Clinical Investigation

General anaesthesia does not contribute to long-term post-operative cognitive dysfunction in adults: A meta-analysis

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ABSTRACT

Context: The contribution of anaesthesia itself to post-operative cognitive dysfunction (POCD) or the potential protective effect of one specific type of anaesthesia on the occurrence of POCD is unclear. **Aims:** This is a meta-analysis evaluating the effects of the anaesthetic technique (regional *vs.* general anaesthesia) on POCD of patients undergoing non-cardiac surgery. **Settings and Design:** Meta-analysis performed in a University affiliated hospital. **Methods:** A search for randomized controlled trials (RCT) comparing regional anaesthesia to general anaesthesia for surgery was done in PUBMED, MEDLINE, EMBASE, EBM Reviews-Cochrane Central Register of Controlled Trials, PsychINFO and Current Contents/all editions in 2009. **Statistical Analysis:** Data were analyzed with comprehensive Meta-analysis Version 2.2.044. **Results:** Twenty-six RCTs including 2365 patients: 1169 for regional anaesthesia and 1196 for general anaesthesia were retained. The standardized difference in means for the tests included in the 26 RCTs was -0.08 (95% confidence interval: –0.17–0.01; *P* value 0.094; I-squared = 0.00%). The assessor was blinded to the anaesthetic technique for 12 of the RCTs including only 798 patients: 393 for regional anaesthesia and 405 for general anaesthesia. The standardized difference in means for these 12 studies is 0.05 (–0.10–0.20; *P*=0.51; I-squared = 0.00%). **Conclusions:** The present meta-analysis does not support the concerns that a single exposure to general anaesthesia in an adult would significantly contribute to permanent POCD after non-cardiac surgery.

Key words: Meta-analysis, post-operative cognitive dysfunction, regional anaesthesia

INTRODUCTION

The incidence of post-operative cognitive dysfunction (POCD), at 3 months after a non-cardiac surgery is estimated at 6.6% for a minor surgery and 9.9% for the major one.[1,2] The contribution of anaesthesia itself to POCD or the potential protective effect of one specific type of anaesthesia on the occurrence of POCD is unclear. Systematic reviews that examined the potential difference in incidence between general and regional anaesthesia have proceeded by vote counting, a technique where a non-significant *P* value is taken as equivalent to the absence of effect.[3,4] It does, however, make sense to sum up the effect of all studies on this topic by a meta-analysis even if the tests used are not the same across all studies, provided that they intended to address the same broad question.[5] The purpose of this study is to determine if there is a difference in POCD in patients operated for non-cardiac surgery under general *vs.* regional anaesthesia.

METHODS

A search for randomized controlled trials (RCT) comparing regional anaesthesia to general anaesthesia for surgery was done in the American National Library of Medicine's PUBMED (limit to human, English or French, Clinical trial, letter, meta-analysis, RCT and Review) in August 2009 with the following keywords: 'postoperative' or 'surgery' and 'neurocogniti*' or 'cogniti*' or 'neuropsycholog*' or 'cerebr*' or 'neuro-behaviour' and 'regional anaesthesia' or 'spinal' or

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'epidural' or 'peripheral nerve block' or 'continuous peripheral nerve block' or "local anaesthetic'; and in MEDLINE 1950 to July 2009, 31; EMBASE 1980 to 2009 Week 32; EBM Reviews-Cochrane Central Register of Controlled Trials third Quarter 2009; PsychINFO 1806 to August week 1, 2009; and current contents/all editions 1993 week 27 to 2009 week 33 with equivalent search terms. The reference list of all articles retrieved and of review articles of the last 5 years were also checked.

Data were extracted from texts, Tables or Figures as required. When a study gave results for more than a test, results of all relevant tests at each selected time point were entered as different outcomes from the same study. When two different results were provided for the following periods: Pre-operative, day 0, day 1, days 2 to 7, day 8 to 1 month, 1 to 3 months or ≥3 months, the latest result available for each one of these periods was retained. Tests used were also classified as proposed by Newman *et al*.: A: Verbal and language skills; B: Memory and learning; C: Attention, concentration, and perception; D: Visual and spatial skills; E: Visuomotor and manual skills; F: Numerical, G: Executive functions, H: Composite measures when feasible and confusion.[3] Data were analyzed with Comprehensive Meta-analysis Version 2.2.044 (www.Meta-Analysis.com) and RevMan 5 (for the risk of biais assessment)(Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.).

RESULTS

The search retrieved 28 RCTs. Data could be extracted from 26 of them [Table 1]. Twenty-six studies included 2365 patients: 1169 for regional anaesthesia and 1196 for general anaesthesia of which 436 patients were submitted to some tests of Newmann's classification A; 1160 to class B tests, 991 to class C tests, 142 to class D tests, 352 to tests classified as B, C, or D, 399 to class E tests, 105 to class F tests, 105 to class G tests, 908 to class H tests while occurrence of confusion was identified for 833 patients. The risk of biais assessment is given in Figure 1. When all possible kinds of tests including confusion at all-time points were considered together there was no statistical difference between the two groups: standardized difference in means –0.08 (95% confidence interval: –0.17 to 0.01; *P* value 0.094) [Figure 2]. There was no significant heterogeneity across the studies (I-squared = 0.00%). There was no influence of the year of publication on the difference between the two techniques; *P* value of the slope 0.29 [Figure 3]. The Funnel plot shows that some small studies favouring general anaesthesia might be missing. A publication bias asessment with the trim and fill technique gave a standardized difference in means closer to zero (–0.03 [–0.12 to 0.06]) [Figure 4]. For 12 studies including 798 patients, 393 for regional anaesthesia and 405 for general anaesthesia, the assessor was blinded to the anaesthetic technique used.[7-9,12,13,15,16,19,22,26,28,29] The standardized difference in means for these 12 studies is 0.05 (–0.10 to 0.20; *P*=0.51; I-squared = 0.00%).

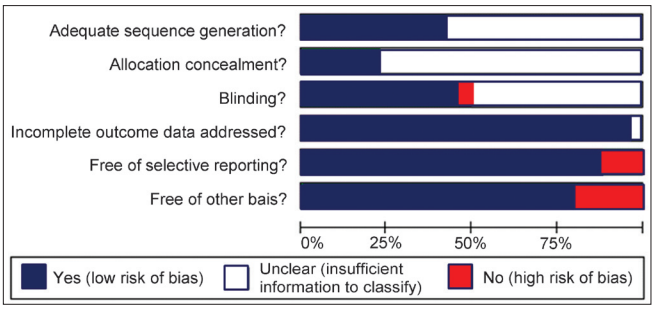

Figure 1: The bias risk assessment of the 26 included studies

DISCUSSION

This study does not support the concept that the drugs used to produce general anaesthesia would induce permanent brain damage after one single exposure in an adult. If this would be the case, one would expect to see a difference between general anaesthesia (use of inhalational agent with tracheal intubation and mechanical ventilation mainly) and regional anaesthesia with spontaneous breathing and sedation only. Therefore, concerns that general anaesthesia would be susceptible to significantly contribute to POCD are not supported by the evidence from RCTs. This study corroborates the conclusion of narrative reviews on this topic.[3,4]

The quality of the studies included in the present meta-analysis is far from being optimal; most of them suffering from various flaws making them susceptible to spurious conclusions at least when the information contained in the reports is considered [Figure 1]. However, when studies with an assessor blinded to the anaesthetic technique used were taken separately, it became even clearer that there is no difference between the two techniques (*P*=0.51). Moreover, even if the *P* value would have been less than 0.05 for the overall analysis instead of 0.09, the effect size would be too small to be clinically relevant. A difference of −0.08 in

Table 1: Characteristics of included studies

Study [References]	*N*	Age	Type of RA	Type of surgery	Surgery length (min)	Tests Newman' classification	Time					
							D0	D1	D 2-7	D 8-M1	M 1-3	≥ M3
Anwer HMF[6]	RA = 30 GA = 30	RA = 28 (26.8-30.0) GA = 27 (25.0-29.0)	CNB	Orthopedic and urologic	RA = 55 (45-80) GA = 50 (33.8-70)	A		x	x			
	RA = 30 GA = 30	RA = 61 (60-63.3) GA = 62 (61.0-64.3)	CNB	Orthopedic and urologic	RA = 57.5 (40-80) GA = 67.5 (35-91.3)	A		x	x			
Asbjorn J[7]	RA = 30 GA = 30	RA = 68.7 GA = 68.8	CNB	Transurethral prostatectomy	RA = 63±29.5 GA = 57±28.2	B			x	x		
Berggren D[8]	RA = 28 GA = 29	RA = 78±8 GA = 77±7	CNB	Femoral neck fracture	RA = 35±10 GA = 31±10	Confusion on OBS			x			
Bigler D[9]*	RA = 20 GA = 20	RA = 80.1±7.2 GA = 77.6±7.2	CNB	Femoral neck fracture	RA = 67±35.8 GA = 59±44.7	H			x			x
Campbell DN[10]	RA = 56 GA = 64	RA = 77.3±7.7 GA = 77.9 ±7.2	PNB	Cataract	RA = 35.8±12.0 GA = 43.9±15.9	B, E, confusion		x		x		x
Casati A[11]	RA = 15 GA = 15	RA = 84 (71-94) GA = 84 (67-88)	CNB	Hip fracture	RA = 80 (45-110) GA = 75 (50-100)	H		x	x			
Chung F[12]	RA = 20 GA = 24	RA = 73 (60-89) GA = 71.5 (60-93)	CNB	Urologic or Gynecologic	RA = 65±4.6 GA = 69±4.2	H, confusion	x	x	x			
Chung F[13]	RA = 22 GA = 22	RA = 72.2±6.1 GA = 71.8±6.1	CNB	Transurethral prostatectomy	RA = 68± 16 GA = 72.5±17.8	H, confusion	x	x	x		x	
Cook PT[14]	RA = 50 GA = 51	RA = 66.4 GA = 67.1	CNB	Lower limb vascular surgery	RA = 145.8 GA = 154.8	Confusion						
Forster A[15]	RA = 32 GA = 34	RA = 74±8 GA = 72±6	CNB	Orthopedic	RA = 185.2±66 GA = 201.7±55.2	H		x	x			
Ghoneim MM[16]	RA = 52 GA = 53	RA = 61.9±13.0 GA = 60.1±16.7	CNB	Hysterectomy, Prostatectomy, or Joint replacement		B, C, D, E, F, G			x			x
Haan J[17]	RA = 22 GA = 18	RA = 71.8±6.2 GA = 71.1±5	CNB	Transurethral prostatectomy	RA = 81.8±27.7 GA = 80.8±38.5	B, C, D, H			x			x
Hole A[18]*	RA = 29 GA = 31	RA = 69.9 (56-84) GA = 71.7 (61-82)	CNB	Total hip replacement	RA = 190±32.3 GA = 207±33.4	Confusion		x	x	x		
Jones MJT[19]	RA = 74 GA = 72	> 60 yrs	CNB	Hip or knee replacement	RA = 107±24 GA = 112±28	B, C, E, H						x
Mann RAM[20]	RA = 30 GA = 30	RA = 71±11.5 GA = 70.3±5.5	CNB	Lower limb amputation		H		x	x			
Maurette P[21]	RA = 18 GA = 15	RA = 81.2 ± 7.3 GA = 84.5 ± 6.8	CNB	Hip fracture	RA = 80.5±12.8 GA = 71.5±20.9	B, C			x			
Nielson WR[22]	RA = 25 GA = 39	RA = 68.0±6.0 GA = 70.1±6.2	CNB	Total knee replacement		A, B, C, H					x	
O'Dwyer P[23]	RA = 138 GA = 138	RA = 55±18 GA = 55±16	LA	Inguinal hernia		B, C, H	x	x	x			x
Papaioannou A[24]	RA = 23 GA = 24	>60 yrs	CNB	Orthopedic, urologic, gynecologic and vascular		H, confusion	x	x	x			
Racle JP[25]	RA = 35 GA = 35	RA = 81.9±0.9 GA = 82.3±1	CNB	Hip fracture	RA = 125±6 GA = 116±1	Confusion		x				
Raeder JC[26]†	RA = 31 GA = 28	RA = 24±6.3 GA = 23±4.8	PNB	Gynecologic	RA = 10.5±2.7 GA = 8.2±3.1	C	x					

Table 1: (*Continued*)

Study [References]	*N*	Age	Type of RA	Type of surgery	Surgery length (min)	Tests Newman' classification	Time					
							D0	D1	D 2-7	D 8-M1	M 1-3	≥ M3
Rasmussen LS[27]	RA = 165 GA = 175	RA = 71.1 (61-83.7) GA = 70.8 (61.3-84.1)	CNB	Orthopedic, urologic, gynecologic, vascular, gastrointestinal and others	RA = 105 (30-245) GA = 100 (30-222)	B, C, D			x			x
Riis J[28]‡	RA = 10 GA = 9	>60 yrs	CNB	Total hip replacement		B, C		x	x			
Somprakit P[29]§	RA = 30 GA = 30	RA = 37.9±13.4 GA = 36.5±12.8	CNB	Orthopedic, urologic and gynecologic	RA = 129.3±64.3 GA = 139.7±72.6	H			x	x		
	RA = 30 GA = 30	RA = 67.2±4.6 GA = 67.9±5.7	CNB	Orthopedic, urologic and gynecologic	RA = 115.6±53.6 GA = 146.5±59.3	H			x	x		
Weber CF[30]	RA = 17 GA = 23	RA = 66±8 GA = 67±9	PNB	Carotid endarterectomy	RA = 86±18 GA = 102±17	B	x	x	x			
Williams-Russo P[31]	RA = 134 GA = 128	Median 69 yrs	CNB	Total knee replacement	RA = 85±33 GA = 88±32	A, B, C, confusion			x			x

*No volatile agent for GA, nitrous oxide fentanyl and pancuronium only. †The GA consisted in IV propofol and nitrous oxide by mask only and patients under RA received IV midazolam 0.1 mg/kg. ‡This study also contained a group with a combination of epidural anaesthesia and GA that has not been retained in the analysis. §Adapted Thai version of the mini-mental. For age and length of surgery values are expressed as mean and SD or median and range or median and percentiles or range as available. GA: General aneesthesia; RA: Regional anaesthesia; LA: Local anaesthesia; CNB: Central neuraxial block; N: Number of patients included in the study or the subgroup; D0 = day 0; D1 = day1, etc…; M = months; M1 = First month after the surgery; M3 = 3 months after the surgery etc…; A: Verbal and language skills; B: Memory and learning; C: Attention, concentration, and perception; D: Visual and spatial skills; E: Visuomotor and manual skills; F: Numerical; G: Executive functions; H: Composite measures; OBS: Organic brain syndrome scale (OBS scale) developed by Gustafson; MSQ: Mental status questionnaire

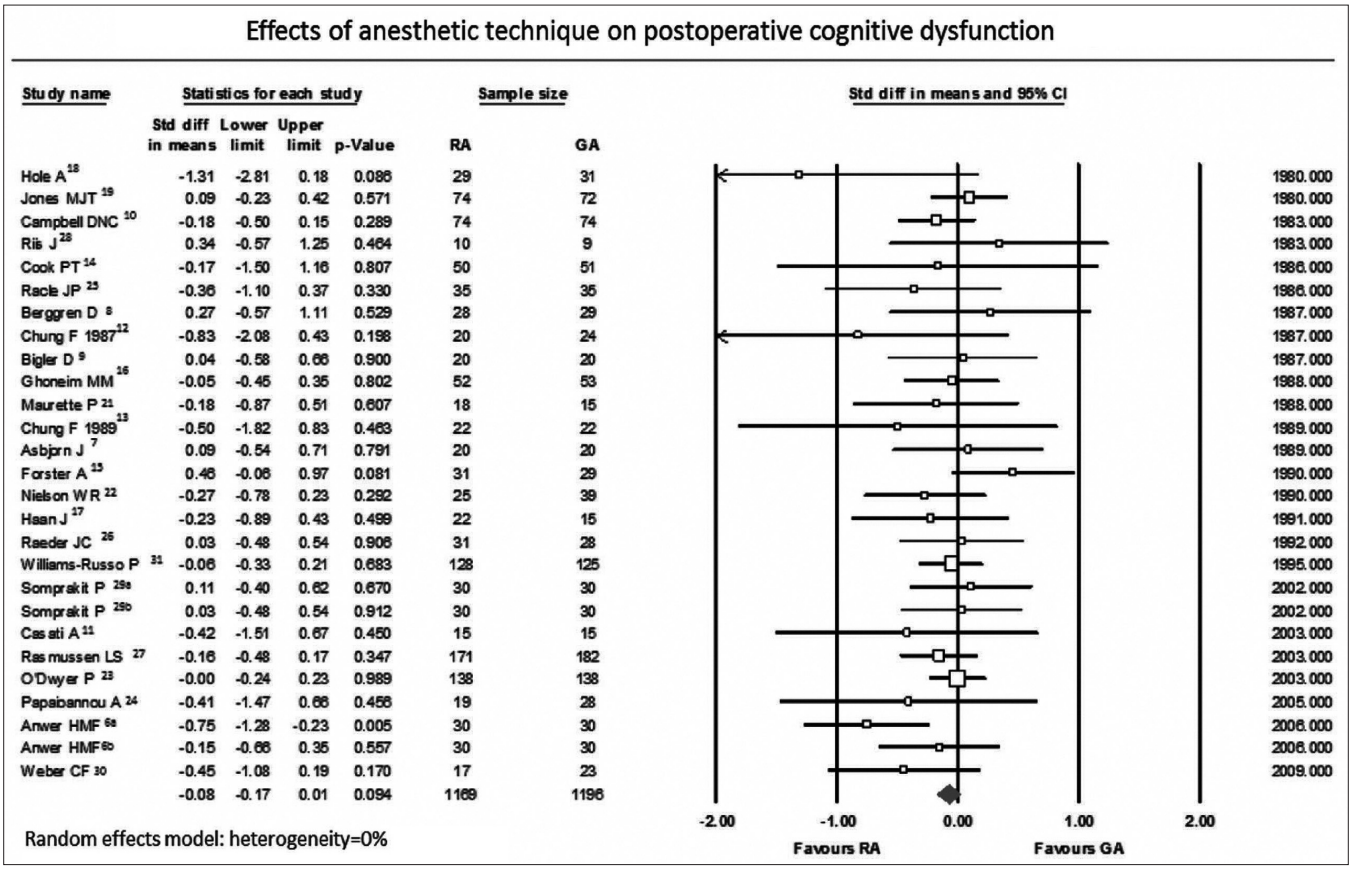

Figure 2: Forest plot. Two studies[6,29] are presented as subgroups (elderlies[a] and young[b]) There was no statistical difference between the two anaesthetic techniques.

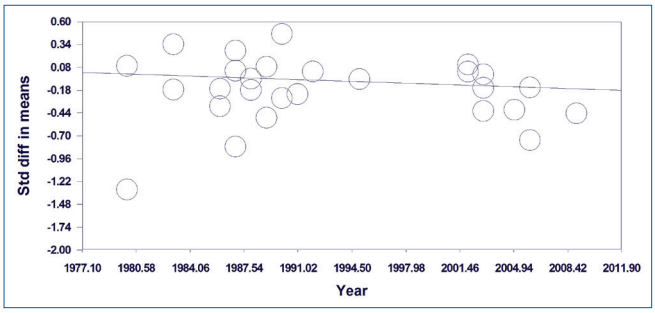

Figure 3: Meta-regression of the effect size by year of publication. *P* value of the slope = 0.29

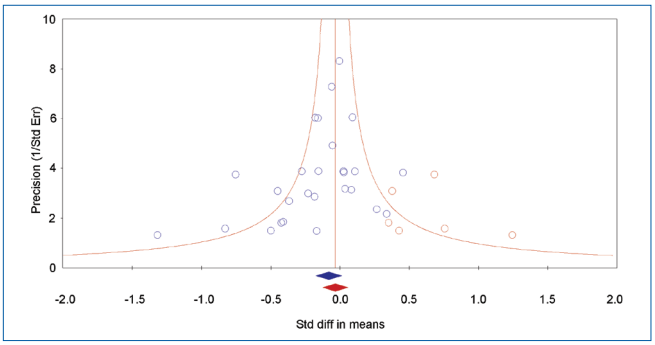

Figure 4: Funnel plot of published studies included (blue dots) with their combined effect size (blue diamond) and after the trim and fill technique (red dots and red diamond)

the standardized difference in means is equivalent to less than 1 point on the mini mental scale, a score that has a maximal value of 30 (standardized difference in means multiplied by a typical standard deviation on that specific scale: $0.08 \times 2.2 = -0.18$).[29,34]

There was no significant heterogeneity across the studies, implying that the difference in means around the point of estimate does not vary more than what is expected by chance alone. There was also no clear influence of the year of publication on the effect size [Figure 3], implying that recent agents would not differ from the oldest one and vice versa. As with every systematic review it is never possible to be certain that all studies are included and that published studies on the topic are not more prone to show a difference in favour of one of the two treatments. It is a known fact that small negative studies are often not published; authors, editors and reviewers being more inclined to give a higher level of priority to large and/or positive trials. For this reason the trim and fill technique was applied in order to compensate for a potential absence of small studies favouring general anaesthesia [Figure 4]. This analysis did not change the conclusion. A language restriction (English or French, the two languages understood enough by the present author and for which no translator would be required) was applied in the present meta-analysis therefore excluding trials from other languages. The effect of language restriction have been recently re-evaluated and, for conventional intervention (as opposed to complementary and alternative medicine), a search limited to the English language is unlikely to introduce a significant bias in the conclusions.[35] Also, considering the fair number of patients included in the trials included in the present meta-analysis (over two thousands), there is no reason to believe that more studies would alter the conclusion. Finally it has to remain clear that the present meta-analysis was not design to detect transient differences between the two techniques. Data were always taken at the latest time point available for each time period and analysed as a whole (similar to an ANOVA for repeated measures).

In conclusion, the present meta-analysis does not support the concerns that a single exposure to general anaesthesia in an adult would significantly contribute to permanent POCD after non-cardiac surgery.

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