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *Br Med J* 2011; **343**: d5928
14. Tunstall ME. The reduction of amnesic wakefulness during Caesarean section. *Anaesthesia* 1979; **34**: 316–9
15. Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during Cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined. *Anesth Analg* 1986; **65**: 723–8
16. Russell IF. Comparison of wakefulness with two anaesthetic regimens. *Br J Anaesth* 1986; **58**: 965–8
17. Tunstall ME, Sheikh A. Comparison of 1.5% enflurane with 1.25% isoflurane in oxygen for Caesarean section: avoidance of awareness without nitrous oxide. *Br J Anaesth* 1989; **62**: 138–43
18. Gaitini L, Vaida S, Collins G, Somri M, Sabo E. Awareness detection during Caesarean section under general anaesthesia using EEG spectrum analysis. *Can J Anaesth* 1995; **42**: 377–81
19. Russell IF. Balanced anesthesia: does it anesthetize? *Anesth Analg* 1985; **64**: 941–2
20. King H, Ashley S, Brathwaite D, Decayette J, Wooten DJ. Adequacy of general anesthesia for Cesarean section. *Anesth Analg* 1993; **77**: 84–8
21. Russell IF, Wang M. Absence of memory for intraoperative information during surgery under adequate general anaesthesia. *Br J Anaesth* 1997; **78**: 3–9
22. Zand F, Hadavi SM, Chohedri A, Sabetian P. Survey on the adequacy of depth of anaesthesia with bispectral index and isolated forearm technique in elective Caesarean section under general anaesthesia with sevoflurane. *Br J Anaesth* 2014; **112**: 871–8
23. Russell IF. Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique. *Br J Anaesth* 1993; **70**: 42–6
24. Russell IF, Wang M. Absence of memory for intra-operative information during surgery with total intravenous anaesthesia. *Br J Anaesth* 2001; **86**: 196–202
25. Kocaman Akbay B, Demiraran Y, Yalcin Sezen G, Akcali G, Somunkiran A. Use of the bispectral index to predict a positive awareness reaction to laryngeal mask airway-Fastrach insertion and intubation. *Acta Anaesthesiol Scand* 2007; **51**: 1368–72
26. Baraka A, Louis F, Noueihid R, Diab M, Dabbous A, Sibai A. Awareness following different techniques of general anaesthesia for caesarean section. *Br J Anaesth* 1989; **62**: 645–8
27. Baraka A, Louis F, Dalleh R. Maternal awareness and neonatal outcome after ketamine induction of anaesthesia for Caesarean section. *Can J Anaesth* 1990; **37**: 641–4
28. St Pierre M, Landsleitner B, Schwilden H, Schuettler J. Awareness during laryngoscopy and intubation: quantitating incidence following induction of balanced anaesthesia with etomidate and cisatracurium as detected with the isolated forearm technique. *J Clin Anesth* 2000; **12**: 104–8
29. Schneider G, Wagner K, Reeker W, Hanel F, Werner C, Kochs E. Bispectral index (BIS) may not predict awareness reaction to intubation in surgical patients. *J Neurosurg Anesthesiol* 2002; **14**: 7–11
30. Slavov V, Motamed C, Massou N, Rebufat Y, Duvaldestin P. Systolic blood pressure, not BIS, is associated with movement during laryngoscopy and intubation. *Can J Anaesth* 2002; **49**: 918–21
31. Sanders RD, Gaskell A, Raz A, et al. Incidence of connected consciousness after tracheal intubation. *Anesthesiology* 2017; **126**: 214–22
32. Mashour GA, Shanks A, Tremper KK, et al. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. *Anesthesiology* 2012; **117**: 717–25
33. Whitlock EL, Villafranca AJ, Lin N, et al. Relationship between bispectral index values and volatile anesthetic concentrations during the maintenance phase of anesthesia in the B-Unaware trial. *Anesthesiology* 2011; **115**: 1209–18
34. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg* 2005; **100**: 4–10
35. Kertai MD, Pal N, Palanca BJ, et al. Association of perioperative risk factors and cumulative duration of low bispectral index with intermediate-term mortality after cardiac surgery in the B-Unaware trial. *Anesthesiology* 2010; **112**: 1116–27
36. Leslie K, Myles PS, Forbes A, Chan MT. The effect of bispectral index monitoring on long-term survival in the B-aware trial. *Anesth Analg* 2010; **110**: 816–22
37. Sessler DI, Sigl JC, Kelley SD, et al. Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. *Anesthesiology* 2012; **116**: 1195–203
38. Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anesthesia: a prospective case study. *Lancet* 2000; **355**: 707–11
39. Osterman JE, Hopper J, Heran WJ, Keane TM, van der Kolk BA. Awareness under anesthesia and the development of posttraumatic stress disorder. *Gen Hosp Psychiatry* 2001; **23**: 198–204
40. Moerman N, Bonke B, Oosting J. Awareness and recall during general anesthesia: facts and feelings. *Anesthesiology* 1993; **79**: 454–64

41. Wang M. Implicit memory, anaesthesia and sedation. In: Davies GW, Wright DB, editors. *Current issues in applied memory research*. London: Psychology Press; 2010. p. 165–84
42. Wang M, Deeprose C, Andrade J, Russell IF. Psychology in the operating theatre. *Psychologist* 2013; **26**: 498–501
43. Zanatta P, Messerotti Benvenuti S, Bosco E, et al. Intra-operative neurophysiological monitoring of the afferent pain pathway in cardiac surgery patients. *Clin Neurophysiol* 2011; **122**: 2093–9
44. Gaskell LA, Hight DF, Winders J, et al. Frontal alpha-delta EEG does not preclude volitional response during anaesthesia: prospective cohort study of the isolated forearm technique. *Br J Anaesth* 2017; **119**: 3–9

Handling editor: H.C. Hemmings Jr