A systematic review of postoperative cognitive decline following open and endovascular aortic aneurysm surgery

RA Benson¹, BA Ozdemir², D Matthews³, IM Loftus²

¹Department of Vascular Surgery, University Hospital of North Midlands, Stoke-on-Trent, UK

²St George's Vascular Institute, St George's Healthcare NHS Trust, London, UK

³Croydon Memory Service, South London and Maudsley NHS Foundation Trust, Croydon, UK

ABSTRACT

OBJECTIVES Postoperative cognitive decline (POCD) is a well-recognised neurological phenomenon following major surgery. Most commonly seen in elderly patients, it has direct links to increased long-term morbidity and reduced quality of life. Its incidence following open and endovascular abdominal and thoracic aneurysm surgery is unclear. The purpose of this systematic review is to collate available evidence for POCD following abdominal and thoracic aortic surgery, and to identify continuing controversies directing future research.

METHODS A MEDLINE search was conducted following the recommendations of the PRISMA guidelines. Terms searched for included but were not limited to: aortic surgery, delirium, postoperative cognitive decline/dysfunction thoracic aortic surgery, abdominal aortic surgery. Reference lists were searched for additional studies.

RESULTS Five observational studies were identified from the literature search. Variation in study methods, cognitive test batteries and thresholds set by the study coordinators did not allow for pooled results. In those studies that did find evidence of decline, risk was linked to age over 65 years, presence of postoperative delirium and decreased years in education.

CONCLUSIONS Evidence thus far suggests that POCD can affect patients following major aortic, non-cardiothoracic as well as cardiothoracic surgery. Future research should focus on using a validated repeatable battery of cognitive tests and a single defined threshold for POCD to allow pooled analysis and more robust conclusions. Larger, adequately powered studies are required to re-evaluate the effect of aortic aneurysm surgery on postoperative cognitive function.

KEYWORDS

Postoperative cognitive decline (POCD) – Cognitive test – Aortic aneurysm surgery

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CORRESPONDENCE TO

RA Benson, E: ruth.benson@gmail.com

Introduction

Postoperative cognitive decline (POCD) involves persistent problems with one or more of day-to-day memory, language skills, attention and learning compared with levels demonstrated preoperatively. Evidence suggests that POCD can act as a precursor for significant functional impairment in the months following surgery, including reduction in reported quality of life, and increased mortality at 1 year.¹ Patients are more likely to experience delayed discharge due to prolonged physical rehabilitation² and increased rates of discharge to nursing homes or other rehabilitation facilities.³ This raises potential medico-legal issues for the consenting surgeon, in terms of clear communication of all possible risks of surgery.

Bedford first proposed the concept of postoperative cognitive decline in 1955, and POCD is now established as a major neurological risk following cardiothoracic surgery.⁴ There

are fewer equivalent studies focusing on procedures for descending or abdominal aortic aneurysm (AAA) surgery, despite similarities between cohorts; that is, the burden of cardiovascular comorbidity, gender distribution and age. Aortic aneurysm repair does not routinely involve thoracotomy or bypass but has increasingly moved towards the use of endovascular techniques, and there is evidence to suggest that a proportion of patients undergoing major vascular surgery are also at risk of POCD.⁵

Delirium has been linked to increased risk of POCD and recent evidence shows that its prevalence is higher in patients who have undergone open aortic surgery when compared with other major vascular surgeries.⁶ It is therefore appropriate to hypothesise that a significant proportion of patients undergoing aortic surgery are likely to show signs of POCD.⁵

As endovascular technology has progressed and results increasingly favour it as an alternative to open repair in

high-risk patients, aortic aneurysm repair has become available to an older, more complex patient cohort. At the same time, the introduction of the national aortic aneurysm screening programme has led to a younger cohort of patients requiring surgery, some of whom will still be of working age. For patients wishing to return to work, there should be awareness of the negative effect cognitive decline may have on insight, especially in patients returning to work in hazardous environments.

This systematic review has identified five prospective observational studies investigating cognitive function following surgery for aortic aneurysm. The studies have included patients undergoing both open and endovascular repair, to provide an up-to-date review of the current status of research into POCD following major aortic surgery and to identify developments in the field.

Methods

A comprehensive literature search of MEDLINE was performed, without time limits. The search included all non-cardiac surgery; postoperative cognitive decline/dysfunction and other analogous terms identified during the search, such as 'transient mental impairment/confusion' and 'cognitive difficulties'.

Studies were included if they had a confirmed aortic surgery population within their cohorts. We have clearly stated which of these the studies have tested for, definitions used, and timing of assessment. Studies were confined to those published in the English language. All studies were reviewed by two authors to confirm suitability for inclusion.

Owing to the variety of cognitive testing used and the heterogeneity of study populations, pooled analysis was not possible. All studies were prospective, cohort studies. There have been no randomised controlled trials in this setting.

Results

The review identified five observational studies describing patients undergoing abdominal and thoracic aneurysm surgery (Table 1).^{5,7-10} Lloyd *et al.*¹⁰ were the only authors to include an endovascular aortic repair (EVAR) cohort ($n = 34$). The largest single identifiable cohort of elective open AAA repair contained 102 patients, studied by Benoit *et al.*⁵ and subsequently Wallbridge *et al.*⁷

Only one study included a distinct control group. Treasure *et al.*⁸ compared 29 patients undergoing elective open aortic surgery with a cohort undergoing major cardiothoracic surgery. There was significant heterogeneity within the five studies. Preoperative testing ranged from 2 days to 18 days, whereas, postoperatively, the testing period ranged from 90 days to 180 days. Data analysis and defined threshold for POCD varied. One group used a greater than 20% decline in over 20% of tests and others a drop in score of one standard deviation or more compared with group score distribution. Variation in test batteries and methods of defining the threshold for cognitive decline means that direct comparison between studies was impossible.

Only two groups successfully identified a cohort of patients reaching their defined threshold for POCD in the period after surgery. The first, Treasure *et al.*,⁸ observed POCD in 50% of patients in the immediate postoperative period following open aortic surgery; that is, before discharge from hospital, and at secondary testing (a mean time post-surgery of 56 days).⁸ In comparison, 73% of the cohort undergoing cardiac surgery reached threshold for POCD at day 8. However, unlike the aortic aneurysm group, who continued to show the same level of cognitive decline at repeat testing at 56 days, incidence among the cardiac cohort had dropped to 37%. POCD was more likely to occur in elderly patients and those demonstrating lower perioperative cerebral perfusion pressures. The team investigated cerebral perfusion in the immediate postoperative period, noting that in the coronary bypass cohort, pressures remained low compared with the aortic control group. They therefore concluded that the aetiology of POCD following aortic surgery must be different to that for cardiac bypass.

Grichnik *et al.*'s⁹ subsequent study of 29 patients undergoing non-cardiothoracic open thoracic and vascular procedures found an incidence of POCD of 44.8%. Mean overall decline in postoperative scores was 15%, compared with a mean drop in score of 24.7% in the POCD cohort. As expected, multivariate analysis indicated significant effects of increasing age both on the risk of developing POCD, and degree of decline in scores. Years of education was shown to influence severity of decline in scores overall but did not show a significant effect on risk of POCD.

Benoit *et al.*⁵ examined 102 patients undergoing open AAA repair, at baseline and at 3 months.⁵ Although weaker test scores were recorded in patients who suffered from delirium, decline in scores did not reach statistical significance. Although no patients reached threshold for POCD, multivariate analysis of covariance analysis indicated that increasing age and years in education led to poorer scores for several of the nine tests used (6/9 and 7/9, respectively). Delirium led to significant declines in the Rey complex figure test and memory tests, and the authors suggested that as these could be considered more complex tests, they were more sensitive to neurological and psychological change. Wallbridge *et al.*'s subsequent study linked delirium to worse patient reported outcomes.⁷

Lloyd *et al.*,¹⁰ the only group to include a cohort of patients undergoing endovascular as well as open surgery ($n = 24$ and $n = 40$, respectively) failed to find evidence of significant cognitive decline in either group. However, following Benoit *et al.*'s lead,⁵ the group also performed a sub-test analysis of cognitive tests, to identify the effects on individual domains that may have been lost during combined analysis. This indicated a significant decline in scores from visual search tasks such as trails tests. Quality of Life scores also demonstrated significant drops in self-reported scores for physical function ($P = -0.001$).

Discussion

Two of the five studies described in this review found a distinct cohort of patients reaching the threshold for POCD

Table 1 Summary of studies investigating postoperative cognitive decline (POCD) following aortic aneurysm surgery

Author	Year	Testing interval (days) ^a	Years of age (range)	Definition of decline	Study participants (n)	Aortic cohorts (n)	Incidence of POCD (%)	Significant variables [P value]
Treasure <i>et al.</i> ⁸	1989	BL 8 56	60 (22–85)	1 SD deviation drop of group distribution compared with preoperative scores on ≥ 2 tests	29	Open AAA 29	56 at 8 days 56 at 56 days	Not assessed
Grichnik <i>et al.</i> ⁹	1999	BL 42–84	60.3 (35–85)	≥ 20% decrement in ≥ 20% of tests	51	Open AAA: 5 Open thoracic AA: 2 AUI: 1	63 TAA 50 AAA 60 AIG 100	Age [.02]
Benoit <i>et al.</i> ⁵	2005	BL 6/DC 90	71 (41–88)	Delirium: DSM-IV Student's <i>t</i> test Mann-Whitney U Fisher's exact test Multivariate analysis of covariance	102	Open AAA: 102	0	Pack years smoked [.001] Low MMSE [.003] No. of psychoactive meds [.005]
Wallbridge <i>et al.</i> ⁷	2011	BL 6/DC 90	69.8 (41–88)	Delirium: DSM-IV POCD: Index score ≥ 2 (1 = 1 SD below group mean per test) Statistical analysis as per Benoit <i>et al.</i>	102	Open AAA: 102	0	Preoperative cognitive difficulty, delirium, length of stay all influenced postoperative cognitive scores but nothing significant
Lloyd <i>et al.</i> ¹⁰	2000	BL 180	EVAR 73 (59–82) Open 73 (59–86)	Wilcoxon signed rank test Mann-Whitney U	82	Open AAA 48 EVAR: 34	0	Deterioration in visual search task [.03]

^aPostoperative day(s) on which testing took place; each row demonstrates a separate testing period; if the postoperative test took place across a number of days, it is shown as a range.
AA = aortic aneurysm; AAA = abdominal aortic aneurysm; AIG = aorto-iliac graft; AUI = aorto-uni-iliac graft; BL = baseline; DC = discharge (testing took place either at day 6 postoperatively or on the day of discharge if sooner); DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; EVAR = endovascular aortic repair; MMSE = Mini-Mental State Examination; SD = standard deviation; TAA = thoracic aortic aneurysm

following major abdominal and thoracic aortic surgery. However, several of the studies included in this review are now historical, test batteries are not current and there are significant discrepancies in the methods used by individual teams preventing pooled analysis to allow for significant results. Despite these limitations, several variables were found to link to poorer cognitive scores postoperatively, such as age over 65 years, smoking history, anaesthesia time and more years spent in secondary education. Grichnik *et al.*'s study⁹ was the first to provide an estimate of the effect of age and years in education on decline in this setting, suggesting that for every 10 years of increasing age, mean scores would see a decline of 4%, reversed by 1.6% for every additional year in education.

One of the studies included in this review investigated the correlation between delirium and risk of POCD in patients undergoing open surgery. Research into delirium following several types of major vascular surgery have identified incidence of delirium of up to 46% following open AAA repair

compared with only 2% after EVAR.¹¹ Factors relating to delirium include pre-existing cognitive impairment and age, and it has been shown to relate to higher rates of discharge to nursing care (38% vs. 8%) and reduction in scores for activities of daily living with effects persisting out to 6 months.⁵ This shows a significant overlap for risk factors and consequences of the two phenomenon, suggesting they could share common pathophysiology.

Microembolic damage

Owing to the need for manipulation of stiff wires around the aortic arch during EVAR, research continues to explore the effects of perioperative microembolisation on postoperative cognition, including its relation to changes on postoperative magnetic resonance imaging (MRI).¹² There is increasing evidence of cerebral microembolisation during endovascular thoracic stenting for dissection and aneurysm, associated with the appearance of new ischaemic lesions on postoperative MRI.¹³ Although there is a well-established association

between atherosclerotic load at the aortic arch and risk of ischaemic stroke following EVAR¹⁴ correlation with cognitive decline is less clear and an obvious avenue for further research.

Postoperative neuroinflammation

Teams studying the effects of the systemic inflammatory response caused by surgery have noted that certain systemic proinflammatory cytokines such as interleukin 6 are able to cross the blood–brain barrier and trigger associated neuro-inflammatory cascades. The blood–brain barrier is thought to become more permeable with increasing age, providing one explanation as to why the risk of POCD is higher in older cohorts.^{15–16} This increased permeability might also explain why delirium has a lower incidence following minimally invasive aortic surgery compared with open repair.¹¹ Alternative biomarkers for monitoring the extent of neurological damage are now being investigated for their sensitivity in detecting subclinical injury and predicting cognitive outcomes, such as glial fibrillary acidic protein.¹⁷ However, in order for them to be useful in the setting of future cognitive research, the link between serum levels and related outcomes needs to be more firmly established.

Other important topics needing to be addressed include the need for test batteries validated in the setting of major surgery, to provide more reproducible and therefore comparable methods of cognitive testing, which will allow pooled analysis and more robust conclusions.¹⁸ Of concern is the suggestion that patients declining to attend repeat testing at 6 months may be the very patients most at risk of suffering from POCD.¹⁹ Benoit *et al.*⁵ recorded an attrition rate of 22% at follow-up (18/82 patients lost to follow-up at 6 months), bringing their results into question (0% reaching threshold for POCD) and suggesting the potential for a type 2 error.

Conclusion

Studies comparing outcomes following open and endovascular repair focus on mortality and reintervention rates, rarely describing the effects on cognitive function or the impact on activities of day-to-day living and independence. The evidence thus far demonstrates clear and significant heterogeneity between study methodologies, threshold for cognitive decline and small study numbers. Although it appears that there is some evidence that POCD is a significant phenomenon following non-cardiothoracic aortic surgery, pooled analysis to allow more accurate conclusions could not be performed. Despite continuing interest in POCD, there has been little progress in the development of preventative or protective strategies. Use of a standardised cognitive testing battery, performed at specified intervals with the addition of MRI imaging and biomarker measurement will improve the investigation of POCD in both a vascular setting and for other specialties, improving the quality of research in the area and allowing the identification of more specific risk factors to guide further research in this field.

Disclosures

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