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COGNITIVE IMPAIRMENT FOLLOWING USE OF ANAESTHETIC AGENTS: A REVIEW OF THE LITERATURE, AND IMPLICATIONS FOR FUTURE PRACTICE

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SUMMARY

Emerging data suggest that both inhalational and intravenous anaesthetics are associated with cognitive decline, particularly in the elderly. Of particular concern, is the phenomenon known as post-operative cognitive decline (POCD), characterised by a transient impairment of memory, concentration, language comprehension and social integration. Implicated in the pathophysiology of POCD is the accumulation of Aβ peptide, and inhibition of cholinergic neurotransmission. Currently used anaesthetic agents differ in their propensity for causing POCD as a result of their differing pharmacological profiles. Coupled with increasing knowledge of patient susceptibility factors, this information allows for modification of clinical practice to minimise the long-term disability that may otherwise accompany POCD.

Key words: *post-operative cognitive dysfunction – anaesthesia - neurotoxicity*

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INTRODUCTION

Advances in surgery and anaesthesia have contributed to the 60% increase in the number of operations performed in the NHS over the last ten years.Whilst mortality attributable to general anaesthesia remains low (Jenkins et al. 2003), attention has been directed towards prevention of anaesthesia-associated morbidity, including cardiac, renal, cerebral and pulmonary sequelae. Emerging data suggest that both inhalational and intravenous anaesthetics are associated with cognitive decline, particularly in the elderly (Bekker et al. 2003). Of particular concern, is the phenomenon known as post-operative cognitive decline (POCD), characterised by a transient (days to weeks) impairment of memory, concentration, language comprehension and social integration (Phillips-Bute et al. 2006). Distinct from post-operative delirium due to its non-fluctuating course, retained consciousness levels and increased mortality rate, POCD may be affecting 15-25% patients undergoing surgery (Bryson et al. 2006). Nevertheless, many studies of POCD to date have lacked the statistical power to disentangle POCD from age-related cognitive decline, and indeed, to disentangle the effects of surgical trauma from that of anaesthetic agents (Dabrowski et al. 2012). Given the widespread use of anaesthetic agents in our aging population, it is crucial to understand the pathophysiology of anaesthetic-induced POCD, with a view to minimise any possible neurotoxicity.

PATHOPHYSIOLOGY OF POST-OPERATIVE COGNITIVE DECLINE

Although its pathophysiology has not been fully elucidated, it is likely that anaesthetic-induced POCD has a multifactorial aetiology, involving a combination of genetic susceptibility, pre- and peri-operative factors. That cerebral vascular disease, systemic hypertension, diabetes mellitus and age are risk factors for POCD (Wolman et al. 1999) lends credence to the hypothesis that POCD is related to vascular insufficiency. Animal models reveal, however, a predominant role for neuro-inflammation in the aetiology of POCD, with Mandal et al. (2009) noting widespread inflammation and Aβ peptide oligomerisation induced by the anaesthetic agents, isoflurane and desflurane. The increased incidence of POCD following surgical trauma, hypothermia and cardio-pulmonary bypass (Diegeleret al. 2000), may thus be a reflection of an increased peri-operative neuroinflammatory response.

The accumulation of Aβ peptide, loss of cholinergic forebrain neurons and positive predictive value of the apolipoprotein E-4 allele in POCD have naturally prompted comparisons with Alzheimer's disease (Xie et al. 2006). In both conditions, the impairments in cognition are likely related to a neurotoxic effect of amyloid β peptide, whose accumulation is increased following exposure to certain anaesthetic agents. Interestingly, Hellstrom-Lindahl et al. (2000) also argue for a role of Aβ peptide in inhibition of cholinergic neurotransmission, independent of its neurotoxic effect. Given the role of the cholinergic system in facilitating learning and memory, such an action provides a plausible mechanism for POCD, but also carries implications for practice.

RELATIONSHIP OF DIFFERENT ANAESTHETIC AGENTS TO POCD

The studies of POCD pathophysiology thus far have indicated that anaesthetic agents, which promote Aβ

peptide aggregation, or inhibit cholinergic transmission, are potential mediators of POCD. However, each anaesthetic agent, by virtue of its pharmacology, molecular mass and mode of delivery, is able to perform these actions with different potency. Using nuclear magnetic resonance spectroscopy, Mandal et al. (2009) show that volatile agents of lower molecular mass (isoflurane, desflurane) are more potent promoters of Aβ peptide oligomerisation, by facilitating interaction of key residues in the peptide. In vivo studies in mice have also demonstrated a calcium-dependent pro-apoptotic effect of isoflurane (Xieet al. 2006). Agents of higher molecular mass (thiopental, diazepam) are unable to interact with these residues, and thus, no oligomerisationis seen.

Likewise, anaesthetic agents differ in their ability to inhibit cholinergic transmission, with ketamine and volatile anaesthetic agents acting as potent antagonists at nicotinic acetylcholine receptors (desflurane at M1, sevoflurane at M1 and M3, and isoflurane at M3 receptor subtypes), and barbiturates acting as potent antagonists at muscarinic acetylcholine receptors. Opioids depress cholinergic transmission, and the action of anticholinesterase drugs (physostgmine, pyridostigmine, neostigmine) is dependent upon their concentration in the cerebrospinal fluid (Fodale et al. 2008). By contrast, clinically used concentrations of propofol show no antagonism of the above receptors, although its action may be potentiated by basal forebrain cholinergic dysfunction (Laalou et al. 2008).

In further support of the increased neurotoxicity of volatile anaesthetic agents, is a prospective randomised study from Liu et al. (2013), which assigned elderly patients undergoing surgery to three different protocols of general anaesthesia: sevoflurane (inhaled), propofol (intravenous) and lidocaine (regional epidural). Those who received inhaled sevoflurane showed an accelerated progression of mild cognitive impairment, according to neuropsychological assessment. Nevertheless, the study was limited by its small sample size, and lack of follow-up cerebrospinal fluid analysis. Interestingly, pre-existing Alzheimer's disease neuropathology may increase vulnerability to the neurotoxic effects of sevoflurane, as found in transgenic studies in mice (Lu et al. 2010).

MOVING FORWARD: IMPLICATIONS FOR CLINICAL PRACTICE

Although estimates of incidence of POCD have been hampered by small sample sizes, varying methods of neuropsychological assessment and lack of consensus on threshold for significant cognitive change (Silverstein et al. 2007), it is indisputable that POCD has long-term impacts on sufferers. The International Study of Postoperative Cognitive Dysfunction (ISPOCD) (Moller et al. 2012) found a reduction in daily activities, earlier retirement, increased dependence of social support and increased mortality associated with POCD. General anaesthesia in children may also lead to neurocognitive impairment, as a result of damage to the developing brain (McCann et al. 2012).

The studies above indicate an increased propensity for low molecular weight, volatile anaesthetic agents to cause POCD (Liu et al. 2013), which must be borne in mind for patients undergoing hip or open cardiac surgery, in particular (Diegeleret al. 2000). In the prevention of POCD, it is also important to consider patient susceptibility; protective anaesthetic and surgical techniques may be recommended in elderly patients or those who are more likely to have a peri-operative inflammatory stress response. Such techniques may involve intra-operative measurements of anaesthetic depth and cerebral oxygenation, which Ballard et al. (2012) describe decrease incidence of POCD and cognitive decline. Nevertheless, these improved anaesthetic techniques may prove futile in those patients who are already vulnerable to the effects of surgical stress.

CONCLUSION

Progress in molecular biology has allowed improved insight into the neuropathology of post-operative cognitive dysfunction (POCD). Use of anaesthetic agents, and volatile agents in particular, has been associated with increased oligomerisation of Aβ peptide and inhibition of cholinergic neurotransmission, which gives rise to a clinical picture of impairment of learning and cognition. In the prevention of POCD, patient susceptibility factors and peri-operative factors must be considered.

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