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Diagnostics, prevention and treatment of postoperative delirium: a literature review

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Abstract

Background: Postoperative delirium (POD) is one of the most common complications of major surgery that can occur in patients of any age, yet it remains largely underdiagnosed and undertreated, increasing the length of the hospital stay and the risk of death.

Aim: To review the latest studies on POD and provide summarized information regarding its diagnostics, prevention, and treatment in current practice.

Methodology: The search was conducted in "MEDLINE" ("Pubmed") and "ScienceDirect" databases using predetermined keywords: postoperative delirium, prophylaxis, incidence, prevalence, prevention, management, treatment, precipitating factors, predisposing factors, risk factors, diagnostic tools. 28 articles published since 2007 were included in this literature review.

Results: Many risk factors of POD are non-modifiable, thus early detection is key to improving patient outcomes. Confusion Assessment Method and its adaptations are the best bedside modalities for both screening and diagnosis. There are pharmacological and non-pharmacological prophylactic interventions, however, antipsychotic prophylaxis can significantly reduce not only POD risk, but also its intensity and duration. Additionally, some biomarkers and instruments are emerging as potential tools for detecting and monitoring POD. The treatment of POD is most associated with the use of antipsychotics as well.

Conclusion: There is still a lot to be desired when it comes to evidence-based therapeutic interventions for postoperative delirium, therefore further research is needed to make reliable use of them in everyday practice and standardize care.

Keywords: postoperative delirium, postoperative complication, prediction care.

1. Introduction

Postoperative delirium (POD) is one of the most common unfavorable postoperative complications that can occur at any age, but mostly among elderly patients, who are experiencing surgery [1]. Brooks et al. (2014) revealed that it complicates the postoperative course by increasing the length of the hospital stay: 11.8 days compared to 3.58 days for patients that did not develop POD, and these patients were discharged more often to a nursing facility (58% versus 18%) [2]. The prevalence of postoperative delirium after general surgery can range from 70% to 87% amongst elderly patients; nevertheless, studies have shown that 40-70% of delirium cases remain unrecognized [3]. This becomes the major field of interest, since the population of older adults is growing and postoperative delirium often becomes unidentified, which leads to other problems, such as not receiving proper treatment as soon as possible [2]. There are many causes of this multifactorial syndrome and they can be divided into two groups: factors that are related to the patient (predisposing), and the ones who trigger the onset of delirium (precipitating factors). Predisposing factors are older age, male sex, comorbidities and any kind of preoperative cognitive impairment. The most impactful precipitating factors are surgery, anesthesia, postoperative pain, anemia, drugs with anticholinergic effect and prolonged bed rest. The successful identification, prevention and treatment of risk factors for POD are associated with a lower incidence of this serious complication and a more suitable patient care. [4] A systematic review and meta-analysis (n=7738) by Hamilton et al. found that patients who develop POD are at increased risk of death [5]. Out of 21.5% patients that developed postoperative delirium, 21.8% died, compared with 8.7% mortality rate for non-delirious patients [5]. Postoperative delirium has drawn significant global interest and a considerable amount of research on its management has been conducted, yet there is still space for improvement. The goal of this literature review is to analyze the most recent data in prevalence, prevention, risk factors, diagnostic tools and treatment options of POD.

2. Materials and methods

The search was performed in "MEDLINE" ("Pubmed") and "ScienceDirect" databases. Keywords used were *postoperative delirium, prophylaxis, incidence, prevalence, prevention, management, treatment, precipitating factors, predisposing factors, risk factors, diagnostic tools.* A total of 12 894 articles were identified of which 28 were included in the literature review. Article inclusion criteria were: written in English language, relevant to the topic, less than 15 years old, containing studies with adults only, patients diagnosed with postoperative delirium after any type of surgery, article type: original research article, meta analysis, systematic review. Article exclusion criteria were: not written in English language, irrelevant to the topic, more than 15 years old, animal studies, studies containing patients younger than 18 years old, patients not diagnosed with postoperative delirium, article type: literature review.

3.Results

3.1 Risk Factors

Many risk factors for delirium are unable to be modified by perioperative providers, but several preventative strategies have been demonstrated to reduce the incidence of POD. Anesthesia providers should prioritize the prevention highly, as there are very few evidence-based therapeutic interventions once a patient develops delirium. The most prevalent predisposing and precipitating factors are specified in Table 1, only the novel ones that require additional investigation are described in the following section.

Predisposing factors			Precipitating factors	
Prevalent	**Neuropsychological**	**Comorbidities**	**Related to the operation**	**Medications**
Old age	Cognitive impairment	Hypertension	Surgical difficulty and duration	Benzodiazepines
Severity of illness	Dementia	Heart failure	Hypothermia	Antihistamines
Alcohol or drug abuse	Structural disease	Ischemic heart disease	Transfusion	Opioids
History of falls	Prior stroke	Chronic obstructive pulmonary disease	Glycemic control	Sedative-hypnotics
Functional impairment	Depression	Obstructive sleep apnea	Postoperative anemia	General anesthetics
Living in institution	Previous delirium	Smoking	Postoperative pain	
		Diabetes mellitus	Renal insufficiency	
		Malnutrition	Atrial fibrillation	
		Low albumin	Infection	
		Chronic kidney disease	Hypoxemia	
		Electrolyte deviations		

Table 1. Predisposing and precipitating factors associated with postoperative delirium [8].

Yang et al. (2016) described the relationship between preoperative psychoactive medications and postoperative delirium [6]. The risk of POD in patients that were taking psychoactive medicines preoperatively was reported to be more than six times the risk of patients without these drugs [6].

Patients that were taking more than three medications preoperatively also had a higher risk of developing POD after hip fracture surgery than patients that were taking fewer [6]. The main drugs to avoid are the ones with anticholinergic effects and benzodiazepines. These medications may interfere with neurotransmission or neuronal control of inflammation and, thus, precipitate delirium development. Observational studies have shown that perioperative benzodiazepine administration is associated with 2 to 2.5 times higher risk of POD [6]. Subanesthetic doses of ketamine can cause psychosis and increased risk of POD, thus it is recommended to avoid it as much as possible. Out of opioids, only meperidine has been associated with the development of POD, while differences in other opioids appear small [6]. Additionally, Gaudreau et al. (2005) found that patients exposed to daily doses of morphine higher than 90 mg were 2.1 times more at risk of developing POD than those who were exposed to smaller doses [7].

It has also been discovered that the number of medical comorbidities and American Society of Anesthesiologists (ASA) physical status class 2 and 3 were important factors in delirium risk assessment [6]. They should be closely monitored because of the increased POD risk [6].

Major surgery can be regarded as a risk factor for POD, as well. Studies reported that patients with cognitive impairment were more prone to developing delirium after hip fracture surgery (OR 3.21, 95% CI 2.26-4.56) [6]. Therefore, cognitive testing should become a part of the standardized program for preoperative clinical assessment.

Fluid fasting is a necessary procedure before operative treatment to allow gastric emptying, but prolonged fasting (>6h) results in dehydration and unnecessary use of intravenous fluids [8]. A large cohort study found that fluid fasting more than 6h is an independent risk factor for developing POD [8].

3.2 Diagnostic Tools

The diagnostics of postoperative delirium has no algorithm, although there are some measures that can be taken to predict and prevent it. POD must be assessed as soon as possible; in that case, there are tools that can be performed quickly and without difficulty. DSM-5 (Diagnostic and statistical manual of mental disorders 5 version) describes the main characteristic of delirium as a disturbance in attention and awareness [1]. Other tools, such as Richmond Agitation-Sedation Scale (RASS), can also assist with detection, since the DSM-5 guidance notes state that critically reduced level of arousal (of acute onset) above the level of coma should be considered as having serious distraction and therefore as having delirium [1].

Arguably the most efficient bedside evaluation tool, with both high sensitivity and specificity, is Confusion Assessment Method (CAM) [4]. The CAM algorithm consists of 4 features: (1) acute change in mental status with a fluctuating course, (2) loss of attention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium is diagnosed when features (1) and (2) are confirmed and (3) or (4) optional [1]. There are also adapted CAM versions for specific patient groups, such as Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), the Brief Confusion Assessment Method (bCAM) for emergency department patients and the 3-Minute Diagnostic Interview for Delirium Using the Confusion Assessment Method (3D-CAM) for general medical patients. These instruments can be used both to verify delirium in suspected cases or for screening in high-risk populations, also quick methods can encourage screening in low-risk individuals [5,9]. However, healthcare personnel needs to be trained to achieve expected accuracy of CAMs [9].

Diagnostic tools are indispensable in clinical practice, but previous studies have shown evidence of biomarkers for revealing and monitoring of postoperative delirium. D. Hauer et al. (2012) found that patients with acute postoperative cognitive dysfunction (ACD)/delirium had higher postoperative inflammatory IL-6 levels on the first postoperative day than patients without acute brain dysfunction [10]. Furthermore, cardiac surgery patients who developed postoperative ACD/delirium had significantly lower preoperative plasma 2-arachidonoylglycerol (2-AG) levels, which is neuroprotective endocannabinoid, both preoperatively and on the first postoperative day [10].

Serum protein S100 was also found to be a diagnostic marker by Al Tmimi et al. (2016) in the trials that observed the time course of S100 protein and the incidence of postoperative delirium [11]. The investigation was made before and during surgery, and postoperatively. It was found during postoperative examination, that in 79% of the patients who developed POD, serum concentrations of S100 protein were below 120 pg/mL. However, further research is required to apply these findings in practice [11].

Electroencephalography (EEG) can also be used as an objective diagnostic instrument for delirium. Sleigh et al. (2020) describes abnormal brain response – burst suppression – as a marker which is not seen in healthy physiology and can lead to cognitive function disorders postoperatively [12]. 15 of 20 patients that had postoperative delirium after cardiac surgery, showed a burst suppression EEG pattern throughout the surgery. These findings are very promising as EEGs are easily obtained in practice, but still more research is needed use EEG as a diagnostic tool for POD. [12]

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3.3 Management

The treatment of delirium is mainly associated with the use of antipsychotics, however when it comes to it occurring postoperatively many other treatments are being investigated and the majority of studies are directed towards prevention rather than treatment. Tagarakis et al. (2012) compared the effect of delirium reduction between haloperidol and serotonin 5HT-3 (5-hydroxytryptamine receptor) antagonist ondansetron in cardiac surgery patients [25]. No statistically significant differences were observed between both intervention groups, as haloperidol improved delirium severity test score by 64% and ondansetron by 61%, however, there was no placebo group to compare these outcomes with as it seemed unethical to leave some of the delirious patients untreated. [25] Another trial was performed in order to find if quetiapine would prove to be efficient in managing POD [26] . It was shown that delirium severity could be reduced quicker when compared to the placebo, mostly due to the improvement of noncognitive aspects of delirium. In general, quetiapine was well tolerated since only one patient was withdrawn from the study due to complains of sedation. [26]

Moreover, it was shown that morphine could be useful when treating the hyperactive type of postoperative delirium. Atalan et al. (2013) compared treatment with morphine and haloperidol showing that those who were given morphine were significantly less likely to need additional sedative medication [27] . There were no statistically significant differences in delirium duration, hospital mortality and length of stay between both groups. However, it was conducted that those patients who received morphine were significantly less likely to be agitated when measured with RASS (Richmond Agitation-Sedation Scale), therefore proving that morphine is a suitable alternative in such circumstances. [27]

Fluvoxamine, as SSRI (Selective Serotonin Reuptake Inhibitor), was also observed to have a positive effect on postoperative delirium [18]. 3 elderly delirious patients were admitted to the psychiatric department after becoming excited postoperatively. They were treated with a 50 mg dose of fluvoxamine and benzodiazepines, for 2 of the patients the dosage of fluvoxamine was increased later. In all three cases a dramatic improvement was observed when measured with DRS (delirium rating scale) [18]. This proposed a hypothesis that sigma-1 receptors could play a role in delirium mechanism and it could be an alternative therapy to antipsychotics. [18] Due to the complexity of postoperative delirium syndrome no therapy is considered to be flawless, however various psychotropic medications could play role in the management of this condition.

3.4 Prevention

Prevention of postoperative delirium can be categorized into risk stratification, risk reduction, early diagnosis and treatment. With appropriate risk stratification, POD could be managed through risk reduction measures and prophylactic interventions [13]. A reasonable percentage (up to 40%) of postoperative delirium is thought to be preventable, but to reach success, all perioperative disciplines should be involved in the effective identification of high-risk patients [16]. Unfortunately, not all effective POD prevention strategies are provided routinely to every surgical patient during their perioperative course [13].

Delirium prevention involves multicomponent evidence-based interventions. Successful program for POD prevention consist of early mobilization, pain management, decreased use of restraints, promoting early communication, medication review, sleep enhancement, nutrition and hydration optimization, and restoration of hearing aids and eyeglasses [8]. Research has found that this type of protocol is associated with lower incidence of postoperative delirium, shorter hospital stay and greater patient satisfaction [14].

The novel use of dexmedetomidine for decreasing the risk of POD was controversial, thus randomized trials with dexmedetomidine in adult surgical patients were conducted [15]. Dexmedetomidine is a highly selective a2-adrenoreceptor agonist, which has sedative, amnestic, sympatholytic and analgesic effects [17]. A study conducted by Wang et al. found that intraoperative dexmedetomidine administration is associated with significantly lower concentrations of stress hormones, CRP (C-Reactive Protein) and tumor necrosis factor-α after surgery [13]. Dexmedetomidine was associated with a significant reduction in POD incidence for cardiac and non-cardiac surgical patients ($p<0.01$) [15]. There is a strong recommendation in ICU (Intensive Care Unit) mechanical ventilation protocols to use sedation with dexmedetomidine as a better choice in terms of the risk of POD compared to lorazepam, midazolam, propofol or morphine [17].

Light sedation is the key to prevent POD. In that case, EEG can be used as a tool to avoid too deep levels of anesthesia [8]. Several large studies evaluated whether EEG helps to reduce the incidence of postoperative delirium and, subsequently, found it beneficial for targeting the depth of anesthesia. While the choice of anesthetic agent does not significantly impact postoperative delirium, the depth of anesthesia does [13].

Appropriate pain management can be considered a preventive measure, as an association between inadequately handled pain and POD development has been established. There is a theory that poorly controlled pain leads to elevated stress response and altered neurotransmission [17]. A number of observational studies have found that preoperative pain is associated with 1.5 to 3 times higher risk of POD, and escalating pain scores have consistently been shown to increase delirium rates [16, 17]. Many studies recommend multimodal analgesia and peripheral nerve blocks as an effective method to improve postoperative pain control and reduce delirium incidence. A study by Rengel et al. have found lower incidence of POD in patients who received the femoral nerve blockade compared to patient-controlled analgesia after total knee replacement surgery [14]. The effective way to prevent inappropriate medication that can lead to postoperative delirium would be to use multimodal analgesia and opioid administration protocols, yet it remains a suggestion and further studies must be conducted [13].

Many drugs have been studied for prophylaxis feasibility, although this is still a major field that needs investigation. Paracetamol and NSAIDS (Non Steroidal Anti Inflammatory drugs) are the components of multimodal analgesia after surgery, moreover these drugs may prevent POD by directly alleviating neuroinflammation [17]. An observational study by Mu et al. found that intraoperative as well as postoperative parecoxib administration reduced the risk of delirium from 11% to 6% [17]. Positive findings were also revealed in a clinical trial of cardiac surgery patients, where postoperative paracetamol intake reduced delirium risk from 28% to 10% [17].

Another example could be corticosteroids: in a recent cardiac surgery trial Tao et al. reported that 100 mg of dexamethasone administered intraoperatively can reduce POD incidence by 20% [8]. Furthermore, a recent meta-analysis reported that perioperative melatonin administration reduces the risk of developing POD even to 40% [13].

Antipsychotic prophylaxis of postoperative delirium

Haloperidol is widely explored regarding this topic with results being ambivalent. In 2012, Wang et al. showed that the prophylactic use of 0,5 mg bolus of haloperidol and continuous infusion of 0,1 mg/h for 12 hours was beneficial [18]. It was found that the incidence of POD was decreased from 23.2% (control group) to 15.3% (haloperidol group), the number of delirium free days was longer and length of ICU stay was shorter [18]. However, results of this study were not confirmed by the other two trials. The severity, persistence and incidence of POD have not been improved significantly by the prophylactic use of haloperidol [19, 20]. A significant reduction of the incidence of POD was found in the subgroup of patients after esophagectomy. [20]. Such conflicting results could be caused by treatment regimen in one of these studies: haloperidol was given only 1 time per day with 2.5 mg dosage [19]. However, with a higher one-time dose administered, no adverse drug effects were noticed. [19]

Olanzapine was also proven to be an effective medication when given beforehand. Larsen et al. (2010) determined that administering 10 mg of olanzapine perioperatively significantly decreases the incidence of POD compared with the placebo group [21]. However, those olanzapine group patients who became delirious, remained in such state significantly longer when compared with the placebo group. [21] Another atypical antipsychotic, risperidone was investigated when patients were given 1 mg of risperidone sublingually just at the time when they regained consciousness after cardiac surgery with cardiopulmonary bypass [22]. The incidence of delirium was significantly reduced from 31.7% (placebo group) to 11.1% (intervention group). [22]

A 2013 meta-analysis by Teslyar et al. suggests that the prophylactic use of both typical and atypical antipsychotics (olanzapine, risperidone, and haloperidol) could reduce delirium risk by 50% [23]. Moreover, in one of the included studies it was shown that even if haloperidol would not reduce the risk of incidence, it could be helpful with delirium intensity and duration. [23] Another meta-analysis concluded that despite the positive effect of Haloperidol on the incidence of delirium, overall hospital stay and intensity of delirium were not reduced [24]. It was also determined that antipsychotics must be given at least to 8 patients in order to prevent one case of delirium [24].

Study	Study type	Surgery type	Sample size	Medication	Incidence of delirium	Other outcomes
Wang et al, 2012 [18]	Prospective, randomized, double-blind, placebo -controlled trial	Noncardiac surgery	457	Haloperidol	Decreased significantly	Shorter intensive care stay, more delirium free days, drug well tolerated
Fukata et al, 2014 [19]	A randomized, open-label prospective trial	Gastro - Intestinal or orthopedic	119	Haloperidol	Decreased insignificantly	No effect on severity and persistence, no side effects registered
Khan et al, 2018 [20]	Randomized double-blind placebo-controlled trial	Thoracic	135	Haloperidol	Decreased insignificantly	Incidence significantly decreased in esophagectomy subgroup
Larsen et al, 2010 [21]	A randomized, controlled trial	Orthopedic	495	Olanzapine	Decreased significantly	Delirium lasted longer and was more severe in olanzapine group
Prakanrattana et al, 2007 [22]	Randomized, double-blinded, placebo-controlled trial	Cardiac surgery with cardiopulmonary bypass	126	Risperidone	Decreased significantly	Time from opening eyes to following commands an independent delirium risk factor
Teslyar et al, 2013 [23]	Meta-Analysis	Various	1491	Typical and atypical antipsychotics	Decreased significantly	All but one of the included studies showed reduced delirium severity and length in the intervention group
Gilmore et al, 2013 [24]	Meta-Analysis	Various	1491 patients	Typical and atypical antipsychotics	Decreased significantly	Delirium duration, severity, hospital stay length did not change

Table 2. Studies on prophylactic use of antipsychotics and their outcomes in postoperative patients.

4. Conclusions

Postoperative delirium is one of the most common complications of major surgery amongst elderly patients, yet it still remains largely underdiagnosed and undertreated, increasing the length of the hospital stay and putting patients at an increased risk of death. In this paper, we gave more attention to the emerging risk factors that perioperative providers should be aware of, but further research is still needed to establish a more reliable relation. As the majority of risk factors of POD are non-modifiable, early detection with specific biomarkers or assessment tools becomes the key to improving patient outcomes.. When it comes to POD prevention, the most explored is antipsychotic prophylaxis, so far pointing out that either typical or atypical antipsychotics could significantly reduce not only POD risk, but also its intensity and duration. Consequently, the treatment of POD is most commonly associated with the use of antipsychotics as well. Nevertheless, there is still a lot to be desired when it comes to evidence-based therapeutic interventions for postoperative delirium, and much further research is needed to make reliable use of them in everyday practice.

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