International Journal of Surgery 34 (2016) 41–46

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Anaesthetics and analgesics; neurocognitive effects, organ protection and cancer reoccurrence an update

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HIGHLIGHTS

- Available anaesthetics, are effective and reassuringly safe, associated to low incidence of toxicology and or side effects.
- We still lack robust evidence to state that one anaesthetic is associated to clear clinical benefit over the other.
- Further high-quality prospective randomised studies addressing risk for postoperative cognitive impairment and neurodegeneration, ischemia/reperfusion injury and cancer reoccurrence are needed.

ARTICLE INFO

Article history:
Received 13 May 2016
Received in revised form
15 August 2016
Accepted 20 August 2016
Available online 22 August 2016

Keywords:
General anaesthesia
Anaesthetics
Sevoflurane
Desflurane
Propofol
Neurocognitive side effects
Postoperative cognitive dysfunction
Organ protection
Cancer reoccurrence

ABSTRACT

Available general and local anaesthetics, third generation inhaled anaesthetics, propofol and amide class local anaesthetics are effective and reassuringly safe. They are all associated to low incidence of toxicology and or adverse-effects. There is however a debate whether anaesthetic drug and technique could exhibit effects beyond the primary effects; fully reversible depression of the central nervous system, dose dependent anaesthesia. Anaesthetics may be involved in the progression of neurocognitive side effects seen especially in the elderly after major surgery, so called Postoperative Cognitive Dysfunction. On the other hand anaesthetics may exhibit organ protective potential, reducing ischemia reperfusion injury and improving survival after cardiac surgery. Anaesthetics and anaesthetic technique may also have effects of cancer reoccurrence and risk for metastasis. The present paper provides an update around the evidence base around anaesthesia potential contributing effect on the occurrence of postoperative cognitive adverse-effects, organ protective properties and influence on cancer re-occurrence/metastasis.

1. Introduction

There is an increasing interest in efficient perioperative care providing rapid recovery. Enhanced recovery pathways and ambulatory surgery program are increasingly adopted [1,2]. Multimodal analgesia, combining non-opioid analgesics, local anaesthesia and lowest effective opioid dose has become standard of care. Ultrasound has further improved performance and success rates for regional blocks. Minimising preoperative fasting, adhering to modern guidelines, goal directed intraoperative fluid therapy and avoidance of prolonged parenteral fluid therapy is becoming standard of care [3].

Available general and local anaesthetics, third generation

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http://dx.doi.org/10.1016/j.ijsu.2016.08.235
1743-9191/

inhaled anaesthetics, propofol and amide class of local anaesthetics are all effective and reassuringly safe. These agents have a low toxicology and serious adverse effects directly related to the compound are most infrequent seen. There is however debate whether anaesthesia may have effects beyond the primary once. This review focus on three areas associated to perioperative care and the potential impact from anaesthesia, anaesthetic agents/technique used; postoperative cognitive dysfunction (POCD), protection against ischemia/reperfusion injury and cancer reoccurrence/metastasis.

2. Postoperative cognitive long term effects, postoperative cognitive dysfunction, POCD

General anaesthetic agents have their primarily effects within the central nervous system; dose dependent and fully reversible depression of brain and spinal cord activities. Modern anaesthetics are fast acting and associated to rapid emergence after cessation of administration [4–6]. Minor residual effects on cognitive performance may last for hours and e.g. driving car is generally not recommended the first 24 h after anaesthesia.

Postoperative neurocognitive side effects, such as emergence agitation and postoperative delirium, are known adverse effects after surgery and anaesthesia. Risk groups are children and the elderly [7]. Emergence agitation and postoperative delirium are commonly short-lasting and self-limiting.

2.1. Anaesthesia and postoperative cognitive dysfunction

It is known that surgery and anaesthesia have more profound effects on the elderly. Residual minor cognitive effects brain function are not uncommon. Bedford (1955) was one of the first who noticed the "*adverse cerebral effects of anaesthesia on old people*" [8]. Older patients often carry more of neurovascular risk factors and have in general less cognitive reserve, and are at higher risk for exhibiting postoperative neurocognitive impairment after the stress associated to surgery, anaesthesia, and perioperative care. The elderly exhibit not uncommonly various degree of long lasting postoperative neurocognitive impairment referred to as postoperative cognitive dysfunction (POCD). Postoperative cognitive dysfunction is however not well defined and there is no consensus around definition, tools for assessment or time when it is best assessed [9]. POCD is a broad syndrome describing more or less subtle postoperative cognitive decline including limitations in memory, decreased intellectual ability and compromised daily functions [10,11]. A robust prevalence is not possible to determine since there are no generally agreed criteria for the assessment or the diagnosis of POCD. No single test can adequately measure cognitive function with acceptable sensitivity. A number of factors needs to be taken into account e.g. age, education and preoperative neurocognitive condition. There is huge variability in reported incidence without doubt related to different test used and assessment [12].

Monk et al. studied the incidence of POCD in different age groups and at different time point after non-cardiac surgery. They found POCD in 36.6% young, 30.4% middle-aged, and 41.4% elderly patients. They also noticed significant difference between all age groups and the age-matched control subjects. POCD was still present at 3 months after surgery in around 6% of you and middle-aged patients and in 12.7% elderly patients [13]. Long term follow up of the affected patients have shown that up to 1% may exhibit "unresolved" POCD up to 2 years after surgery [14]. Ballard et al. found age to increase both the incidence and the duration [15]. They found cognitive impairment among elderly still after 52 weeks as compared to age-matched controls.

Age and preoperative mild cognitive impairment predispose for POCD [16–18]. Other factors that have been shown to increase the risk for developing neurocognitive side effects are the neurohumoral inflammatory surgical stress response, thromboembolism, ischemia (hypoperfusion, hypoxemia), re-operation, postoperative infection, polypharmacy, long lasting surgery and anaesthesia [12,13].

The neuro-biochemical mechanism behind the cognitive declaim is still not known [19]. Sato et al. performed MRi studies in patient having undergone breast cancer surgery and age matched controls [20]. The results suggest that changes in brain structure, particularly in the thalamus, may occur shortly after surgery and may be associated with attentional dysfunction. Rappold et al. found a negative relationship between higher plasma levels of the brain-specific protein glial fibrillary acid protein (GFAP) and cognitive performance at 1 month after non-cardiac surgery [21]. The involvement of neuroinflammation is increasingly supported from basic research [22]. Anaesthesia technique and drug choice seems to play only a minor role for prolonged cognitive impairment [23,24].

2.2. Anaesthesia and development of dementia

The question whether perioperative care and/or POCD may predispose for the development of dementia has also been raised [25]. The effect of anaesthetic drugs is studied in various experimental settings. In vitro and multi-dimensional NMR studies have shown that inhaled anaesthetics may promote amyloid β-peptide (AP) oligomerization and increase Ap-induced neurotoxicity [26,27]. Animal studies also provide evidence that exposure to inhaled anaesthetic agents can impair memory [28] and induces caspase-3 activation and increased levels of Aβ [29,30]. Altered calcium regulation has been identified as a possible mechanism for anaesthetic associated neurocognitive damage [31]. Potential neurodegenerative effects associated to surgery/anaesthesia are however complex and cumbersome to study in the clinical setting. Postoperative neurocognitive impairment in patients is generally considered to resolve. Subtle cognitive changes can persist for weeks or more but has generally been seen as reversible [32]. Whether surgery and anaesthesia potentially may accelerate the onset and progression of neurodegenerative dementia in patients at risk is not known [33]. Evered et al. found in long-term (7.5 year) follow up of patient having undergone cardiac surgery, coronary artery by-pass grafting, a significant higher prevalence of dementia as compared to controls [34].

2.3. Reducing potential risk for neurocognitive side effects associated to anaesthesia

There are studies that suggest that titrating anaesthetic depth with an EEG-based anaesthetic depth monitoring can improve not only early recovery, awakening but also improve more protracted recovery and reduce the number of patients showing neurocognitive side effects. It may reduce the occurrence of postoperative confusion/delirium, and also more prolonged postoperative cognitive decline, postoperative cognitive dysfunction [35–40]. The association between early and late cognitive side effects and possible neurodegenerative sequel is not known. The impact of oxygenation and perfusion of the brain during anaesthesia and surgery on the development of postoperative cognitive adverse effects is also discussed. Available studies show no significant correlation with "mild hypoxemia" or "hypertensive episodes" during surgery and anaesthesia for developing postoperative neurocognitive impairment [14,41,42]. There are however recent studies suggesting that the new near infrared