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REVIEW

Early postoperative cognitive decline—are there any preventive strategies for surgical patients in the emergency setting?

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Abstract

Postoperative neurocognitive impairments following surgery are a growing concern, especially in the elderly population, since it is associated with a significantly increased risk of morbi-mortality in the postoperative period. Among them, delirium or the early postoperative cognitive decline is associated with a further risk of prolonged cognitive dysfunction and it may quicken long-term cognitive impairment or postoperative cognitive dysfunction (POCD). The current knowledge regarding preventive strategies for delirium is not focused anymore only on pharmacological and behavioral management strategies in the postoperative period, but also supports the preoperative cognitive training programs. Since preoperative cognitive evaluation and proactive interventions to optimize surgical patient outcomes are rather impossible in the emergency setting, what are the appropriate preventive strategies that can be implemented in day-to-day practice? In this review, we try to highlight the most recent experimental and clinical strategies, and outline the most relevant recommendations for clinicial practicioners based on the available data.

Keywords

Delirium; POCD; Preventive strategies; Emergency surgery

1. Introduction

Neurocognitive disorders arising after a surgical intervention are a heterogenous group of new cognitive impairments, which comprises both the fluctuating and typically short postoperative delirium and the long-term and more subtle problem of postoperative cognitive dysfunction (POCD) [1]. The incidence of early postoperative cognitive decline is estimated between 20% and 45% in elderly patients undergoing surgery [2]. In the absence of a universal definition and standardized assessment criteria, data concerning POCD incidence are rather scarce, although it may affect up to 54% of adults over 65 in the first week following surgery, with no regards to the type of surgery and/or anesthetic technique [1, 2].

Ever since the first reports of postoperative cognitive decline after cardiac and non-cardiac surgery were published as early as 1887 [3, 4], interest in this topic has continued among the scientific community as evidenced by a significant number of insightful papers [4].

Moreover, neurocognitive impairments can lead to an overall higher morbi-mortality and increase in healthcare costs [1]. Both health and economic burdens related to postoperative neurocognitive disorders are likely to increase in the future due to an ageing society, increasing life expectancy, as well as a growing surgical population over 65 [5].

Although several hypotheses have been proposed to be responsible for the pathophysiology of neurocognitive disorders, the entire mechanism is poorly understood [1, 4]. These include neuroinflammation triggered by surgical trauma, malfunction of the blood-brain barrier, which may be involved in a neural activity breakdown, as well as neurotransmitter abnormalities [6, 7]. This timeline of events can continue long after a surgical procedure and cessation of inflammation processes, thus contributing to a new cognitive impairment or escalate the preexisting one [1].

Various risk factors have been proposed to promote the development of these neurocognitive disorders, among which advanced age is constantly opening the list [1, 8]. Although constantly highlighted as risk factors, both neurocognitive decline prior to surgery and frailty syndrome couldn't be authenticated as unquestionable risk factors by the current evidence [9, 10]. This theory is supported by a long-term retrospective analysis which failed to demonstrate a speed up in neurocognitive decline after non-cardiac surgery even in patients with Alzheimer's disease [11]. Despite the fact that several biomarkers were identified as highly sensitive for neurodegenerative disorders, such as Apolipoprotein E4 (APOE-4), their presence was not found compatible with the development of postoperative neurocognitive disorders [12]. A slight relationship between plasma levels of cytokines, such as interleukin-

6 (IL-6) and S100 calcium-binding protein β (S100β), and postoperative neurocognitive disorders was identified, but no other inflammatory markers studied have shown any statistical involvement [13]. More recent reports indicate that tau protein/β-amyloid ratio increases in the cerebro spinal fluid after a surgical procedure, independent of the class of anesthetic used, additionally raising doubt about the foretelling quality of the biomarkers [1, 14]. Chronic inflammatory disorders such as diabetes mellitus, metabolic syndrome or atherosclerosis have been pinpointed as favouring factors for postoperative cognitive decline, as well as anesthetic drugs, duration of the surgical procedure and pain [15, 16]. No significant difference was found between emergency or elective surgery settings in regards to the incidence of early postoperative cognitive decline [17]. In a large prospective trauma patients study, more relevant predisposing risk factors were identified, such as preexisting dementia, cardiac insufficiency and multidrug regimen, and also relevant precipitating risk factors including cerebral edema, pneumonia and brain inflammation [17, 18]. In spite of these reports, the study models implemented and lack of homogeneous populations limit the clinical value of these risk factors for every day practice.

Successful prophylaxis and treatment of the cognitive dysfunctions following surgery have not been demonstrated, although prehabilitation and cognitive training are encouraged in an effort to optimize the postoperative cognitive outcome in elective surgery settings [4, 19, 20]. The current review will address an essential need to integrate ongoing research into delirium prevention for surgical patients in the emergency settings, since once delirium occurs, both pharmacological and non-pharmacological interventions have a slight effect on severity and duration of the episode or likelihood of recurrence.

2. Therapeutic interventions: from experimental to clinical findings

As already mentioned, neuroinflammation plays an important role in developing learning and memory disorders and is responsible for further cognitive decline in the postoperative period. In particular, high molecular group box 1 protein (HMGB1), which is abundantly released at the hippocampus level in surgical settings, seems to play the leading role in postoperative cognitive dysfunctions emergence and may represent a future marker for it [21]. In a murine study, elevated HMGB1 after surgery served as a molecular target for neutralizing antibody in order to alter its functional capacity and prevent thus postoperative cognitive dysfunctions [21, 22]. These results are endorsed by recent findings that HMGB1 level is raised in patients with postoperative cognitive decline after gastrointestinal surgery [23].

Recent data from animal studies demonstrates the harmful effects derived from reactive oxygen species (ROS) accumulation and oxidative damage on hippocampus and prefrontal cortex, leading to memory impairment [24]. Correspondingly, new cognitive impairments following coronary artery bypass surgery were reported in a human study, as a result of nitric oxide (NO) elevated concentration [25].

Another interesting hypothesis derives from the anti-inflammatory result of the vagal efferents and it implies that vagomimetic agents can limit neuro-inflammation [26]. One study in murine receiving the cholinesterase inhibitor physostigmine after a surgery procedure, exhibited a depletion in hippocampal IL-1β (Interleukin-1 β) and TNF α (Tumor necrosis factor α) concentration and hippocampal damage [1]. Even though anticholinergic drugs are well known for their involvement in the development of cognitive impairment, it is unclear if using vagomimetic agents in human population is beneficial [1].

Since inflammation is an important pawn in precipitating postoperative cognitive disorders, several trials proposed anti-inflammatory strategies. A murine study of surgery-induced cognitive impairment, focused on the aspirin effect on resolvins production in order to catalyse the resolution phase of inflammation, and reported an attenuated memory dysfunction [27]. Other animal studies directed the anti-inflammatory therapy also towards the cyclooxygenase 2 (COX-2) enzyme and demonstrated a decline of short-term deficits in recognition memory after surgery [28, 29]. Although there are no ongoing registered clinical trials analyzing the potential benefits of non-steroidal anti-inflammatory drug or selective COX-2 inhibitors in preventing cognitive decline after surgery, older studies showed encouraging results for parecoxib and celecoxib [1, 30, 31].

Recent research proposes the broad-spectrum antibiotic minocycline as an unconventional therapy for reducing cognitive impairment events, due to its anti-neuroinflammatory properties by blocking interleukin production [1, 32]. It is unclear if preoperative administration of minocycline is responsible for preventing postoperative cognitive decline, or rather just reducing memory impairment [32, 33].

As for the effects of the potent anti-inflammatory dexamethasone on incidence of postoperative neurocognitive decline, the current reports are highly variable, with encouraging results only in animal models [1, 4]. A randomized clinical trial of patients receiving dexamethasone intraoperative failed to demonstrate a benefit in both early and late cognitive decline following surgery [34].

Although there are currently no registered clinical trials, cytokine inhibition therapy may represent a hidden target for preventing neurocognitive decline in the postoperative period. Several animal studies have shown advantages following preoperative administration of anti-TNFα antibody, IL-1 or IL-6 receptor antagonist and reduced postoperative memory impairments [35–37].

In regard to antioxidative therapy, statins have been proposed to be valuable in improving neurocognitive disorders including both dementia and postoperative delirium, due to its ability to reduce the levels of oxidative species [38, 39]. Although currently there are no clinical studies underway to investigate this favourable result of statins, previous randomized controlled trials demonstrated a significant reduction on early postoperative memory impairment by using statin therapy [39, 40].

Another widely utilized drug with antioxidant properties and proposed for protective cognitive effects is *N-acetylcysteine* [41]. The Post-Anaesthesia *N-acetylcysteine* Cognitive Evaluation (PANACEA) trial is currently the single ongoing study

conducted to evaluate the usefulness of *N-acetylcysteine* in postoperative cognitive decline, and no results have been published by this time [42].

Although better known as an auxiliary scavenger treatment for acute ischemic stroke and as therapy for amyotrophic lateral sclerosis, edaravone may attenuate memory impairments as demonstrated in a murine study [43]. Due to its both anti-oxidative stress and anti-inflammatory effects, edaravone may also exhibit neuro-protective mechanism in humans, but the hypothesis is not sustained by any data at-present [4].

In an effort to improve the postoperative neurological outcome, an increasing number of studies have proposed dexmedetomidine as a neuroprotective agent [44]. As already demonstrated in animal experimental models, apart from being a well-known sedative, amnestic and analgesic, this well-known highly selective α2-adrenoceptor agonist can modulate neuroinflammation by increasing HMGB1 resolution through a vagomimetic action and reducing pro-inflammatory cytokines, possess an anti-apoptosis and anti-oxidative stress role [44, 45]. Several human studies compared dexmedetomidine infusion to placebo saline infusion during non-cardiac surgery and the results were encouraging [46–49]. In the intervention groups, researchers identified a lower level of pro-inflammatory cytokines, a significantly lower incidence of early postoperative cognitive dysfunctions, and also if delirium occurred the duration of the event was shorter in dexmedetomidine groups [46–49]. An important number of registered clinical trials examining the efficacy of dexmedetomidine on postoperative cognitive decline are ongoing, but so far, no data have been published [4].

According to recent data, the antiviral agent amantadine has also been proved to promote the production of glial cell line-derived neurotrophic factor (GDNF), an important neuroprotective agent involved in the modulation of glial growth and microglial activation [50]. In a rat model study, animals treated with GDNF showed an attenuated neuroinflammation profile, and also a reduction of learning and memory impairment after surgical intervention in the early postoperative period, compared to the control group [51]. At the moment there are no data to support clinical use of amantadine in humans.

Other candidate treatments proposed for preventing postoperative cognitive decline are local anesthetics such as lidocaine and bupivacaine [4]. Due to its quality in reducing peripheral inflammation, lidocaine was administered in bolus and infusion during both cardiac and spinal surgery, but the results were not convincing [52, 53]. Presently, there are two registered randomized controlled trials looking into the benefits of using local anesthetics in preventing postoperative cognitive decline, but no results have been published [4].

Due to its NMDA (N-Methyl-D-aspartic acid) receptor antagonism quality, ketamine has been proposed as an effective neuroprotector agent, although clinical data are rather ambiguous in regard to ketamine ability to prevent or improve postoperative cognitive impairment [54–56].

Melatonin has also been advocated in cognitive decline, due to its known properties of adjusting production of pro- and anti-inflammatory cytokines, and scavenging free radicals molecules [57]. Animal model studies evaluated exogenous melatonin effect after exposure to the volatile anesthetic isoflurane and the results indicated an improvement in the sleep-wake pattern due to circadian rhythm resetting [58, 59]. The published studies in human subjects validated the previous findings regarding the sleep-wake cycle and also indicated a preserved neurocognitive function in the immediately postoperative period in patients receiving melatonin [60, 61]. No noticeable impact on long-term postoperative cognitive dysfunction was observed [60].

Considerable attention has been recently paid to investigate the promise of cannabinoids as therapeutic agents in mediating inflammatory responses [62]. A murine study has demonstrated an improvement of the hippocampal-dependent memory loss of mice in the early postoperative period after they received agonists of cannabinoid receptor type 2 (CB2R) [63]. These findings corroborate with a diminished pro-inflammatory cytokines level in the hippocampus and prefrontal cortex several days after surgery [63]. At the present there are no human data on the consequences of cannabinoids on postoperative cognitive impairments, although this may stand for a future study subject as cannabinoids agents are suggested as treatment for a variety of neuropsychiatric disorders including depression, epilepsy, multiple sclerosis, Parkinson's disease, Alzheimer's disease [64, 65].

3. Current anesthetic strategies for preventing postoperative delirium in emergency settings

Because in emergency settings time is not our ally, the benefit of urgent intervention outweighs the need for cognitive and functional assessments as it would delay the time to surgery. Both emergent and urgent procedures may allow for a limited time of evaluation and medical intervention, and consequently expose patients at an increased risk for perioperative complications [66]. In order to early recognize vulnerable patients with high risk for postoperative delirium development, a brief evaluation of the cardiopulmonary status, prescribed and over-the-counter medication review, as well as nutrition status and bad habits are recommended, if at all possible [66]. Several studies pointed out the utility of biomarkers for preoperative risk prediction in developing postoperative cognitive impairments [67, 68]. While there is no strong evidence to promote measuring of an extensive panel of inflammatory markers to predict early or long-term cognitive disorders, there is reasonable data recommending the utility of preoperatively CRP (C-reactive protein) levels in patients' risk stratification to develop postoperative delirium [69–71]. According to one of these studies, patients with preoperative CRP levels of 5 mg/dL showed a 4.8-fold higher risk for delirium compared to those with lower CRP levels, and each 1.0 mg/dL increase in postoperative CRP levels was correlated with up to 15.8% increase in postoperative delirium risk [71]. The evaluation of CRP perioperatively may facilitate to pinpoint higher risk patients and proceed to an individualized intervention.

Although shaping anesthetic techniques was hypothesized to decrease the incidence of early cognitive disorder, both spinal and general anaesthesia seem to involve similar risks [72–74]. Changes in brain functional connectivity has been related to

both peripheral nerve block and spinal anesthesia as a result of deafferentation on pain sensitivity [75, 76]. In regard to choosing the right intravenous anesthetic agent, there is no current answer given by literature [77]. Although none of them has proven a significant benefit in preventing postoperative cognitive impairments, a possible neuroprotective effect was attributed to propofol [77]. As for volatile anesthetics, there are some studies which suggest a favorable cognitive outcome when using volatile agents like sevoflurane or desflurane, or at least indicate them to be a safer alternative for patients with preexisting cognitive disorders [66, 78–80]. Despite the fact that the current trend in anesthesia favours opioid-free anesthesia, there is no published evidence of the impact of this technique on neurocognitive impairment [81].

Even if there is moderate evidence to support a link between benzodiazepines and a new neurocognitive decline, current reports recommend avoiding them, particularly in high-risk patients as they can augment the severity and prolong the duration of the neurocognitive impairment [4, 82]. In comparison to benzodiazepines, dexmedetomidine used in bolus and infusion combination considerably lowered the incidence of delirium or at least reduced the intensity of the episode following non-cardiac surgery [47–49]. Furthermore, dexmedetomidine facilitated early extubation in patients who required mechanically ventilation in ICU (Intensive Care Unit) [83].

Another intraoperative approach assessed in a small number of studies implies monitoring depth of anaesthesia through neuromonitoring. Bispectral index (BIS) and more recently, entropy guided anaesthesia was proposed to influence the incidence of both early and long-term cognitive impairment [4, 84, 85]. Furthermore, a favourable outcome is more likely when cerebral oxygenation monitoring is associated [86].

In postoperative settings, we may be tempted to administer antipsychotic medication as prophylactic treatment for delirium. This practice is neither upheld nor encouraged by current evidence [87].

Adequate pain management has been advocated to reduce postoperative complications, including postoperative cognitive impairment, although no robust evidence in regard to prescription has been suggested [66]. Research published data is rather conflicting. Pain control in patients with preexisting neurocognitive impairment may be even more challenging due to inefficient communication and poor understanding by the health staff [66]. Although opioids are linked to delirium development, there is strong evidence that tramadol and meperidine can increase the risk of delirium compared with other opioids [88]. Postoperative patient-controlled epidural analgesia may be more efficient during the immediate recovery period, but its presumed benefits of prevention for neurocognitive impairment are not convincing [4, 89]. As for parenteral analgesia, COX-inhibitors like parecoxib have been successfully linked with the decrease of postoperative delirium incidence [89].

4. Recommendations

Despite extensive research efforts on the subject, early postoperative cognitive decline, especially in emergency settings, remains poorly understood and explained. Even if delirium has an unclear pathophysiology, several risk factors may precipitate delirium occurrence. In an effort to prevent this neurocognitive impairment, our primary target in the perioperative period may be the modifiable risk factors. Minimally invasive surgery or laparoscopic procedures are more advisable as they seem to limit the inflammatory response and thus reduce the likelihood of developing postoperative cognitive decline.

If possible, discuss preoperative with the patient and their family about the potential occurrence of neurocognitive impairments, particularly for high-risk patients.

Although no definitive peri-operative management has been shown to play a decisive role, several strategies may be considered. The routine use of benzodiazepines should be discouraged, especially for elderly population, and reserved only for anxiety alleviation and patients at-risk to develop alcohol withdrawal syndrome. Depth of anesthesia monitoring and monitoring of cerebral oxygenation in selected patients, may be considered if available, although further studies are needed in order to establish a significant role for them in decreasing postoperative neurocognitive impairment. General inhalational anesthesia is preferable to intravenous anesthesia, and among the volatile anesthetics, both sevoflurane and desflurane were found to be superior to other inhalational anesthetics. Although the present trend is to avoid opioid administration, there is no strong evidence to support this approach for a better cognitive outcome. Since there are few scenarios which permit the replacement of opioids entirely, especially in emergency settings, we consider that judicious use of opioids may reduce unwanted postoperative risks.

In regards to choosing the anesthetic technique, there are no potential benefits described for regional anesthesia, with reference to cognitive function. Also, in emergency settings, there are few scenarios when the surgical procedures may be safely performed under regional anesthesia. Regardless the anesthetic technique far more important is hemodynamic optimization, since normal tissue perfusion may ensure a better cognitive function and also maintaining normoxemia and normocapnia. Normothermia and normoglycemia are also strongly advocated, especially in cardiac surgery and neurosurgery. For patients requiring mechanical ventilation support in the immediate postoperative period, dexmedetomidine proved to be so far a unique sedative agent as it can reduce the incidence of early postoperative decline.

In the postoperative period other factors may appear to contribute as well. Among them, optimal pain control through a multimodal approach which should include reduced doses of opioids and non-opioid analgesics, maintaining a proper sleep wake schedule, ensuring correct nutrition, limiting the use of intravenous lines when possible, seem to be strongly related to a better and faster recovery during the postoperative period, and thus minimizing the length of stay.

Last but not least, we must not forget that hospital environment is often fast-paced, and healthcare providers are associated with unfamiliar faces. Therefore, is up to us to improve confidence and offer reassurance to the patient by creating a positive and quiet environment, allow family visits at patient's bedside, as well as using the appropriate tone and form of language in order to communicate efficient may strengthen the bundle of preventive measures for postoperative

delirium.

Postoperative cognitive outcome is strongly related to the entire perioperative period, and even in emergency surgical settings a multicomponent intervention is more advisable, although current evidence in this field is rather scarce. Further studies are necessary to develop effective preventive strategies and evidence-based treatment protocols to reduce postoperative delirium in patients undergoing emergency surgical procedures.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AMC, RU—designed the research study. AMC—performed the research. CC, LM, RU and IMG—analyzed the data. AMC and LM—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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