The Effect of General Anaesthesia on Post-operative Cognitive Function in the Ambulatory Setting: A Literature Review

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Abstract

This review focuses on the post-operative recovery of cognitive function following general anaesthesia in day case surgery. A MEDLINE and bibliography search of the current literature revealed 41 articles that were included in this analysis. The effects of the inhalational agents sevoflurane, desflurane and isoflurane along with intravenous propofol were examined. An earlier return to baseline cognitive function was found in the sevoflurane and desflurane groups though this was only statistically significant within the first hour of recovery. However, these agents were associated with considerable nausea and vomiting when compared to propofol. Post-operative cognitive dysfunction in the elderly undergoing ambulatory surgery was also addressed in this review. Current evidence on this subject appears limited, though there is some data suggesting a link between the two..

Keywords: Cognitive function, ambulatory surgery, postoperative cognitive dysfunction, inhalational anaesthetics.

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Introduction

There have been a number of studies reporting that following surgical procedures under general anaesthesia (GA) many patients experience significant delays in regaining full cognitive functions, notably learning, memory, attention, concentration and verbal capabilities. [1] There appears little doubt that a definite decline in neurological ability occurs following GA, yet the degree of functional decline and the speed of recovery has considerable inter-patient variability and may also be associated with the type, depth and length of anaesthesia as well as the surgical procedure itself.

The extent of cognitive deterioration following surgery has a significant impact on the health of the patient during the immediate post-operative period and is associated with prolonged hospital recovery, greater morbidity and delays in functional recovery. [2] This is of considerable importance for patients admitted for day case surgery and for those considered more vulnerable to the effects of anaesthesia, i.e. the elderly. This review focuses primarily on these two subsets of patients and systematically examines the evidence for and the extent of cognitive deterioration in these groups.

Methods

A MEDLINE search of peer reviewed, published, full text articles in the English language between the years of 1980–2007 was performed. Papers examining the cognitive effects of the inhalational anaesthetic agents sevoflurane, desflurane and isoflurane were identified by using search terms including, but not limited to: cognitive function, post-operative cognitive decline, general anaesthesia (including listing the aforementioned anaesthetic agents), day case surgery and ambulatory setting. Additional methods of accessing articles were through reviewing the bibliography of the relevant articles.

Papers included in this review required a study size of at least 20 subjects who had their cognition assessed pre-operatively and post-operatively using one of the acknowledged cognitive tests (eg. digit-symbol substitution test, mini mental state, cognitive failings questionnaire). Articles analysed in this review include randomised control trials, observational studies, previous review articles and case control studies.

Exclusion criteria included anaesthetics in the paediatric setting, studies in which patients stayed in hospital for longer than one night post-operatively and those involving only single subjects i.e. case reports and case series.

General Anaesthesia in Ambulatory Surgery

In an era where many elective procedures are being performed in day case units, delays in patients regaining full mental capacities following general anaesthesia has significant implications for the viability of such units. Advances in anaesthetics have seen the development of drugs with a shorter onset, reduced duration of action and fewer side effects [3]. Consequently it is expected that patients will achieve levels of cognition in-line with their pre-operative state within hours of the procedure and thus allow same day discharge to occur.

The short and long term effects of these newer volatile agents on post-operative cognition have not been systematically reviewed. Several studies report differences in the timing of and recovery from GA depending on the anaesthetic used. While most suggest patients achieve pre-operative cognitive function within hours of the procedure some studies suggest that the effects may last much longer than anticipated and affect a patient's functional capabilities for several days. [4]

Choice of anaesthetic agent and cognitive function

Propofol vs sevoflurane

Research in Italy [5] examined the post-operative recovery in patients undergoing day surgery and anaesthetically maintained with either

propofol or sevoflurane. Cognitive function, assessed using the digit-symbol substitution test (DSST) was significantly decreased at 60, 90 and 120 minutes post-operatively in patients given propofol. Although this study only had a small sample size thus reducing the reliability of the conclusion, similar findings of improved cognition in patients given sevoflurane have been reported in a number of other investigations.[6,7]

These results conflict with those of Larsen and colleagues who compared the cognitive function in patients after remifentanil and propofol anaesthesia to those given desflurane or sevoflurane. Those subjects randomised to the remifentanil/propofol arm were achieving 87% and 98% correct answers to DSST questions at 30 and 60 minutes respectively, whilst the sevoflurane arm only achieved 78% correct answers at 30 minutes after termination of the anaesthetic. [8]

One should also be aware of a report by Sanou and colleagues which found that up to three hours after cessation of propofol anaesthesia patients still had a noticeable reduction in higher cognitive functions, but by 6 hours levels had returned to the preoperative state. [9]

Propofol vs desflurane

Of the papers comparing the outcome after propofol or desflurane anaesthesia two found a significant difference in post-operative cognitive functioning. An investigation by Apfelbaum [10] found that not only was recovery much faster in the desflurane group, but subjects achieved higher psychomotor scores one hour after anaesthesia compared to those given propofol. After one hour there was no difference between the groups. These results were concordant with the findings of an earlier study comparing post-operative cognitive function using the same anaesthetic criteria. [11] Other studies comparing the two agents have not examined the cognitive impairment, but have concluded that desflurane consistently results in a more rapid recovery after anaesthesia than propofol. [12,13]

Propofol vs isoflurane

Maintenance with propofol compared to isoflurane has also been studied by a number of investigators. [3,14,15] Pollard [14] found that psychomotor functioning in both study groups (i.e. those given either propofol or isoflurane) had returned to baseline characteristics at 24 hours. However, in the immediate period following surgery propofol was associated with an increased ability to maintain concentration and speed in the cognitive tasks set. Similar outcomes have also been demonstrated by Valanne. [15]

Sevoflurane vs desflurane

Studies comparing recovery following maintenance with either desflurane or sevoflurane in the ambulatory setting have found convincing evidence of more rapid recovery in those patients given desflurane. [16,17] However, attainment of psychomotor function following anaesthesia has produced less compelling evidence. A study by Tarazi [18] examined the percentage of patients able to perform DSST during the postoperative period. Sevoflurane was associated with marginally better results, particularly in the first 15 and 30 mins after termination of the anaesthetic, but later the differences were considerably smaller and throughout the 2 hour post-operative period examined there were no significant differences between the two agents. These results are consistent with other investigations [16,19] which also suggest that there is no significant difference in cognitive dysfunction following anaesthesia with sevoflurane or desflurane for day-case surgery.

Sevoflurane vs Isoflurane

It has been shown that for prolonged operations of greater than 1 hour, sevoflurane offers a faster recovery of cognition when compared to isoflurane. [20,21]Yet, although not extensively investigated, this recovery profile does not appear to be replicated in the ambulatory setting. A recent study by Mahajan and colleagues examined the cognitive recovery profiles of 71 elderly patients undergoing ambulatory surgery and anaesthetised with either sevoflurane or isoflurane. They examined the extent of cognitive impairment at 1, 3 and 6 hours post-operatively and concluded that there was no statistical difference between the groups during this period. [22]

Other investigators have produced evidence to the contrary. The Sevoflurane Multicenter Ambulatory Group, compared the recovery profile of the two inhalational © 2008, International Association for Ambulatory Surgery7 agents and found patients maintained with sevoflurane performed better in the psychomotor tests at 60 mins post procedure than those given isoflurane. [23]

Issues surrounding cognitive testing in the ambulatory setting

Many of the tests used to measure the degree of cognitive deterioration have considerable limitations which will affect the degree of neurological impairment detected in the patient. With some of the more simple tests employed in the studies, (DSST, MMSE), there is the potential for patients to "learn" the correct responses. This is the so-called "practise effect" which has been documented in a number of investigations. [24,25,26] Patients who are able to adapt to the tests in such a way will appear to have higher levels of cognition than suggested by the investigations.

Other issues affecting the test include variability resulting from different examiners administering the test, time of day the test was performed and distractions in the examining room, especially if performed as a bed side test on the ward. [26] Consequently it has been suggested that rather than using one single test, as was the case in several trials reviewed [1,2,8,11], a test battery (i.e using multiple cognitive function tests) such as that used in the ISPOCD study [27] may be more appropriate.

This too however has been reported to have significant limitations. The results of the ISPOCD study show that the degree of decline detected in the population increased as the number of test parameters increased. For example, when only one test was used the percentage of patients found to have an element of cognitive decline was 0.6%, whereas at five test parameters 29% of patients had detectable cognitive impairments. [26]Thus as more parameters are included there appears to be a greater likelihood of identifying at least one area of cognitive deterioration.

Limitations of the studies

The conclusions made from these studies with regards to which agent offers optimal post-operative cognitive recovery must be held with some significant caution. Although many of the studies suggest some form of cognitive decline occurs following surgery, the methods by which the authors conducted their anaesthesia and the tests used to measure cognitive deterioration varied quite considerably across the papers reviewed.

1. The depth of anaesthesia induced and maintained for the procedures may have a significant impact on the patient's recovery profile. [28] Several trials [1,2] used the bispectral index (BIS) to ensure that all groups studied were anaesthetised to the same comparable depth. This will assist in the post-operative period when comparing the effects of the anaesthetic. Many other studies [8,10,11,16,22] did not use such methods to rule out confounding factors and consequently the conclusions offered by these papers may not be as accurate or indeed as viable as others.

2. The lack of a universally accepted method of measuring cognition means that the authors used tests with somewhat different sensitivities. There has been extensive research into the DSST with regards to its efficacy [29,30] and consequently it was used as the main method of cognitive evaluation in several papers.

Table 1 Early, intermediate and late cognitive effects of anaesthetic agents used in the trials analysed in the review. (Prop = propofol, sevo = sevoflurane, remi = remifentanil, des = desflurane, iso = isoflurane).

Study	Maintenance anaesthetic used	Cognitive effects early (30 min)	Cognitive effects intermediate (60 min)	Cognitive effects late (>60 min)	Conclusion
Peduto [5]	Prop vs sevo	Sevo better	Sevo better	Sevo better	Sevo better
Raeder [6]	Prop vs sevo	Sevo better	No difference	No difference	Sevo faster up to 60 min
Wandel [7]	Prop vs sevo	Sevo better	Sevo better	Sevo better	Sevo better
Larsen [8]	Remi vs sevo vs des	remi<des<sevo		No difference	Remi faster up to 60 min
Apfelbaum [10]	Prop vs des	Des better	No difference	No difference	Des better up to 60 min + more rapid recovery
Song [12]	Prop vs des	Des better	Des marginally better	No difference	Des better up to 60 min
Van Hemelrijck [13]	Prop vs des	Des better	Des better	No difference	Des better up to 60 min
Pollard [14]	Prop vs iso	Prop better	No difference	No difference	Prop better in early stages
Valanne [15]	Prop vs iso	Prop better	Prop better	Prop better	Prop better
Nathanson [16]	Sevo vs des	No difference	No difference	No difference	No difference
Wellborn [17]	Sevo vs des	No difference	No difference	No difference	No difference
Tarazi [18]	Sevo vs des	Sevo better	No difference	No difference	Sevo better in early stages
Mahajan [22]	Sevo vs iso	No difference	No difference	No difference	No Difference
Philip [23]	Sevo vs iso	Sevo better	Sevo better	No difference	Sevo better in early stages

[8,16,23] Nevertheless a number studies measured their outcome by different means (Maddox Wing Test,[10,14] Mini mental state exam [1,2,22]). There exists a possibility that the findings of one study using, for example the MMSE may not have been replicated if another, more sensitive test had been employed; thereby suggesting that the results may be more dependent on the measuring tool used rather than the anaesthetic regime implemented.

3. Within individual studies the method for induction was maintained as a constant, however inter-paper differences in drugs used to induce anaesthesia showed some considerable variability which may lead to a difference in the final outcome of the paper. Similarly, the residual effect of drugs required as premedication or for use intra-operatively may influence the post-operative cognitive recovery in certain patients. [3]

Neuropsychological testing for cognitive deterioration – does statistical difference equate to clinical significance?

The question remains, therefore, whether cognitive function needs to be formally assessed as a routine measurement of fitness for discharge. Currently it is not standard practise to assess neurological function following general surgical procedures. Following operations in the ambulatory setting, most patients are discharged within 6 hours of the operation. Neurological testing in the studies outlined above have shown that regardless of the anaesthetic used, there appears to be some form of statistical decline in cognition in the immediate post-operative period. Yet by one hour following surgery the studies report little, if any difference between the anaesthetics used.

One may infer from this that early statistical differences (i.e. within the first hour), although interesting to note and potentially useful in pre-operative planning, should not significantly affect patient care plans or discharge times.

Anaesthetic Implications

Post-operative recovery following general anaesthesia needs to take into account numerous factors including post-operative nausea and vomiting, analgesia, time spent in PACU and time to discharge. The success or otherwise of the anaesthetics used in the studies has been analysed solely on the basis of post-operative recovery of cognitive function. Consequently the implications drawn from these studies relate purely to the ability to fully regain mental capabilities after general anaesthesia.

The ideal anaesthetic for day case surgery must not affect mental capabilities for long periods of time. The use of volatile agents that have a lower solubility and thus are more rapidly eliminated from the body leading to a decreased exposure to the anaesthetic appears to have some correlation to the recovery of cognitive function. The papers suggest that sevoflurane and desflurane, both of which have relatively low solubilities, have favourable cognitive effects over isoflurane (higher solubility) and propofol.

Although the inhalational agents provide an earlier return of cognitive

function, they are associated with considerable nausea and vomiting when compared to propofol.[3] A balance must be found between drugs that provide a rapid recovery of post-operative cognition with those that have minimal side effects. Additionally, in the current climate of unprecedented financial attention being paid to the NHS and where rapid turnover of patients is a fundamental to hospital outcome, anaesthetists need to be aware of the costs associated not only with the agents themselves but also those incurred by prolonged hospital stay following surgery.

The studies offer statistical evidence that sevoflurane and desflurane offer equal and superior outcomes to isoflurane and propofol. However these advantages appear exclusively limited to the immediate (<1hour) post-operative period. The clinical implications of this would therefore appear much less significant considering that very few patients would be discharged within this time period.

Post-operative Cognitive Dysfunction in the elderly population undergoing minor/ambulatory surgery

Post-operative cognitive dysfunction (POCD) is defined as a decline in mental capabilities such as concentration, memory, perception and problem solving abilities which last for weeks or months following surgical procedures.[31] The risk of developing POCD appears closely related to increasing age and type of surgery. Numerous studies have shown significant associations between cardiac surgery and the development of POCD in the elderly population. More recently this link has been extended to major non-cardiac surgery and there exists extensive reviews of these subject areas. [32,33] The development of POCD after ambulatory surgery, although not as extensively investigated, has also produced some viable evidence which, until now, has not been collated and reviewed.

A recent study by the ISPOCD2 investigators [34] enrolled 372 patients aged 60 and over who were admitted for minor procedures involving either 1 night's postoperative stay or same day discharge. All patients underwent general anaesthesia. They found that at 7 days and 3 months post procedure 6.8% and 6.6% of patients had some form of POCD respectively. However, when examined more closely, the incidence of cognitive failings at 7 days was significantly higher in those patients who spent 1 night in hospital (Table 2). They suggested that hospital stay significantly effects the development of POCD in the immediate post-operative period. [34]

Table 2 Adapted from Canet J. et al Cognitive dysfunction after minor surgery in the elderly. [34]

	Incidence of POCD	
Risk	**7 days**	**3 months**
All patients	6.8%	6.6%
Inpatient	9.8%	8.8%
Outpatient	3.5%	4.5%

Although these findings are consistent with others,35 the results must be interpreted with caution. The apparent large difference between the inpatient and outpatient incidence of POCD may not be a true reflection on the development of cognitive decline but rather more directly related to patient comorbidities and hospital factors. Those patients in the same day discharge group were generally fitter than their counterparts in the inpatient cohort; similarly patients were not randomised into the two groups, the decision being left to individual hospital protocols and the physician's preference. [34] Consequently direct comparisons and concrete conclusions are difficult to gain with certainty from this trial. Nevertheless, it does highlight that even after minor surgical procedures the elderly may still be at risk of developing some form of cognitive dysfunction.

Rohan et al [36] also examined the effect of general anaesthesia on the development of POCD in the elderly population (aged ≥73) undergoing minor procedures. Although patient recruitment numbers were significantly lower than in the previous trial (30 cf. 372), the authors still found a significant increase in cognitive deterioration in the first 24 hours following surgery; 47% of patients had experienced POCD, compared to only 7% of the control group. Clearly the small sample size of this study may cause the results to be disproportionately high yet the close matching of the control and study group combined with the strict adherence to guidelines [37] relating to the measuring of POCD give the results some significant strength.

The suggestion that cognitive decline occurs within the first 24 hours post-operatively and may continue for up to 3 days has considerable implications on the immediate care and advice given to patients. However, there is also evidence to suggest that patients are capable of full cognitive capabilities at the time of discharge from ambulatory surgery. [38]

Cohen [38] compared patients admitted for day case surgery involving either local or general anaesthesia and examined their post-operative cognitive function prior to discharge. In contrast to the findings of the previous papers, the authors found no clinically significant cognitive deterioration in patients given either local or general anaesthetic and concluded that patients could safely be discharged with full cognitive function on the same day as surgery. These conclusions however carry considerable caveats. Not only was the sample size particularly small (20 patients) but the age range of the subjects was much broader than in the previous papers (range from 21–45). The development of POCD in middle aged patients has been shown to be much reduced when compared to the elderly population [39, 40] which may account for the low occurrence of cognitive failings in this study.

At 24 hours post procedure, Heath [41] produced findings in line with the Cohen study in that there appeared to be no deterioration in cognitive function in their cohort of patients undergoing surgery. There was however a detectable difference at 1 and 2 hours after termination of the anaesthetic.

The results from a study by Tzabar [4] appear to offer further evidence of an apparent prolonged cognitive decline of up to 3 days in patients receiving general anaesthesia for day case surgery. Cognitive deterioration was measured by asking patients to fill in a cognitive failings questionnaire during the 3 days following surgery. As the answers to this survey required patients to individually complete the forms at home, problems of patient apathy in correctly answering the questions and potential for subjects to become confused or uncertain as to the exact timing of events means that the accuracy of the answers given may not be as high as other cognitive tests carried out under the supervision of healthcare practitioners.

Anaesthetic Implications

The papers published appear to present conflicting evidence as to the extent of POCD following ambulatory surgery. Whilst there appears to be some evidence of a link between the two, the limited number of trials specifically examining this area of anaesthesia makes definite conclusions challenging. Similarly, significant problems of patient recruitment and inconsistencies in the data collection methods between each paper create difficulties in detailing with any certainty the incidence of POCD in this group of patients.

Nevertheless, the research indicates the potential for a link to exist and consequently physicians should be cautious in their post-operative care plans, particularly with regards to elderly patient discharge. The possibility of POCD presenting late, (i.e. after 24 hours) suggests that patients should be monitored for longer periods of time and their mental state closely monitored for subtle signs of decline. The PACU provides a suitable opportunity to assess these areas, yet the vast number of methods available for testing cognitive function presents problems in ensuring adequate assessment has been made.

The need to develop a standardised cognitive function test has already been discussed. Such a test would identify those patients whose cognition has been significantly impaired following surgery and thus improve patient safety regarding discharge times and advice. It would also allow further research into this area of anaesthetics to confirm or refute the evidence as it currently stands.

Conclusions

Cognitive decline following anaesthesia in the ambulatory setting may be significantly more prevalent that previously realised. It appears that the inhalational agents offer a faster return to the pre-operative cognitive state than their intravenous alternatives, yet the considerable side effects of these drugs also need consideration. The need for close post-operative observation of neurological decline in addition to functional recovery needs to take place. Before policies concerning the immediate care of ambulatory patients are significantly altered further research into postoperative cognitive function needs to be undertaken and methods of testing such variants standardised.

Post-operative cognitive decline in patients undergoing day case procedures also requires further investigation. Preliminary studies suggest there may be an associated deterioration in cognitive function; however the papers are limited and provide conflicting evidence. Nevertheless, the suggestion that POCD may develop up to and beyond 24 hours post procedure should be taken seriously and physicians and patients should be vigilant for subtle signs of cognitive impairment.

Learning points

- Inhalational agents offer superior cognitive recovery profiles when compared to the commonly used intravenous agent propofol
- Sevoflurane and desflurane should be considered for ambulatory surgery if rapid cognitive recovery is required amongst the elderly population may also occur in the ambulatory setting

Future research

- An agreement needs to be made regarding which neurological test is most appropriate to evaluate cognitive decline in the immediate postoperative period
- Further research into POCD in the ambulatory setting is required to determine the extent of the condition following minor operative procedures

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