

## Cognitive Dysfunction after Surgery: An Emergent Problem

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### Abstract

Postoperative cognitive dysfunction (POCD) results as a large problem that causes a reduction in the quality of life and increases morbidity and mortality especially in elderly patients. The increased age of patients undergoing surgery has made evident the problem and several studies evaluated pathogenesis and implemented a targeted therapy.

This review analyses POCD, delirium and mild cognitive impairment (MCI) definition, risk factors and physiopathology with an analysis on anaesthesia technique influence. Unlike the postoperative delirium, POCD is more difficult to diagnose because of several tests that must be administered in the pre and postoperative period, even at a distance of time. Furthermore adequate depth of anaesthesia, monitored with Bispectral Index (BIS) or Electroencephalography (EEG), reduces the cognitive dysfunction incidence.

Currently the pathogenesis is not well understood although neuro inflammation plays a central role while the importance of anaesthesia techniques has not established.

**Keywords:** Cognitive dysfunction; Delirium; Mild cognitive impairment; Anaesthesia complication; Elderly

### Introduction

The continuous progress in anaesthetic and surgical techniques has made surgical procedures possible, also for elderly patients. It is estimated that 30% of all surgical procedures are performed on older people. However the postoperative complications are still frequent in this population bracket, although morbidity and mortality have been reduced. In fact improving the preoperative function and modifying the anaesthetic and surgical techniques, have led to the reduction of cardiovascular, metabolic, pulmonary and respiratory complications. But a worrying and growing problem has been identified: namely the postoperative neurological modifications, also known as the postoperative cognitive dysfunction (POCD), which can create difficulties to be prevented and even more difficulties to be treated [1-3].

The postoperative neurophysiological dysfunction is a risk factor that has not been taken into consideration, until a few years ago, namely from the time in which an increased number of elderly patients underwent anaesthesia and surgery. This problem is not something new and is perceived intuitively by family members. In fact, it is not uncommon to hear relatives saying "my husband or my life is not the same anymore after the surgical procedure". So this has been recognized as a relevant postoperative problem, not only from a perioperative aspect, but also in the long term since the cognitive impairment can progress to dementia [4], however a clinical definition of perioperative cognitive dysfunction was introduced in order to understand the diagnostic difference and their implication in prognosis and therapy.

In particular, this review will examine the definition of delirium, mild cognitive impairment (MCI) and postoperative cognitive dysfunction (POCD), although it will specifically focus its attention on the POCD.

### Delirium

The postoperative delirium is a common adverse event present in about 20 to 60% of elderly hospitalized patients. It occurs just after surgery but has a higher frequency in ventilated hospitalized Intensive Care Unit (ICU) subjects and it remains a relevant clinical problem and a true medical emergency [5,6]. Delirium appears rather early during the

postoperative period and most frequently during the first postoperative day, generally within 24 to 72 h after the surgical procedures and is characterized by a sudden change of attention and thought, with mental status fluctuations. Its duration varies from a few days up to a few weeks and is associated with a cognitive decline and increased morbidity and mortality [7].

It must be distinguished through the emergence of delirium in those patients who wake up from anaesthesia, which is transient and takes place in young people [8]. In many cases symptomatology disappears after a few days or weeks, but it can also persist and induce progressive cognitive decline leading to dementia. In the SAGES (Successful Aging after Elective Surgery) study, Inouye et al. reported biphasic behaviour in patients with and without cognitive decline: major cognitive decline occurred after one month, a comparable recovery of function was observed after two months, but, most importantly, an accelerated decline was observed, in patients, 36 months after anaesthesia or surgery [9]. Gross et al. confirm that POCD, following delirium, can accelerate the cognitive decline in Alzheimer's patients [10].

Delirium can appear in 3 forms: namely in the hyperactive, hypoactive and mixed form. The hyperactive form occurs in a quarter of the cases and can be easily recognised, while the hypoactive form appears with fatigue and reduced activity, which is often mistaken for sleepiness. Delirium can be diagnosed in the Intensive Care Unit (ICU) by utilising the confusion assessment method (CAM), while the Nursing Delirium Screening Scale is effective in the recovery room. Both processes have

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a high level of sensibility and specificity [11,12]. Although several pathologies have been identified as risk factors, for postoperative delirium, the physiological factors have an important role. Patients undergoing hip surgery regional anaesthesia have unexpected major risk factors, for postoperative delirium, while the recent administration of low doses of Dexmedetomidine has significantly reduced these complications, although there is no convincing evidence showing the effectiveness of a pharmacological treatment or prevention [13-15]. Delirium remains grossly unrecognized, during routine clinical practice, and should be handled as a true emergency.

### Mild Cognitive Impairment

Mild cognitive impairment (MCI) is a clinical entity characterized by greater memory impairment than expected, for age and education, and represents a transition phase between the normal age cognitive modification and the early state of the Alzheimer's disease [16,17]. The MCI can evolve in the POCD in the postoperative period so that a preoperative careful assessment by a neuropsychological test is indispensable to detect cognitive decline. Randolph et al. introduced a set of sensitive useful tests in making MCI diagnosis: the repeatable battery for the assessment neuropsychological status (RBANS) [18].

RBANS is a short and comprehensive neuropsychological battery, consisting of 12 sub tests administered individually in order to evaluate five different cognitive domains: immediate memory, visuospatial/constructional, language, attention and delayed memory. RBANS can be administered in 30 minutes obtaining an index score for each of five domains. This test allows evaluation in patients aged 20 to 80 years, suffering from organic, neuropsychological and psychiatric problems.

Kotani et al. validated the effectiveness of RBANS to assess neuropsychological status before and after administration of arachidonic acid (ARA) and docosahexaenoic acid (DHA). This study suggested that dietary supplementation improved MCI in patients with organic brain damage or aging [19].

The presence of preoperative cognitive impairment is a significant risk factor, for the onset of postoperative cognitive dysfunction. This problem is particularly relevant for anaesthesiologists. Trowbridge et al. has found a high MCI prevalence (up to 30%) in urogynecologic patients who are over 85 years [20]. Other authors rated an even higher prevalence in the elderly surgical population undergoing elective surgery [21]. The concept that surgical procedure and anaesthesia in patients with MCI might influence or damage neurological function has been highlighted by Silbert. In this study, all the patients were evaluated for the presence of MCI by the administration of seven neurological tests. The subjects with MCI have shown an increased incidence of postoperative dysfunction and a persistent cognitive decline between 3 and 12 months after surgery [22]. This conclusion has been confirmed by Liu et al. which demonstrated a higher incidence of cognitive decline that was mostly relevant in subjects exposed to sevoflurane when compared with subjects undergoing intravenous or epidural anesthesia [23].

### Cognitive Dysfunction

Cognitive function is a mental process of perception, memory, attention and information processing. The mind works out the external information, organises these inputs in order to obtain the orientation in time and space, develops the language, learning, concentration and executive function for the daily activity. A cognitive dysfunction is defined as a change in one or more of these functions: attention, working memory, perceptual and motor ability. However cognitive dysfunction

is a sneaky cognitive decline that is often difficult to diagnose and can only be revealed by means of a series of neuropsychological tests. The series of neuropsychological tests, used in ISPOCD1 and IPOCD2 (International Study of Postoperative Cognitive Dysfunction), are suitable and sensitive to detect POCD, during the postoperative period [24]. The tests were obviously developed in the English language and consequently they must be translated and adapted in order to be used in other countries.

Neuropsychological tests should be administered before and after surgery, at different times, because cognitive deterioration appears soon after surgery and diminishes after days or weeks, in most patients, but it can persist for several weeks, months and years [25]. The diagnosis is very difficult, since neuropsychological assessment should be administered preoperatively and then postoperatively, but the administration of these tests take time and should be performed in a better way by a specialist. The assessment of cognitive function is based on the results from the preoperative and postoperative tests. The exact time to administer the test is not clear. Sometimes the correct "practice effect", which can be present when performing neuropsychological tests, repeated over time, is used as a control group [26,27].

It follows that the exact incidence is not known and is likely to be underestimated, until the introduction of a simple and sensitive test. Most POCD studies have several methodological issues: namely the POCD definition is not standardized, the tests are not uniform and the tests are performed at different times during the postoperative period [28].

For example, the Mini Mental State Examination (MMSE) assesses reasoning, spatial-temporal orientation and memory but it cannot be used to study POCD. The ISPOCD Working Group conducted several studies and submitted a number of recommendations. The neuropsychological tests have been discussed and a consensus statement has been established [29,30]. POCD is defined as a score of more than 2.0 tests. The POCD reported incidence varies from 7 to 71%, after 7 postoperative days and 6-56% after two or three months.

In particular, the effects of anaesthetics are difficult to evaluate, in humans, due to the presence of pre-existing degenerative neurological processes, multiple organic comorbidity and surgical stress.

### Physiopathology

The physiopathology for POD and POCD is not understood very well. Despite the extensive research conducted on POCD, during recent years, the pathophysiological mechanisms remain unclear and have to be determined. However, progress has been made with regards to pathogenesis. Neuro inflammation seems to play a prominent role in the development of neurological cognitive decline, as demonstrated in the neurodegenerative disease, like the Parkinson's and Alzheimer's diseases, in relation to aged-related cognitive decline. Anaesthesia and surgery can act synergistically. The correlation between pro-inflammatory cytokines and delirium seems to be demonstrated. A reduction of cholinergic activity or an increase of dopamine, due to pro-inflammatory cytokines, with the activation of microglia induced neural injury and onset of postoperative delirium. An increase of interleukin-6, interleukin 1 $\beta$ , interferon, cortisol tumour necrosis factor-alpha (TNF- $\alpha$ ) has demonstrated that it reduces cholinergic activity [31,32]. Many biomarkers, in postoperative POCD, are correlated to postoperative inflammation and they are implicated in the progression of neurodegenerative disease and POCD. An increase of pro-inflammatory cytokines seems to represent a link between

inflammation and microglia priming responding to signals of other immune cells, such as mast cells, which can be peripherally activated by surgical trauma [33].

Microglia are immune cells that, when activated, play an important role in the development and in maintaining inflammation through the release of inflammatory mediators that cause neuronal damage, resulting in apoptosis and cognitive decline, especially in elderly patients [34]. Other inflammatory mediators have a correlation with the POCD: protein S100A8, modifications of pro-inflammatory and regulatory CD4+ T cells reduce the endotoxin immunity [35,36]. An increased deposition of amyloid peptide and astrocyte gliosis have been also implicated in short term POCD, by showing a similar mechanism in the Alzheimer's disease [37]. Neuro inflammation can be implicated since this has been experimentally highlighted by Wang et al. The administration of minocycline, namely an antibiotic that inhibits the pro-inflammatory cytokines production and promotes the release of anti-inflammatory cytokines from microglia, induces a reduction of cognitive impairment [38]. The administration of N-Acetyl cysteine could impair POCD through an anti-oxidative and anti-inflammatory effect that suppresses the activation of neural inflammatory cells by the production of glutathione, a potent anti-oxidative and anti-inflammatory agent [39]. Skvarc et al. undertook a promising study in order to evaluate the effect of orally supplemented N-Acetyl cysteine on the day before and four days after surgery. The drug suppresses or reduces the cognitive impairment [40].

These increased biomarkers for the inflammation in the central nervous system and peripherally correlate with the cerebral grey modifications during the in experimental studies on animals and humans. The target for anaesthesia is the central nervous system and the intraoperative cerebral modifications that can persist in the postoperative period, even when the effect of anaesthetic disappears.

In particular, the loss of cerebral grey matter has been demonstrated especially in those areas involved in the cognitive function in those patients undergoing surgery: hippocampus and cerebral cortex. Lower hippocampal volume or hippocampal volume reduction, after surgery, has been correlated with POCD as a perioperative risk factor [41]. Using a cerebral MRI, Sato et al. evaluated the grey matter volume in 32 patients undergoing surgery for breast cancer. During the immediate postoperative period, the grey matter volume reduction, especially thalamus, was correlated with a POCD decline, especially in the attention domain [42].

However during an experimental study on mice, Valentim et al. reported different effects in relation to different concentration of isoflurane. Lower concentration of anaesthetic seems to be more dangerous than higher concentration. In fact, a major apoptosis of hippocampal cells and spatial learning impairment has been reported in those cases where a lower concentration of isoflurane has been employed [43-45].

## Anaesthesia

Whether the type of anaesthesia can influence POCD is largely a matter of debate.

Volatile anaesthetic seems independent risk factors, at least, in some animal studies. Exposition of aged rats to volatile anaesthetic isoflurane can induce cognitive deficit, through the activation of hippocampal IL 1  $\beta$  by NF-kB signalling in aged rats [46]. However other authors have not confirmed the decline of spatial memory in young rats, after sevoflurane and desflurane exposition [47]. The

direct effect of volatile anaesthetics, on neuronal cells, has been demonstrated during experimental studies of inducing neurologic dysfunction that does not seem to be comparable with the different volatile anaesthetics. Isoflurane, a recently less utilized anaesthetic, has been demonstrated as being more cytotoxicity and apoptotic than desflurane and sevoflurane and can be retained as a contributory cause [48]. Conversely, propofol seems to have a protective effect by reducing the enzymatic cascades, which induces cytotoxicity. However, results between propofol and anaesthetic inhalation are elusive. Egawa et al. have not found significant differences on the POCD and the cerebral oxygenation, between propofol and sevoflurane, in patients undergoing lung surgery and the same results have also been confirmed by other authors, after minor surgery, highlighting the fact that inflammation is not the single cause [49,50]. Qiao et al. have found, in a group of patients undergoing resection for oesophageal carcinoma, a significant reduction of the POCD in subjects anaesthetised with propofol or after the administration of corticosteroids, thus highlighting the relevant role played by inflammation.

Two studies evaluated the effect of opioids in order to evaluate the effect of stress on POCD.

The effects of opioids have been marginally evaluated and only a few studies have been published. A study conducted on 622 patients, undergoing major abdominal surgery, evaluated whether the administration of fentanyl on bolus or the continuous infusion of remifentanyl, at 0.15 to 0.25 mg/Kg/min can modify the pro-inflammatory cytokines and the postoperative period. The depth of anaesthesia was monitored with BIS. The relevance of the study arises from a low incidence of POCD, namely 19.2%, with a lack of significance between the two groups, although the pro-inflammatory IL6 was higher in the fentanyl group, until the seventh day. A suppression of pro-cytokines, by morphine and other opioids, can reduce the expression of inflammation but it does not seem to have any effect on the POCD incidence [51].

Other studies obtained the same results. A comparison of high or low doses of fentanyl showed a higher incidence of POCD, but only during the first week, after three and twelve months while Rasmussen et al. have not demonstrated a difference in the POCD, in the remifentanyl or sufentanyl group, although the duration of ventilation and a low SvO<sub>2</sub> was correlated with postoperative cognitive decline [52,53].

The choice of loco-regional anaesthesia seems to be an optimal technique in order to reduce nociceptive afferents, postoperative pain and reduction of inflammation. The effect of spinal and epidural anaesthesia has been studied, especially in orthopaedic surgery, which is a type of surgery that is particularly present in older patients with preoperative cognitive decline. Several articles and reviews have been published but a definitive response is not clear, also in this case. However a conclusion cannot be reached despite a great number of prospective and randomised studies. The reason is due to the heterogeneity of studies: different types of surgery, methodology of studying POCD, evaluation timeframe and postoperative analgesia. In particular, most studies were undertaken in elderly patients, in orthopaedic surgery and different types of postoperative analgesia, especially morphine. A study, which was conducted very well by Rasmussen et al. Did not find any difference in the POCD incidence, between general, spinal or epidural anaesthesia, but the mortality was different, as predictable [54]. Davies et al. in a systematic review comparing general vs. loco-regional anaesthesia, in 16 random controlled study found only 4 studies that reported a difference between general vs. loco-regional anaesthesia: the old study by Hole reports a better result in loco-regional groups in line with the Mandal



study that reports a significant difference in MMSE, in verbal fluency and immediate and delayed memory tests. The limitation related to the studies is in respect of the number of patients, the different anaesthesia technique, epidural spinal and the study timing and tests employed in relation to the particular specific neurophysiological tests [55-57].

In the same year, Scott et al. evaluated the POCD incidence in patients undergoing total joint arthroplasty, in meta-analysis, that investigated 1,089 patients in 17 studies, but only two studies reported a control group. Despite the studies performed over a number of years, which had many differences in the administration of cognitive test and the type of anaesthesia, the surgery seems to show only little or no impact on the cognitive function, especially after 3 to 6 months from the hospital discharge. A reduction in the immediate verbal recall has only been reported in the early postoperative days [58].

### Risk factors

If anaesthesia cannot be a risk factor then what are the contributing factors? The risk factors can be correlated to patients. The leading causes are the frailty of the elderly patients, preoperative cognitive impairment, vascular dementia, Alzheimer's disease, alcohol or drug abuse and cultural level. Vulnerability to POCD can be related to the loss of volume in specific prefrontal and temporal areas and especially to the reduction of synaptic activity and reduction of brain neurotransmitters [59,60]. The existence of a different behaviour, between young and aging brains, is clinically obvious in an anaesthetised patient: the MAC or the effect of propofol and opioids concentration, during surgery, reduces with the increase in age. Until when and for what is the anaesthetic titrate dose required, especially in patients at risk or having POCD: an adequate depth of anaesthesia by monitoring, with BIS or EEG, puts the subject at a lower anaesthetic concentration thus reducing the probability of the onset of delirium and the incidence of POCD [61,62]. Another risk factor is the occurrence of intraoperative and postoperative hypoxemia and the uncontrolled postoperative pain [63,64]. It is a known fact that severe hypoxia damages the brain and the presence of long periods of low oxygen tension can induce cerebral damage. However, a large number of perioperative factors, in addition to those already mentioned, are linked to the POCD, namely fasting, fluid balance, sleep deprivation, pain and psychological trait.

### Conclusion

From the introduction of the POCD concept, by Bedford in 1955, several studies have been undertaken, recognising it as a large problem: reduction in the quality of life through the impairment of daily activity, increased morbidity and mortality between 1 to 5 years, especially after specific surgery: cardiac, orthopaedic and emergency surgery [65]. Since a high percentage of patients undergoing anaesthesia and surgery are elderly or very elderly, then it is important to look at the postoperative period for cardiovascular and pulmonary complications, but also to the postoperative cognitive dysfunction, delirium and POCD. The real impact and prevalence of this condition is not known as POCD but it can only be detected by neuropsychological test. Only delirium and a severe postoperative deficiency can be detected.

However although several researches have started to elucidate some black points of pathophysiology, few progress towards the prevention and therapy that has been achieved. There is no doubt that neuro inflammation plays a pivotal role in its onset but the exact role of anaesthesia and surgery is not well defined. Specific anaesthetics have been deemed to favour the postoperative cerebral modifications as a type of surgery but the results are inconclusive, especially if the POCD

is evaluated at distance of 3 to 12 months [66]. Clinical intraoperative and postoperative risk factors have been elucidated, but only specific studies have been undertaken for prevention or therapy. Strengthening intraoperative monitoring, with particular attention to cerebral oxygenation and depth of anaesthesia, specific neuro protective techniques or drugs are not currently available and sporadic publications have outlined the protective effect of some drugs. In particular, animal studies have shown that the administration of lidocaine inhibits the production of cytokines and, in humans, this effect is demonstrated by the administration of dexmedetomidine, which is able to reduce inflammatory response and early POCD [67-69].

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