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FAKTORI RIZIKA ZA NASTANAK POSTOPERATIVNOG DELIRIJUMA

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SAŽETAK

Pojava postoperativnog delirijuma (POD) prepoznata je poslednjih decenija kao važan klinički sindrom, naročito kod starijih bolesnika koji se podvrgavaju hirurškom lečenju. Cilj ovog preglednog rada se odnosio na ispitivanje preoperativnih, intraoperativnih i postoperativnih faktora koji mogu da dovedu do nastanka POD. Faktori rizika za nastanak POD su brojni, a što je najznačajnije, mnogi se mogu modifikovati. Neki od najznačajnijih faktora rizika za nastanak POD su starije životno doba, zloupotreba alkohola, preoperativno lošiji funkcionalni i kognitivni status, prisustvo depresije i demencije. Veća učestalost javljanja POD zabeležena je kod pacijenata podvrgnutih kompleksnijim operativnim zahvatima kao što su kardiohirurške, vaskularne i ortopedske operacije frakture kuka. Uočeno je da nakon hitnih operativnih zahvata POD se 1,5 do 3 puta češće javlja nego kod elektivnih planiranih operativnih procedura. Takođe, intraoperativno krvavljenje i primena transfuzije su identifikovani kao značajni faktori rizika za nastanak POD. Da bi se izbegli kognitivni deficiti uzrokovani dužom ekspozicijom anesteziji, istraživanja su pokazala da titracija anestetika praćenjem bispektralnog indeksa, kao i evociranih auditivnih potencijala, može smanjiti prekomernu izloženost anesteticima i samim tim smanjiti rizik od postoperativne kognitivne disfunkcije. Poznavanje faktora rizika i identifikacija pacijenata sa povećanim rizikom predstavljaju osnovu strategije za prevenciju ovog sindroma. Trenutni dokazi sugerišu da perioperativno izbegavanje upotrebe benzodijazepina, kao i adekvatna perioperativna kontrola bola, predstavljaju ključne mere za redukciju rizika od POD.

Ključne reči: postoperativni delirijum, kognitivni deficit, faktori rizika, starije osobe

Uvod

Delirijum se prema Međunarodnoj klasifikaciji bolesti (MKB-10, F 05) definiše kao etiološki nespecifičan organski cerebralni sindrom koji karakterišu istovremeni poremećaji svesti i pažnje, percepcije, razmišljanja, pamćenja, psihomotornog ponašanja, emocija i ritma budnost-spavanje (1). Pojava postoperativnog delirijuma (POD) prepoznata je poslednjih decenija kao važan klinički sindrom, naročito kod starijih bolesnika koji se podvrgavaju hirurškom lečenju (2). Klinička prezentacija ovog sindroma veoma je varijabilna. Najčešće se klasifikuje na osnovu motornih i pridruženih psihomotornih karakteristika. Pacijent može imati hiperaktivni oblik delirijuma, koga karakterišu nemir, konstantni pokreti i agitacija, ili hipoaktivni delirijum koga karakterišu usporenost ili nedostatak pokreta, nereagovanje i oskudne govorne sposobnosti. Kod nekih pacijenata može se javiti mešoviti tip poremećaja, odnosno javlja se hiperaktivna i hipoaktivna faza u kratkom vremenskom periodu (2). U većini do sada objavljenih istraživanja POD najčešće nastaje prvog postoperativnog dana, ređe drugog ili trećeg, a simptomi najčešće traju od 1 do 3 dana (2,3). Ovaj sindrom je čest problem kod bolesnika u jedinicama intenzivnog lečenja (JIL) i udružen je sa važnim kliničkim ishodima, uključujući povećan broj dana provedenih na mehaničkoj ventilaciji, produženu hospitalizaciju, veće troškove lečenja i smrtnost (4,5).

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RISK FACTORS FOR THE OCCURRENCE OF POSTOPERATIVE DELIRIUM

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SUMMARY

The occurrence of postoperative delirium (POD) has been recognized in recent decades as an important clinical syndrome, especially in elderly patients undergoing surgical treatment. The aim of this review was to examine the preoperative, intraoperative and postoperative factors that can lead to the occurrence of POD. The risk factors for developing POD are numerous, and most importantly, many can be modified. Some of the most significant risk factors for the occurrence of POD are older age, alcohol abuse, preoperatively worse functional and cognitive status, presence of depression and dementia. A higher incidence of POD was observed in patients undergoing more complex surgical procedures such as cardiac, vascular and orthopedic hip fracture operations. It was observed that after emergency surgical procedures POD occurs 1.5 to 3 times more often than during elective planned surgical procedures. Also, intraoperative bleeding and the application of transfusion were identified as significant risk factors for the occurrence of POD. In order to avoid cognitive deficits caused by longer exposure to anesthesia, research has shown that anesthetic titration by monitoring the bispectral index, as well as evoked auditory potentials, can reduce excessive exposure to anesthetics and thus reduce the risk of postoperative cognitive dysfunction. Knowledge of risk factors and identification of patients at increased risk are the basis of a strategy for the prevention of this syndrome. Current evidence suggests that perioperative avoidance of benzodiazepine use as well as adequate perioperative pain control are key measures to reduce the risk of POD.

Keywords: postoperative delirium, cognitive dysfunction, risk factors, older age

Introduction

According to the International Classification of Diseases (ICD-10, F 05), postoperative delirium is defined as an etiologically non-specific organic cerebral syndrome characterized by the simultaneous disorders of consciousness and attention, perception, thinking, memory, psychomotor behavior, emotions and the sleep-wake cycle (1). In recent decades, postoperative delirium (POD) has been recognized as an important clinical syndrome, especially in older patients undergoing surgical treatment (2). The clinical presentation of this syndrome is highly variable. It is most often classified based on the motor symptoms and associated psychomotor characteristics. A patient may have a hyperactive form of delirium characterized by restlessness, constant movements and agitation, or a hypoactive delirium which is characterized by sluggishness, or lack of movement, unresponsiveness, and poor speech abilities. In some patients, a mixed form may occur, that is, both the hyperactive and hypoactive forms occur in a short period of time (2). In the majority of studies, which have been published so far, POD most often occurs on the first postoperative day, less often on the second or third, and the symptoms usually last from 1 to 3 days (2,3). This syndrome is a common problem in patients in intensive care units (ICUs) and it is associated with important clinical outcomes, including the increased number of days spent on

Prema dosadašnjim istraživanjima učestalost javljanja POD kod hirurških pacijenata veoma je varijabilna i zavisi od dijagnostičkih kriterijuma, ispitivane populacije, kao i vrste hirurške procedure. Prema podacima vodiča za klasifikaciju mentalnih poremećaja DSM-5 (engl. *Diagnostic and Statistical Manual for Mental Disorders, fifth edition*) delirijum se javlja kod 15-53% starijih pacijenata nakon operacije i kod čak 70-87% bolesnika smeštenih u JIL (4). Veća prevalencija POD zabeležena je kod pacijenata podvrgnutih kompleksnijim operativnim zahvatima kao što su kardiohirurške, vaskularne i ortopedske operacije frakture kuka (4).

Patofiziologija ovog sindroma i dalje nije u potpunosti razjašnjena, ali je očigledno da nastaje kao rezultat interakcije više činilaca koji se u literaturi najčešće opisuju kao predisponirajući i precipitirajući faktori. Faktori rizika za njegov nastanak su brojni, vezani su kako za samog bolesnika tako i za operativnu proceduru, i što je najznačajnije mnogi od njih se mogu modifikovati. Najčešće se u literaturi klasifikuju kao faktori vezani za pacijenta i faktori vezani za operativnu proceduru ili kao preoperativni, intraoperativni i postoperativni faktori. Iako je prevalencija javljanja POD-a visoka, veliki broj kliničkih slučajeva je nedijagnostikovan, smatra se da se jedan broj slučajeva može prevenirati (5).

Cilj ovog preglednog rada je ispitivanje preoperativnih, intraoperativnih i postoperativnih faktora koji mogu da dovedu do nastanka POD.

Metode

U okviru ovog preglednog rada za pretraživanje literature korišćene su tri bibliografske baze podataka: PubMed, WoS, i Scopus. Pretraživanje literature je sprovedeno za period 2010-2023. godine, a korišćene ključne reči su bile: POD, faktori rizika, preoperativni, operativni i postoperativni. U radu su prikazani rezultati samo onih istraživanja koja su bila objavljena na engleskom jeziku.

Preoperativni faktori rizika

Starost i pol

Starost bolesnika predstavlja jedan od najviše ispitivanih i najznačajnijih sociodemografskih faktora rizika za nastanak POD-a, a pokazano je da uzrast iznad 65 godina predstavlja nezavistan faktor rizika za nastanak ovog sindroma (6). Meta-analiza, koja je ispitivala faktore rizika za nastanak POD-a nakon kardiohirurških operacija, obuhvatila je četrnaest studija sa ukupno 13.286 pacijenata (7). U devet studija starost bolesnika predstavljala je faktor rizika za nastanak POD-a. Sedam od njih pokazalo je da rizik od nastanka POD-a raste sa povećanjem starosti bolesnika za svaku godinu, dok su dva istraživanja pokazala da je starost preko 65 godina značajno udružena sa povećanim rizikom od nastanka POD-a (7).

Sistematski pregled literature i meta-analiza podataka koji su ispitivali faktore rizika za nastanak POD-a nakon operacije frakture kuka uključili su 44 studije sa ukupno 104.572 pacijenta (8). Dvadeset studija pokazalo je značaj starosti u nastanku POD-a, a rezultati meta-analize ovih studija sugerišu da je starije životno doba značajan faktor rizika kod bolesnika posle operacije preloma kuka. Što se tiče pola, u ovom istraživanju 32 studije su pokazale povezanost pola i nastanka POD-a, a objedinjeni rezultati pokazali su da su osobe ženskog pola manje podložne nastanku POD-a. Ipak, rezultati ispitivanja pola kao faktora rizika rezlikuju se u drugim istraživanjima. U sistematskom pregledu literature faktora rizika kod starijih bolesnika koji su podvrgnuti gastrointestinalnim operativnim zahvatima, pol nije bio povezan sa nastankom POD-a (9), a meta-analiza podataka o faktorima rizika kod bolesnika nakon operacije kičme pokazala je da osobe muškog pola imaju manji rizik od nastanka ovog sindroma (10).

Nivo obrazovanja

Važnost kapaciteta kognitivne rezerve pacijenata kao faktora rizika za nastanak postoperativnih kognitivnih deficita prepoznata je u mnogim dosadašnjim istraživanjima (11,12). Najčešće korišćen indikator kognitivne rezerve jeste nivo obrazovanja, zbog izloženosti mozga mentalnim aktivnostima koje mogu uticati na to da se proces nastanka demencije odloži.

Feinkohl i sar. su sproveli meta-analizu podataka iz literature da bi ispitali povezanost kognitivne rezerve pacijenata i nastanka postoperativne kognitivne disfunkcije (11). Petnaest studija, sa ukupno 5.104 pacijenta uključeno je u istraživanje. Rezultati su pokazali da je viši nivo edukacije, odnosno duže vreme provedeno u obrazovanju, povezano sa smanjenim rizikom od nastanka postoperativnih kognitivnih deficita. Svaka godina provedena duže u obrazovanju bila je udružena sa smanjenjem rizika

mechanical ventilation, prolonged hospitalization, higher medical costs and mortality (4,5).

According to previous research, the incidence of POD in surgical patients is highly variable and depends on the diagnostic criteria, the examined population, and the type of surgical procedure. According to the Manual for the classification of mental disorders DSM-5 (Diagnostic and Statistical Manual for Mental Disorders, fifth edition), delirium occurs in 15-53% of elderly patients after surgery and even in 70-87% of patients hospitalized in the ICUs (4). A higher prevalence of POD has been reported in patients undergoing more complex surgical procedures, such as cardiac, vascular surgeries and hip fracture surgeries (4).

The pathophysiology of this syndrome has not been completely elucidated, but it is obvious that it occurs as a result of the interaction of several factors that are most often described in the literature as predisposing and precipitating factors. The risk factors for its occurrence are numerous, and they are related both to the patient himself and to the surgical procedure, and most importantly, many of them can be modified. They are most often classified in the literature as factors related to the patient and factors related to the surgical procedure, or as preoperative, intraoperative and postoperative. Although the prevalence of POD is high, and a large number of clinical cases are not diagnosed, it is believed that a number of cases can be prevented (5).

The aim of this review was to examine the preoperative, intraoperative and postoperative factors that can lead to the occurrence of POD.

Methods

In this review, three bibliographic databases PubMed, WoS, and Scopus were used for literature search. The literature search was conducted for the period 2010-2023, and the following keywords were used: POD, risk factors, preoperative, operative and postoperative. The review presents only the results of those studies published in the English language.

Preoperative risk factor

Age and gender

The patient's age is one of the most studied and most important socio-demographic risk factors for the occurrence of POD, and it has been shown that age over 65 years is an independent risk factor for the occurrence of this syndrome (6). A meta-analysis that examined the risk factors for the occurrence of POD after cardiac surgery included fourteen studies with a total of 13.286 patients (7). In nine studies, the patient's age was a risk factor for the occurrence of POD. Seven of them showed that the risk of developing POD increased with the patient's age for each year, while two studies showed that the age over 65 years was significantly associated with the increased risk of developing POD (7).

A systematic literature review and meta-analysis of data that examined the risk factors for POD after hip fracture surgery included 44 studies with a total of 104,572 patients (8). Twenty studies showed the importance of age for the occurrence of POD, and the results of meta-analysis of these studies suggested that older age was a significant risk factor in patients after hip fracture surgery. As far as the gender variable is concerned, in this research, 32 studies showed a connection between gender and the occurrence of POD, while the pooled results showed that women were less susceptible to the occurrence of POD. However, the results of examining gender as a risk factor were different in other studies. In a systematic literature review of risk factors in elderly patients undergoing gastrointestinal surgery, gender was not associated with the occurrence of POD (9), while a meta-analysis of data on risk factors in patients after spine surgery showed that males had a lower risk of developing this syndrome (10).

Level of education

The importance of the patient's cognitive reserve capacity as a risk factor for the occurrence of postoperative cognitive deficits has been recognized in many previous studies (11,12). The most commonly used indicator of cognitive reserve is the level of education, due to the exposure of the brain to mental activities that can influence the process of dementia occurrence to be postponed.

Feinkohl et al. conducted a meta-analysis of literature data in order to examine the connectedness between the patient's cognitive reserve and the occurrence of postoperative cognitive dysfunction (11). Fifteen studies, with a total of 5104 patients were included in the research. The results showed that a higher level of education, that is, longer time spent in

nastanka za 10%. U istraživanju *Alvarez-Bastidas* i sar. koje je uključilo pacijente podvrgnute različitim operativnim procedurama, POD je zabeležen kod čak 44% pacijenata koji su bili neobrazovani, sa oko 2 puta većom šansom da dobiju POD u odnosu na one sa bilo kakvim obrazovanjem (12).

Bračni status

Prema nekim istraživanjima, i bračni status predstavlja značajan faktor rizika za razvoj postoperativnog delirijuma. Ispitivanjem preoperativnih faktora rizika kod pacijenata nakon transuretralne resekcije prostate, procenat pacijenata koji su u braku bio je značajno manji u grupi koja je razvila POD nego u grupi bez POD-a, što je sugerisalo da status samca, razvedenog ili udovca može predstavljati faktor rizika za nastanak POD-a (13). Za razliku od ovog istraživanja, studija koja je uključila 358 uroloških bolesnika pokazala je da bračni status ne korelira značajno sa nastankom POD-a nakon transuretralne resekcije prostate (14). Međutim, u sistematskom pregledu literature, koji je takođe uključio populaciju uroloških pacijenata, status neoženjen/neudata predstavljao je faktor rizika za nastanak POD-a, pored dužeg vremena trajanja operacije, muškog pola i starijeg životnog doba (15). Takođe, u navedenoj studiji *Alvarez-Bastidas* i sar., 66% pacijenata koji nisu imali stabilan partnerski odnos iskusilo je pojavu POD-a (12).

Komorbiditeti

Ispitivanjem skora Američkog udruženja anesteziologa (engl. *American Society of Anesthesiologists score* - ASA) kao faktora rizika za nastanak POD-a, došlo se do oprečnih rezultata, mada većina istraživanja ukazuje na njego značaj. U meta-analizi *Lee* i sar., koja je uključila 12 istraživanja koja su ispitivala faktore rizika nakon kolorektalne hirurgije, ASA skor nije bio značajno različit kod pacijenata koji su imali POD i onih koji ga nisu imali (15). Međutim, meta-analiza podataka iz literature o faktorima rizika za POD među starijim bolesnicima podvrgnutih hitnim ili elektivnim gastrointestinalnim operacijama, pokazala je značaj ovog parametra. Istraživanje je obuhvatilo 11 studija sa ukupno 1427 pacijenata a značajno veći rizik od nastanka POD-a imali su pacijenti sa ASA skorom 3 i više (9). Meta-analiza *Wu* i sar., pokazala je da pacijenti ASA statusa 1 i 2 imaju manji rizik za razvoj POD-a nakon operacije preloma kuka (8).

Prema nekim autorima i hronična opstruktivna bolest pluća (HOBP) predstavlja važan faktor rizika za nastanak POD-a. Patofiziološki mehanizam dejstva objašnjava se hroničnom hipoksijom koja kod ovih bolesnika dovodi do disfunkcije mozga i opadanja kognitivnih funkcija. Testiranjem ovih funkcija pokazano je da su one značajno snižene kod bolesnika sa HOBP (16).

Velika meta-analiza, koja je uključila 43 istraživanja i ukupno 13.179 hirurških pacijenata, isključujući kardiohirurške operacije, pokazala je da su kardiovaskularne bolesti, u prvom redu hipertenzija, najčešći komorbiditet bolesnika koji su razvili POD (17). Slično istraživanje među pacijentima nakon operacije kičme, koje je obuhvatilo 40 studija, pokazalo je da prisustvo komorbiditeta uopšte kod pacijenata značajno povećava rizik od nastanka POD (17). Meta-analizom 13 studija pokazano je da hipertenzija predstavlja značajan faktor rizika za nastanak ovog sindroma nakon hirurgije kičme (10).

Dobro je poznato da hiperglikemija predstavlja značajan faktor rizika udružen sa lošijim ishodom operativnog lečenja. Većina istraživanja sugeriše da postoji veza između dijabetes melitusa i nastanka postoperativnih kognitivnih deficita. Bolesnici sa dijabetes melitusom (DM), naročito oni sa lošom dugoročnom kontrolom glikemije, mogu biti u povećanom riziku od nastanka POD-a usled mikrovaskularnih promena na mozgu koje mogu dovesti i do kognitivnih disfunkcija. Opservaciona kohortna studija u koju je uključeno 3178 pacijenata nakon kardiohirurške operacije, pokazala je da su pacijenti koji su razvili POD češće bili dijabetičari (18). U univarijantnoj analizi podataka dijagnoza DM-a bila je udružena sa povećanim rizikom od nastanka POD-a, dok je multivarijantnom analizom pokazano da su preoperativno povišene vrednosti glikoiziliranog hemoglobina (HbA1c) faktor rizika za nastanak POD-a, bez obzira na dijagnozu dijabetes melitusa (18). Meta-analizom faktora rizika nakon kardiohirurških operacija utvrđeno je, takođe, da DM predstavlja značajan faktor rizika (7). Ispitujući uticaj perioperativne hiperglikemije na neurokognitivne ishode nakon operacije *Hermanides* i sar. su, u svom sistematskom pregledu literature, pokazali da DM predstavlja faktor rizika za razvoj POD, i da je akutna perioperativna hiperglikemija udružena sa nastankom POD i postoperativnih kognitivnih deficita nezavisno od dijagnoze DM (19).

education, was associated with a reduced risk of postoperative cognitive deficits. Each year spent longer in education was associated with a 10% risk reduction. In the study by Alvarez-Bastidas et al. that included patients who were exposed to different surgical procedures, POD was noted in as many as 44% of patients who were not educated, with about two times higher chance of developing POD compared to those who were educated (12).

Marital status

According to some studies, marital status is also a significant risk factor for the development of postoperative delirium. Examining preoperative risk factors in patients after transurethral resection of the prostate, the percentage of married patients was significantly lower in the group that developed POD than in the group without POD, which suggested that single, divorced or widowed status may be a risk factor for the development of POD (13). In contrast to this research, a study that included 358 patients showed that marital status did not significantly correlate with the occurrence of POD after transurethral resection of the prostate (14). However, in a systematic literature review that also included the population of urological patients, single status represented a risk factor for the occurrence of POD in addition to the longer duration of surgery, male gender and older age (15). Also, in the above mentioned study by Alvarez-Bastides and associates, 66% of patients who did not have a stable partner relationship experienced the occurrence of POD (12).

Comorbidities

Conflicting results were obtained when the American Society of Anesthesiologists score (ASA score) was examined as a risk factor for the occurrence of POD, although the majority of studies indicate its importance. In a meta-analysis by Lee and associates, which included 12 studies that examined risk factors after colorectal surgery, the ASA score was not significantly different in patients who had POD and those who did not have it (15). However, a meta-analysis of literature data on risk factors for POD among elderly patients undergoing emergency or elective gastrointestinal surgeries, showed the importance of this parameter. The research included 11 studies with a total of 1427 patients, and patients with the ASA score 3 and higher than 3 had a significantly higher risk of developing POD (9). A meta-analysis by Wu and associates showed that patients with the ASA status 1 and 2 had a lower risk of developing POD after hip fracture surgery (8).

According to some authors, chronic obstructive pulmonary disease (COPD) is also an important risk factor for the development of POD. The pathophysiological mechanism of action is explained by chronic hypoxia, which in these patients leads to brain dysfunction and decline in cognitive functions. Testing of these functions showed that they were significantly reduced in patients with COPD (16).

A large meta-analysis that included 43 studies and a total of 13,179 surgical patients, excluding cardiac surgeries, showed that cardiovascular diseases, primarily hypertension, were the most common comorbidities in patients who developed POD (17). A similar study among patients after spine surgery, which included 40 studies, showed that the presence of comorbidities in general significantly increased the risk of developing POD (17). A meta-analysis of 13 studies showed that hypertension was a significant risk factor for the development of this syndrome after spine surgery (10).

It is well-known that hyperglycemia is a significant risk factor associated with a worse outcome of surgical treatment. The majority of studies suggest that there is a relationship between diabetes mellitus and the occurrence of postoperative cognitive deficits. Patients with diabetes mellitus, especially those with a poor long-term control of glycemia may be at increased risk of developing POD due to microvascular changes in the brain that may also lead to cognitive dysfunctions. An observational cohort study, which included 3178 patients after cardiac surgery, showed that patients who developed POD had diabetes more frequently (18). In the univariate data analysis, the diagnosis of DM was associated with the increased risk of developing POD, while the multivariate analysis showed that the elevated values of glycosylated hemoglobin (HbA1c) before surgery were the risk factor for developing POD regardless of the diagnosis of diabetes mellitus (18). A meta-analysis of risk factors after cardiac surgeries also found that DM was a significant risk factor (7). In their systematic literature review, Hermanides and associates examined the influence of perioperative hyperglycemia on neurocognitive outcomes after surgery and they showed that DM

Pshijatrijski i neurodegenerativni komorbiditeti takođe su udruženi sa povećanim rizikom od nastanka POD. Ova činjenica naročito se odnosi na bolesnike koji preoperativno imaju demenciju ili depresiju. Naime, smatra se da hirurški stres dovodi do nastanka neuroinflamacije, a preoperativno smanjen kapacitet bolesnika da prevaziđe ovo inflamatorno stanje može doprineti nastanku perioperativnih neurokognitivnih poremećaja. Preoperativno prisutna demencija kod bolesnika predstavljala je najjači faktor rizika za nastanak POD-a u istraživanju *Iamaroon* i sar. (20). U studiju je uključeno 249 pacijenata iz svih oblasti hirurgije osim kardiohirurgije. Multivarijantnom analizom pokazano je da jedino demencija i starost bolesnika preko 75 godina predstavljaju nezavisne faktore rizika za nastanak POD (20). Interesantna je i studija *Sprung* i sar. koja se bavila ispitivanjem rizika za nastanak POD-a kod pacijenata sa preoperativno prisutnim blagim kognitivnim oštećenjem ili demencijom, kao i povezanost između nastalog POD-a i naknadnog razvoja blagog kognitivnog oštećenja ili demencije kod preoperativno kognitivno normalnih starijih pacijenata (21). U studiji su potvrđeni raniji nalazi da u opštoj hirurškoj populaciji stariji bolesnici sa blagim kognitivnim oštećenjem imaju veći rizik za razvoj POD-a u poređenju sa bolesnicima bez kognitivnog oštećenja. Takođe, kod starijih bolesnika koji su prethodno imali normalan kognitivni status, a koji su razvili POD nakon operacije, veća je verovatnoća da će se naknadno dijagnostikovati demencija ili blaži kognitivni poremećaji (21).

Depresija predstavlja najznačajniji psihijatrijski komorbiditet koji je dokazani faktor rizika za nastanak POD-a. Prisustvo depresije na više načina može da ugrozi postoperativni tok i odloži oporavak bolesnika, a mnoge studije su pokazale da ona predstavlja nezavistan faktor rizika za nastanak POD-a. Velika meta-analiza sprovedena na kardiohirurškim bolesnicima uključila je 97 studija, koje su obuhvatale podatke od 60.479 pacijenata podvrgnutih operaciji aortokoronarnog bajpasa (22). Značajni preoperativni faktori rizika za razvoj POD-a, koji su imali najveću veličinu efekta na njegov nastanak, bili su prisustvo kognitivnog oštećenja, prethodni moždani udar, depresija, aritmija, periferna vaskularna bolest, bubrežna slabost, indeks telesne mase >30 kg/m^2, diabetes melitus, hipertenzija i starija životna dob (22). Prisustvo depresije predstavljalo je takođe i umereni faktor rizika za razvoj kognitivnog deficita u prvih 1 do 6 meseci nakon ove operacije (22). Preoperativno prisutna depresija identifikovana je kao faktor rizika za nastanak POD-a i u prethodno navedenoj velikoj meta-analizi *Chen* i sar. (7). Takođe je, analizom podataka o POD'u, nakon operacije kičme kao jedan od 18 faktora rizika za nastanak POD-a identifikovano prisustvo depresije kod bolesnika (10).

Prekomerna upotreba alkohola

Mnoga istraživanja pokazala su negativni uticaj prekomerne upotrebe alkohola na kognitivne funkcije starijih osoba. Prekomerna upotreba alkohola prema mnogim istraživanjima predstavlja nezavisan faktor rizika za nastanak delirijuma nakon hirurških procedura, a meta-analiza *Abate* i sar. je pokazala da je nastanak POD-a dva puta češći kod pacijenata koji hronično koriste alkohol (17). Takođe, u meta-analizi koja je obuhvatila istraživanja faktora rizika za nastanak POD-a nakon operacija na gastrointestinalnom traktu, anamnestički podatak o prekomernoj upotrebi alkohola je identifikovan kao značajan (9). U velikoj meta-analizi, nakon operacija zgloba kuka i kolena, korišćenje alkohola je predstavljalo jedan od značajnih faktora rizika za POD (23). Međutim, za razliku od ovih istraživanja, sistematskim pregledom literature ispitujući faktore rizika među urološkim bolesnicima, upotreba alkohola nije identifikovana kao značajni faktor rizika za nastanak POD (24).

Vrednosti serumskih albumina

Najveći broj studija ispitivao je uticaj poremećaja elektrolita, prvenstveno natrijuma i kalijuma, anemije i niske vrednosti albumina na nastanak POD-a. Meta-analiza o faktorima rizika za POD nakon kolorektalne hirurgije pokazala je da, pored starosti bolesnika i pozitivne anamneze za prethodni delirijum, niske vrednosti serumskih albumina predstavljaju faktor rizika za nastanak ovog sindroma (15). U sistematskom pregledu literature koji su sproveli *Sholc* i sar. ispitivan je veliki broj laboratorijskih parametara kao potencijalnih faktora rizika za nastanak POD-a, ali je samo nivo albumina pokazao značajnost (9). Grupa bolesnika kod kojih se razvio POD imala je značajno niže vrednosti ovog parametra (9). Rezultati skorašnje velike meta-anlize pokazuju da kod bolesnika nakon totalne artroplastike kuka ili kolena faktore rizika za razvoj POD-a predstavljaju nizak nivo albumina i hemoglobina (23).

was a risk factor for the development of POD, as well as that acute perioperative hyperglycemia was associated with the development of POD and postoperative cognitive deficits independently of the diagnosis (19).

Psychiatric and neurodegenerative comorbidities are also associated with the increased risk of developing POD. This fact especially refers to patients who have dementia or depression preoperatively. Namely, it is believed that surgical stress leads to neuroinflammation, and the preoperatively reduced capacity of the patient to overcome this inflammatory state can contribute to the emergence of perioperative neurocognitive disorders. The preoperatively present dementia in the patient was the strongest risk factor for the occurrence of POD in the study by Iamaroon and associates (20). The study included 249 patients from all field of surgery except cardiac surgery. A multivariate analysis showed that only dementia and the patient's age over 75 years were independent risk factors for the development of POD (20). The study by Sprung et al. is also interesting and it examined the risk of developing POD in patients with preoperatively present mild cognitive impairment or dementia, as well as the association between emerging POD and the subsequent development of mild cognitive impairment or dementia in elderly patients with preoperatively normal cognitive functions (21). Earlier findings that in the general surgical population, older patients with mild cognitive impairment had a higher risk of developing POD compared to patients without cognitive impairment were confirmed in the study. Also, in elderly patients who previously had a normal cognitive status and who developed POD after surgery, dementia or mild cognitive disorders were more likely to be diagnosed subsequently (21).

Depression represents the most significant psychiatric comorbidity, which is a proven risk factor for the occurrence of POD. The presence of depression can endanger the postoperative course and postpone the patient's recovery in several ways, while many studies have shown that it is an independent risk factor for the development of POD. A large meta-analysis, which was conducted on cardiac surgical patients, included 97 studies with the data on 60,479 patients undergoing coronary artery bypass graft surgery (22). Significant preoperative risk factors for the development of POD, which had the greatest influence on its onset, included the presence of cognitive impairment, previous stroke, depression, arrhythmia, peripheral vascular disease, renal insufficiency, body mass index > 30 kg/m^2, diabetes mellitus, hypertension and older age (22). The presence of depression was also a moderate risk factor for the development of cognitive deficit in the first 1 to 6 months after this operation (22). The preoperatively present depression was identified as a risk factor for the occurrence of POD in the above mentioned large meta-analysis by Chen and associates (7). Also, the analysis of data on POD after spine surgery showed the presence of depression in these patients as one of the 18 risk factors for the occurrence of POD (10).

Alcohol abuse

Many studies have shown the negative influence of alcohol abuse on the cognitive functions of the elderly. According to many studies, alcohol abuse is an independent risk factor for the occurrence of delirium after surgical procedures, and a meta-analysis by Abate et al. showed that the occurrence of POD was two times more frequent in patients who used alcohol chronically (17). Also, in a meta-analysis that included research on risk factors for the occurrence of POD after gastrointestinal surgeries, anamnestic data on alcohol abuse was identified as significant (9). In a large meta-analysis, after hip and knee surgeries, alcohol use was one of significant risk factors for POD (23). However, in contrast to these studies, a systematic literature review, which examined the risk factors among urological patients, alcohol use was not identified as a significant risk factor for the development of POD (24).

The values of serum albumin

The largest number of studies examined the influence of electrolyte imbalance, primarily sodium and potassium, anemia and low values of albumin on the development of POD. A meta-analysis of risk factors for POD after colorectal surgery showed that, in addition to the patient's age and a positive history of previous delirium, a lower albumin level was a risk factor for the occurrence of this syndrome (15). In a systematic literature review conducted by Scholz and associates, a large number of laboratory parameters were examined as potential risk factors for the occurrence of POD,

Intraoperativni faktori rizika

Intraoperativni faktori rizika najčešće su klasifikovani kao faktori vezani za anestezju i faktori vezani za operaciju.

Faktori vezani za anesteziju

Dosadašnja istraživanja su pokazala da češće podvrgavanje opštoj anesteziji može da dovede do pojave kognitivne disfunkcije kod pacijenata. Intraoperativne vrednosti srednjeg arterijskog pritiska i parcijalnog pritiska ugljen dioksida predstavljaju fiziološke varijable koje su usko povezane sa nastankom POD-a. Zato je prilikom primene opšte anestezije neophodno prevenirati nastanak intraoperativne hipotenzije i hipokapnije naročito kod starijih bolesnika zbog njihovog uticaja na redukciju cerebralnog krvnog protoka. Sistematski pregled literature koji je istraživao globalnu prevalenciju i faktore rizika POD-a među hirurškim pacijentima isključujući kardiohirurške operacije, pokazao je da se POD javlja oko 3 puta češće nakon operacija koje se izvode u opštoj anesteziji u odnosu na one koje se izvode u uslovima regionalne anestezije (17).

Randomizovana multicentrična studija poredila je efekte primene regionalne anestezije (spinalne, epiduralne, kombinovane spinalne i epiduralne) i opšte anestezije (intravenske, inhalacione) kod 950 pacijenata starijih od 65 godina kod kojih je urađena operacija frakture kuka (25). Regionalna anestezija bez sedacije nije značajno smanjila nastanak POD-a u odnosu na opštu anesteziju. POD je zabeležen kod 6,2% pacijenata kod kojih je primenjena regionalna anestezija i kod 5,1% pacijenata kod kojih je primenjena opšta anestezija (25). Nasuprot tome, meta-analiza podataka je pokazala da primena opšte anestezije za totalnu artroplastiku zgloba kuka ili kolena predstavlja faktor rizika za nastanak POD-a i da primena spinalne anestezije može smanjiti ovaj rizik (23).

U meta-analizi uticaja različite tehnike anestezije kod operacija kuka na nastanak POD-a rezultati su bili različiti kod uključenih studija (8). Pet studija uključenih u analizu pokazalo je povezanost između primene regionalne anestezije i nastanka POD-a. Rezultati meta-analize pokazuju da ova vrsta anestezije predstavlja potencijalni faktor rizika i da će pacijenti kod kojih je za ovu vrstu operacije primenjena regionalna anestezija verovatno razviti POD u postoperativnom toku. Isto tako, u ovoj analizi utvrđen je i značajan uticaj primene opšte anestezije na nastanak POD-a, nakon isključenja dve studije da bi se rešila heterogenost (8). Analizom podataka među urološkim operacijama nije utvrđena značajnost primene ni opšte ni regionalne anestezije na razvoj POD-a (24).

Mnoga istraživanja sprovedena su sa ciljem da se ispitaju efekti dubine anestezije na nastanak POD-a, ali su rezultati kontroverzni i dalje predstavljaju predmet debate. Da bi se izbegli kognitivni deficiti uzrokovani dužom ekspozicijom anesteziji, istraživanja su pokazala da titracija anestetika praćenjem bispektralnog indeksa (BIS), kao i evociranih auditivnih potencijala, može smanjiti prekomernu izloženost anesteticima i samim tim smanjiti rizik od postoperativne kognitivne disfunkcije (26). Multicentrična randomizovana klinička studija pratila je pojavu POD-a kod 655 pacijenata, koji su podvrgnuti velikim operativnim zahvatima u prvih pet dana postoperativno (27). Pokazano je da smanjena dubina anestezije smanjuje i rizik od nastanka POD-a. Incidencija POD-a u grupi sa vrednostima BIS 50 (plića anestezija) bila je 19%, a u grupi sa vrednostima BIS 35 (dublja anestezija) 28%. Nakon godinu dana praćenja pacijenti iz grupe koja je dobila pliću anesteziju pokazali su značajno bolje kognitivne funkcije u odnosu na one koji su za vreme operacije bili u duboljoj anesteziji (27). Zato i internacionalni vodiči za postoperativni delirijum preporučuju intraoperativnu upotrebu kontinuiranog EEG monitoringa, naročito kod starijih bolesnika, radi praćenja dubine opšte anestezije odnosno izbegavanja preterano duboke anestezije u cilju smanjenja njegove incidencije (28).

Sistematski pregled literature upoređivao je efekte inhalacione i totalne intravenske anestezije na nastanak kognitivnih deficita kod starijih bolesnika u nekardiohirurškim granama hirurgije. Istraživanje je uključilo 28 randomizovano kontrolisanih studija sa ukupno 4507 ispitanika a rezultati nisu pokazali jasne dokaze prednosti jedne ili druge vrste anestezije u smanjenju nastanka POD-a (29). Analizom efekata upotrebe različitih inhalacionih anestetika sevoflurana, izoflurana i desflurana na nastanak POD, takođe nije utvrđena razlika u njihovom uticaju na nastanak POD (29). (29).

Vrsta anestetika koji se primenjuje tokom operacije nije bila značajan faktor rizika za POD, ali je dosta istraživanja pokazalo da perioperativna upotreba opioida može biti uzrok njegovog nastanka (30). Takođe, premedikacija benzodijazepin-

however, only the level of albumin proved to be significant (9). The group of patients, in whom POD developed, had significantly lower values of this parameter (9). The results of a recent large meta-analysis have shown that in patients after total hip or knee arthroplasty, risk factors for the development of POD are low levels of albumin and hemoglobin (23).

Intraoperative risk factors

Intraoperative risk factors are most commonly classified as factors related to anesthesia and factors related to surgery.

Factors related to anesthesia

Earlier studies have shown that frequent general anesthesia can lead to can lead to the occurrence of cognitive dysfunction in patients. Intraoperative values of mean arterial pressure and partial pressure of carbon dioxide are physiological variables that are closely related to the occurrence of POD. Therefore, when general anesthesia is applied, it is necessary to prevent the appearance of intraoperative hypotension and hypocapnia, especially in older patients due to their influence on the reduction of cerebral blood flow. A systematic literature review, which examined the global prevalence and risk factors for POD among surgical patients excluding cardiac surgeries, showed that POD occurred about 3 times more often after surgeries performed under general anesthesia in comparison to those performed in the conditions of regional anesthesia (17).

A randomized multicentric study compared the effects of regional anesthesia (spinal, epidural, combined spinal and epidural) and general anesthesia (intravenous, inhalation) in 950 patients older than 65 years who underwent hip fracture surgery (25). Regional anesthesia without sedation did not significantly reduce the occurrence of POD compared to general anesthesia. POD was reported in 6.2% of patients who received regional anesthesia and in 5.1% of patients who received general anesthesia (25). In contrast, a meta-analysis of data showed that the use of general anesthesia for total hip or knee arthroplasty was a risk factor for the occurrence of POD and that the use of spinal anesthesia could reduce this risk (23).

In a meta-analysis of the influence of different techniques of anesthesia in hip surgery on the occurrence of POD, the results were different in included studies (8). Five studies included in the analysis showed the connectedness between the application of regional anesthesia and the occurrence of POD. The results of meta-analysis showed that this kind of anesthesia was a potential risk factor and that patients who received regional anesthesia for this type of operation would probably experience the occurrence of POD. In addition, in this analysis, a significant influence of general anesthesia on the occurrence of POD was found, after two studies had been excluded in order to solve the heterogeneity (8). The analysis of data related to urological surgeries did not show the significance of the application of either general or regional anesthesia on the development of POD (24).

Many studies have been conducted with the aim of examining the effects of the depth of anesthesia on the occurrence of POD, but the results are controversial and are still the subject of debate. In order to avoid cognitive deficits caused by longer exposure to anesthesia, research has shown that anesthetic titration by monitoring the bispectral index (BIS), as well as auditory evoked potentials, can reduce the excessive exposure to anesthetics and thus reduce the risk of postoperative cognitive dysfunction (26). A multicentric randomized clinical trial has observed the occurrence of POD in 655 patients who underwent major surgeries in the first five days postoperatively (27). It has been shown that that the reduced depth of anesthesia also reduces the risk of POD occurrence. The incidence of POD in the group with the target values of BIS 50 (shallow anesthesia) was 19% and in the group with the values of BIS 35 (deeper anesthesia) 28%. After one year of follow-up, the patients from the group that received shallow anesthesia showed significantly better cognitive functions compared to those who received deeper anesthesia (27). Therefore, international guidelines for postoperative delirium recommend the intraoperative use of continuous EEG monitoring, especially in elderly patients, in order to monitor the depth of general anesthesia, i.e. to avoid excessively deep anesthesia in order to reduce its incidence (28).

A systematic literature review compared the effects of inhalational and total intravenous anesthesia on the occurrence of cognitive deficits in elderly patients in non-cardiac branches of surgery. The research included 28 randomized

ima predstavlja značajan faktor rizika za nastanak POD-a pa vodič Evropskog udruženja anesteziologa za postoperativni delirijum sugeriše perioperativno izbegavanje upotrebe benzodijazepina osim kod veoma anksioznih bolesnika (28).

Faktori vezani za operaciju

Faktori rizika vezani za operaciju odnose se najviše na vrstu hirurške procedure i povezani su sa stepenom operativnog stresa. Kardiohirurške operacije, operacije aneurizme abdominalne aorte kao i ortopedska operacija frakture kuka predstavljaju zahvate sa povišenim rizikom za nastanak POD-a (7,8). Ovaj sindrom predstavlja jednu od najčešćih komplikacija nakon kardiohirurgije, a prema rezultatima meta-alnalize *Chen* i sar. učestalost varira od 4.1% do 54.9% (7). Treba naglasiti da nisu sve vrste kardiohirurških operacija podjednako povezane sa pojavom ovog sindroma. Nakon operacije srčanih valvula učestalost javljanja POD je veća u odnosu na operacije aortokoronarnog bajpasa. Isto tako, nisu sve ortopedske operacije podjednako visoko rizične za razvoj POD-a. Među njima, operacija preloma vrata butne kosti predstavlja najrizičniju operaciju za nastanak ovog sindroma jer se najčešće radi o starijim pacijentima koji su lošijeg opšteg stanja, operacija se češće izvodi kao hitna procedura, a intenzitet postoperativnog bola je značajan (7,8,17,22,23).

Još jedan bitan faktor vezan za operaciju jeste hitnost procedure. Pokazano je da je nakon hitnih operativnih zahvata POD 1,5 do 3 puta češći nego kod elektivnih planiranih operativnih procedura (8,31). Takođe, intraoperativno krvavljenje i primena transfuzije predstavljali su značajan faktor rizika za nastanak POD u više sistematskih pregleda literature (8,9,23).

Postoperativni faktori rizika

U postoperativnom periodu, intenzitet postoperativnog bola i primena pojedinih lekova, prvenstveno opioida, utvrđeni su kao faktori rizika za nastanak POD-a zbog njihovog efekta na centralni nervni sistem. U prospektivnoj kohortnoj studiji koja je uključila 581 pacijenta predviđenih za velike nekardijalne operativne zahvate, utvrđeno je da jak intenzitet postoperativnog bola, kao i upotreba visokih doza opioida, povećavaju rizik za nastanak POD-a kod svih pacijenata (32). U vodiču Evropskog udruženja anesteziologa za postoperativni delirijum jedna od preporuka za njegovu prevenciju jeste redovna adekvatna procena intenziteta i blagovremeno kupiranje postoperativnog bola. Posebno je naglašena važnost redovne procene intenziteta postoperativnog bola kod dementnih bolesnika upotrebom različitih validnih skala za njegovo merenje kod ove populacije. Preporučuje se pacijent kontrolisana analgezija (engl. *Patient-controlled analgesia*, PCA) kao najbolja vrsta analgezije ukoliko je pacijent u stanju da njenom upotrebom sam pronađe pravi balans između adekvatne analgezije i minimalne doze opioida. Pažljiva titracija dubine anestezije vođena neuromonitoringom i adekvatna perioperativna kontrola bola predstavljaju najefikasnije strategije zasnovane na dokazima koje smanjuju rizike nastanka POD-a (28). Pored navedenih, značajni postoperativni faktori rizika jesu i produžen boravak na mehaničkoj ventilaciji kao i produžen boravak u JIL prema rezultatima meta analize koja je ispitivala faktore rizika za nastank POD nakon kardiohirurških operacija (7).

Zaključak

Često javljanje POD-a u različitim hirurškim granama ukazuje na značaj ovog problema, a identifikacija brojnih faktora rizika za njegov nastanak doprinosi redukciji ili eliminaciji njegovog javljanja. Identifikacija pacijenata sa povećanim rizikom predstavlja osnovu strategije za prevenciju ovog sindroma. Trenutni dokazi sugerišu da perioperativno izbegavanje upotrebe benzodijazepina, pažljiva titracija dubine anestezije vođena monitoringom i adekvatna perioperativna kontrola bola kod rizičnih bolesnika predstavljaju najefikasnije strategije koje minimiziraju rizike nastanka POD-a.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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controlled studies with a total of 4507 participants, and the results did not show clear evidence of the advantages of one or the other type of anesthesia in reducing the occurrence of POD (29). The analysis of the effects of the use of different inhalational anesthetics sevoflurane, isoflurane and desflurane on the occurrence of POD also no difference was found in their influence on the occurrence of POD (29).

The type of anesthetic, which is administered during operation, was not a significant risk factor for POD, but many studies have shown that the perioperative use of opioids may cause its occurrence (30). Also, premedication with benzodiazepines is a significant risk factor for the occurrence of POD, and therefore, the Guideline of the European Society of Anesthesiology for Postoperative Delirium suggests the perioperative avoidance of the use of benzodiazepine except in very anxious patients (28).

Factors related to surgery

Risk factors related to surgery refer mostly to the type of surgical procedure and they are associated with the degree of operative stress. Cardiac surgeries, abdominal aortic aneurysm surgery, as well as hip fracture surgery are procedures with the increased risk of POD (7,8). This syndrome presents one of the most common complications after cardiac surgery, and according to the results of one meta-analysis conducted by Chen and associates, the incidence varies from 4.1 to 54.9% (7). It should be emphasized that not all types of cardiac surgeries are equally associated with the occurrence of this syndrome. After heart valve surgery, the incidence of POD is higher in comparison to coronary artery bypass surgery. Likewise, not all orthopedic surgeries have equally high risk for the development of POD. Among them, femoral neck fracture surgery represents the most risky operation for the occurrence of this syndrome, because it is mostly performed in older patients with a poor general condition, as an emergency procedure, while the intensity of postoperative pain is significant (7,8,17,22,23).

Another important factor related to the surgery is the emergency of the procedure. It has been shown that after emergency surgical procedures, POD was 1.5 to 3 times more common than during elective planned surgical procedures (8,31). Also, intraoperative bleeding and the use of transfusion were significant risk factors for the occurrence of POD in several systematic reviews of literature (8,9,23).

Postoperative risk factors

In the postoperative period, the intensity of postoperative pain and the use of certain drugs, primarily opioids, have been established as risk factors for the occurrence of POD due to their effect on the central nervous system. In a prospective cohort study, which included 581 patients planned for major non-cardiac surgeries, it was found that the strong intensity of postoperative pain, as well as the use of high doses of opioids increased the risk of POD in all patients (32). In the guide of the European Association of Anesthesiologists for postoperative delirium, one of the recommendations for its prevention is regular adequate assessment of the intensity and timely relief of postoperative pain. The importance of regular assessment of postoperative pain intensity in demented patients using different valid scales for its measurement in this population is particularly emphasized. Patient-controlled analgesia (PCA) is recommended as the best type of analgesia if the patient is able to use it to find the right balance between adequate analgesia and the minimum dose of opioids. Careful titration of the depth of anesthesia guided by neuromonitoring and adequate perioperative pain control are the most effective evidence-based strategies to reduce the risks of POD (28). In addition to the above, significant postoperative risk factors are a prolonged stay on mechanical ventilation and a prolonged stay in the ICU according to the results of a meta-analysis that examined risk factors for the onset of POD after cardiac surgery (7).

Conclusion

The frequent occurrence of POD in various surgical branches indicates the importance of this problem, while the identification of numerous risk factors for its occurrence contributes to the reduction or elimination of its occurrence. The identification of patients at increased risk is the basis of the strategy for the prevention of this syndrome. Current evidence suggests that perioperative avoidance of benzodiazepines, the careful titration of the depth of anesthesia guided by monitoring, and adequate perioperative pain control in high-risk patients are the most efficient strategies that minimize the risk of POD development.

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Competing interests

The authors declared no competing interests.

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