

## SEMINAR FOR PHYSICIANS *SEMINAR ZA LEKARE U PRAKSI*

University of Novi Sad, Faculty of Medicine Novi Sad<sup>1</sup>  
Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica<sup>2</sup>  
Oncology Institute of Vojvodina, Sremska Kamenica<sup>3</sup>

Seminar for physicians  
*Seminar za lekare u praksi*  
UDK 616.1-089:616.89-008.42]-06/-08  
<https://doi.org/10.2298/MPNS2204133P>

### DELIRIUM IN CARDIAC SURGERY – RISK FACTORS AND PREVENTION

#### *DELIRIJUM U KARDIOHIRURGIJI – FAKTORI RIZIKA I PREVENCIJA*

Mihaela PREVEDEN<sup>1,2</sup>, Andrej PREVEDEN<sup>1,2</sup>, Ranko ZDRAVKOVIĆ<sup>2</sup>, Nina DRAČINA<sup>1,2</sup>,  
Vladislava ĐORIĆ<sup>2</sup> and Milanka TATIĆ<sup>1,3</sup>

#### Summary

**Introduction.** Delirium is defined as an acute change in mental status that leads to disturbance in perception, thinking, memory, attention, emotional status, as well as sleep rhythm disorders and is most often reversible. Postoperative delirium is an acute mental disorder that develops after cardiovascular surgery with an incidence of 20 - 50% of operated patients. This complication is associated with a longer hospitalization, longer stay in the intensive care unit, as well as increased morbidity and mortality. **Risk Factors.** The risk factors are divided into preoperative, intraoperative and postoperative. The most common preoperative risk factors are older age, stenosis of the carotid arteries, previous cerebral diseases, depression, diabetes, hypertension, low ejection fraction of the left ventricle, as well as heart rhythm disorders. Intraoperative risk factors include the type of surgery, type of anesthesia, duration of extracorporeal circulation, and duration of aortic clamp. The most important postoperative risk factors include the use of psychoactive drugs, prolonged pain, the use of opioid drugs, duration of mechanical ventilation, and the length of stay in the intensive care unit. **Prevention.** Prevention is a very important aspect that is most often focused on intraoperative and postoperative precipitating factors. Preventive treatment includes pharmacological and non-pharmacological methods. The main recommendation refers to avoiding routine use of antipsychotics. **Conclusion.** Continuous infusion of dexmedetomidine compared to propofol reduces the incidence of postoperative delirium. Non-pharmacological approach consists of a series of procedures that are carried out postoperatively, such as the protocol that includes monitoring of Awakening, Breathing, Coordination, Delirium, Early mobility, and Family engagement.

**Key words:** Delirium; Thoracic Surgery; Risk Factors; Dexmedetomidine; Postoperative Complications

#### Introduction

Delirium is defined as an acute change in mental status that leads to disturbance of perception, thinking, memory, attention, emotional status, as well as sleep

#### Sažetak

**Uvod.** Delirijum se definiše kao akutni poremećaj mentalnog statusa koji dovodi do narušavanja percepcije, razmišljanja, pamćenja, pažnje, emocionalnog statusa, kao i poremećaja ritma spavanja i najčešće je reverzibilnog karaktera. Postoperativni delirijum podrazumeva akutni poremećaj mentalnog statusa koji se javlja u kardiovaskularnoj hirurgiji sa incidencijom od čak 20–50% operisanih pacijenata. Ova komplikacija sa sobom nosi dužu hospitalizaciju, duži boravak u jedinici intenzivnog lečenja, kao i povećan morbiditet i mortalitet. **Faktori rizika.** Faktori rizika se dele na preoperativne, intraoperativne i postoperativne. Najčešći preoperativni faktori rizika su starije životno doba, stenoza karotidnih arterija, ranija cerebralna oboljenja, depresija, dijabetes, hipertenzija, niska ejectiona frakcija leve komore, kao i poremećaji srčanog ritma. U intraoperativne faktore rizika spadaju vrsta operativnog zahvata, vrsta anestezije, dužina trajanja ekstrakorporalne cirkulacije, dužina trajanja aortne kleme. U najznačajnije postoperativne faktore rizika spadaju upotreba psihoaktivnih lekova, prolongirana bol i upotreba opioidnih lekova, vreme trajanja mehaničke ventilacije i dužina boravka u jedinici intenzivnog lečenja. **Prevenција.** Prevenција predstavlja veoma značajan aspekt koji je najčešće fokusiran na intraoperativne i postoperativne precipitirajuće faktore. Preventivni tretman se može podeliti na farmakološke i nefarmakološke metode. Osnovna preporuka odnosi se na izbegavanje rutinskog davanja antipsihotika. **Zaključak.** Kontinuirana infuzija deksmedetomidina u poređenju sa propofolom smanjuje incidenciju postoperativnog delirijuma. Nefarmakološki pristup se sastoji od niza postupaka koji se sprovode postoperativno, kao što je ABCDEF protokol (Buđenje, Disanje, Koordinacija, Praćenje delirijuma, Rana mobilnost i Porodično angažovanje).

**Кljučне речи:** delirijum; grudna hirurgija; faktori rizika; deksmedetomidin; postoperativne komplikacije

rhythm disorders and is most often reversible [1]. According to the American Psychiatric Association, the diagnosis of delirium can be made if the patient has a disorder of attention, a disorganized flow of thoughts, or an altered level of consciousness that develops over

**Abbreviations**

POD	– postoperative delirium
ECC	– extracorporeal circulation
ICU	– intensive care unit
LV	– left ventricle
ABCDE	– Awakening, Breathing, Coordination, Delirium monitoring, Early mobility and Family engagement

a short period of time and has a fluctuating course during the day [2].

Postoperative delirium (POD) is an acute mental disorder that occurs after major surgical procedures. The POD is a complication that most often develops in cardiovascular surgery with an incidence of as much as 20 - 50% of operated patients. After an emergency surgery, POD occurs 1.5 to 3 times more often than after an elective surgery. It can develop in all age groups, but more often after a surgery performed in older patients, with an incidence rate of 5 - 52%, depending on the general condition of the patient and the extent of the surgery. It usually occurs in the first five postoperative days [1, 3].

This complication is associated with a longer hospitalization, a longer stay in the intensive care unit (ICU), as well as increased morbidity and mortality. Although POD is reversible, it often leads to permanent consequences, since it may trigger the development of numerous complications that lead to permanent damage, loss of independence and disability. All this affects the health condition and quality of life of both the patients and their families, and from the economic aspect, leads to higher costs of treatment [4, 5]. Due to these facts, it is very important to prevent the development of delirium, especially in patients who, due to their age, health condition or type of surgical intervention, are at increased risk for developing POD [1, 4–6].

**Risk Factors**

Although the prevalence of delirium after cardiac surgery varies, there are predictors that may indicate patients at increased risk for developing POD. Risk factors are divided into preoperative, intraoperative and postoperative factors (**Table 1**) [7–13].

Among the most common preoperative risk factors for the development of POD is older age, especially in patients older than 65 years. These patients have more comorbidities, and therefore are at a greater risk for developing postoperative complications. Stenosis of the carotid arteries, previous cerebral diseases, depression, diabetes, hypertension, low ejection fraction of the left ventricle (LV), as well as heart rhythm disorders are conditions that lead to disorders of autoregulation of cerebral circulation and thus cause hypotensive periods and non-pulsatile blood flow when using a pump for extracorporeal circulation (ECC) during cardiac surgery [8–10]. The use of alcohol and cigarettes is also a significant predictor [8, 9]. Several studies have proven that these preoperative predisposing factors increase the possibility of POD up to seven times [10]. Unfortunately, these predisposing factors can hardly be influenced, therefore prevention should be focused on perioperative risk factors which, together with all the above-mentioned preoperative factors, will affect a higher incidence of POD and other complications that occur after cardiac surgery [14–16].

Intraoperative risk factors include type of surgery, with a higher incidence of POD after heart valve surgery due to the greater possibility of microembolization and the development of ischemic brain lesions, as well as emergency cardiac surgeries. In addition to the type of surgery, the type of anesthesia is also a risk factor. It has been proven that POD in non-cardiac surgery patients occurs in 21% of cases after general anesthesia, while after regional anesthesia it

**Table 1.** Risk factors for the development of postoperative delirium**Tabela 1.** Faktori rizika za razvoj postoperativnog delirijuma

Preoperative/Preoperativni	Intraoperative/Intraoperativni	Postoperative/Postoperativni
Older age/Starije životno doba	Type of surgery/Vrsta operacije	Psychoactive drugs/Psihoaktivni lekovi
Carotid artery stenosis Stenoza karotidnih arterija	Type of anesthesia Vrsta anestezije	Pain Bol
History of cerebral diseases Ranija cerebralna oboljenja	Pump duration for ECC Trajanje pumpe za EKC	Mechanical ventilation Mehanička ventilacija
Depression Depresija	Aortic clamp duration Trajanje aortne klemo	Anemia Anemija
Diabetes mellitus/Dijabetes melitus		Septic state/Septično stanje
Hypotension/Hipotenzija		Length of stay in ICU/Dužina boravka u JIT
Low LV ejection fraction Niska ejekciona frakcija LK		Length of hospitalization Dužina hospitalizacije
Arrhythmia/Aritmije		Electrolyte imbalance/Elektrolitski disbalans
Alcoholism/Alkoholizam		
Nicotinism/Nikotinizam		

Legend: ECC – extracorporeal circulation; ICU – intensive care unit; LV – left ventricle

Legenda: EKC – ekstrakorporalna cirkulacija; JIT – jedinica intenzivne terapije; LK – leva komora

occurs in 13% of cases. The ECC duration and aortic clamp duration are also significant factors for the development of POD [9, 10, 14, 15]. There are different theories as to how a longer duration of ECC is associated with a higher incidence of POD. Hypotensive periods, non-pulsatile blood flow and the release of pro-inflammatory mediators in blood contact with parts of the ECC machine are considered to play the most important role, which lead to increased permeability and damage to the blood-brain barrier [10, 14, 15]. However, randomized studies comparing on-pump and off-pump operations showed no difference in the incidence of postoperative cognitive impairment [12]. A logical explanation may be the increased possibility of microembolization by fragments of atherosclerotic plaques that are released into the bloodstream during these surgeries, regardless of whether an ECC pump is used or not. Placement of an aortic cannula and aortic clamp also increases the risk of embolization of cerebral blood vessels and thereby increases the possibility of POD [10, 15]. In addition to possible embolization with parts of atherosclerotic plaques, there is also a possibility of air embolism if at the end of the operation, the air that gets into the arterial circulation is inadequately removed and compromises the cerebral circulation [10, 14–16].

The most important postoperative risk factors include the use of psychoactive drugs, such as benzodiazepines, prolonged pain, use of opioid drugs, duration of mechanical ventilation, septic condition, anemia, hyponatremia, length of stay in ICU and length of hospitalization [8–10, 14–16].

### Prevention

Delirium is considered to be a postoperative complication that can usually be prevented, thus prevention is a very important aspect which should receive more attention. Given that the preoperative condition of the patient, his comorbidities and habits can hardly be influenced, most often prevention is focused on intraoperative and postoperative precipitating factors for the occurrence of POD [13]. Preventive treatment can be divided into pharmacological and non-pharmacological methods [10, 13, 14].

So far, preventive pharmacological therapy has shown mixed results. The main recommendation is to avoid routine administration of antipsychotics. Numerous studies have shown that sedation with benzodiazepines causes the development of POD both in cardiac and noncardiac surgeries [13, 17, 18]. Anticholinergics, corticosteroids, certain opioids such as meperidine, and polypharmacy, which implies simultaneous use of more than five drugs at the same time, should be avoided. In recent years, more importance has been given to dexmedetomidine in the prevention of POD. Dexmedetomidine is a potent  $\alpha_2$  agonist that has anxiolytic, sedative, analgesic, and sympatholytic effects. Continuous infusion of dexmedetomidine results in hypnosis and sedation, without respiratory depression, and it may provide earlier postoperative extubation of pa-

tients and prevent variations in blood oxygen levels. Also, compared to propofol, dexmedetomidine reduces the incidence of postoperative delirium, reduces the duration of mechanical ventilation and enables earlier extubation of the patient. This reduces the complications of mechanical ventilation, the mortality and morbidity of these patients, as well as the length of stay in the ICU and the length of hospitalization [18–24].

Non-pharmacological methods are necessary in the prevention of POD and have shown very good results [13]. In addition to the effort to minimize intraoperative precipitating factors, such as giving an adequate indication for surgery, choosing the best operative technique, reducing the usage of the ECC, aortic clamps, avoiding periods of hemodynamic instability, electrolyte imbalance, adequate pain management and adequate hydration, the non-pharmacological approach is very important, and it includes a series of procedures that are carried out postoperatively. In the ICU, the protocol consisting of Awakening, Breathing, Coordination, Delirium monitoring, Early mobility and Family engagement (ABCDEF) is used daily. This protocol involves the implementation of tests of awakening and spontaneous breathing with the aim of reducing the length of sedation and mechanical ventilation and all the complications they involve. Also, it implies frequent daily reorientation of patients, which refers to the return of wearing glasses, hearing aids, access to calendars, watches, newspapers. Facilitating contact with relatives is one of the most important preventive measures in the occurrence of POD [25–27].

It is very important to provide patients with a day-night rhythm. If possible, patients should be provided with daylight during the day, and lights should be turned off at night. Melatonin is a hormone that plays a significant role in the cycle of sleep and wakefulness, and if its secretion is impaired, it leads to sleep disorders and a higher incidence of POD. Randomized studies have shown that exogenous melatonin supplementation can reduce the development of delirium in ICU in cardiac surgery patients [28, 29].

Another non-pharmacological prevention measure is noise reduction, which means reducing the volume of devices, alarms, telephones, and loud conversation both among the staff and the patients. The World Health Organization has prescribed the upper limit of noise in hospitals, which is 35 dB during the day and 30 dB at night [7, 26, 27]. Early mobilization of patients plays an important role in postoperative recovery, therefore special attention should be paid to it. Patients should start feeding themselves and taking care of personal hygiene as early as possible [27–31]. Family engagement in patient's recovery and early contact with relatives represents an addition to the aforementioned ABCDE protocol. The latest research demonstrated that the ABCDEF protocol is more complete and has showed positive short term clinical outcomes including lower mortality, shorter stay in ICU and shorter hospitalization, as well as lower incidence of POD [32, 33]. Alternative methods include music

therapy and massage. Studies in which relaxing music was played during mechanical ventilation and sedation showed that these patients experienced less anxiety and reduced physiological response to stress [7, 10, 13].

It should also be noted that Emoto et al. proved that the new DELTA - Delirium Team Approach program, reduces the incidence of POD in cardiovascular surgery from 53% to 37%. This program consists of three components: education of medical staff, rational use of drugs that induce POD, as well as screening and assessment of risk factors for the development of POD. What is most remarkable about this program is its simplicity. The use of these very simple principles is associated with a significant reduction in cognitive impairment after cardiovascular surgery [31].

### Conclusion

It has already been proven that the identification of high-risk patients, prevention and routine evaluation of the development of delirium in intensive care

units are the most important points in reducing the incidence of postoperative delirium. Although protocols for the prevention of delirium have been established, studies examining their application in everyday practice are lacking. Future research should be based on a more detailed examination of the effectiveness and safety of pharmacological prevention, as well as non-pharmacological measures such as the policy of open visits in intensive care units, digital contact with family and friends, as well as alternative methods. Certainly, a multidisciplinary approach to the recovery of patients with proven postoperative delirium is very important, in order to reduce disability and permanent consequences.

Prevention and recognition of postoperative delirium should be of much greater importance for the health system and one of the key points in improving perioperative care of patients, reducing disability, and thus economic prosperity of both individuals and institutions.

### References

- Mossie A, Regasa T, Neme D, Awoke Z, Zemedkun A, Hailu S. Evidence-based guideline on management of postoperative delirium in older people for low resource setting: systematic review article. *Int J Gen Med.* 2022;15:4053-65.
- American Psychiatric Association. *Diagnostic and statistical manual of mental disorders DSM-5-TR.* 5th ed. Washington: American Psychiatric Association; 2013. 947 p.
- Reddy SV, Ikkal JN, Srinivasamurthy A. Postoperative delirium in elderly citizens and current practice. *J Anaesthesiol Clin Pharmacol.* 2017;33(3):291-9.
- Grover S, Avasthi A. Clinical practice guidelines for management of delirium in elderly. *Indian J Psychiatry.* 2018;60 (Suppl 3):S329-40.
- Daiello LA, Racine AM, Yun Gou R, Marcantonio ER, Xie Z, Kunze LJ, et al. Postoperative delirium and postoperative cognitive dysfunction. *Anesthesiology.* 2019;131(3):477-91.
- Migirov A, Chahar P, Maheshwari K. Postoperative delirium and neurocognitive disorders. *Curr Opin Crit Care.* 2021;27(6):686-93.
- Banh HL. Management of delirium in adult critically ill patients: an overview. *J Pharm Pharm Sci.* 2012;15(4):499-509.
- Chen H, Mo L, Hu H, Ou Y, Luo J. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis. *J Cardiothorac Surg.* 2021;16(1):113.
- Greaves D, Psaltis PJ, Davis DHJ, Ross TJ, Ghezzi ES, Lampit A, et al. Risk factors for delirium and cognitive decline following coronary artery bypass grafting surgery: a systematic review and meta-analysis. *J Am Heart Assoc.* 2020;9(22):e017275.
- Fatehi Hassanabad A, Bahrami N, Novick RJ, Ali IS. Delirium and depression in cardiac surgery: a comprehensive review of risk factors, pathophysiology, and management. *J Card Surg.* 2021;36(8):2876-89.
- Rundshagen I. Postoperative cognitive dysfunction. *Dtsch Arztebl Int.* 2014;111(8):119-25.
- Krenk L, Rasmussen LS. Postoperative delirium and postoperative cognitive dysfunction in the elderly – what are the differences? *Minerva Anesthesiol.* 2011;77(7):742-9.
- Cortés-Beringola A, Vicent L, Martín-Asenjo R, Puerto E, Domínguez-Pérez L, Maruri R, et al. Diagnosis, prevention, and management of delirium in the intensive cardiac care unit. *Am Heart J.* 2021;232:164-76.
- Jannati Y, Bagheri-Nesami M, Sohrabi M, Yazdani-Cherati J, Mazdarani S. Factors associated with post-surgical delirium in patients undergoing open heart surgery. *Oman Med J.* 2014;29(5):340-5.
- Joudi M, Fathi M, Harati H, Joudi M, Izanloo A, Rahdari A, et al. Evaluating the incidence of cognitive disorder following off-pump coronary artery bypasses surgery and its predisposing factors. *Anesth Pain Med.* 2014;4(4):e18545.
- De Somer F. End-organ protection in cardiac surgery. *Minerva Anesthesiol.* 2013;79(3):285-93.
- Tatić M, Mišković Skeledžija S, Zdravković R, Gojković M, Kovač A, Zubić M. Sedation in the intensive care unit. *Med Pregl.* 2019;72(3-4):123-30.
- Wang G, Niu J, Li Z, Lv H, Cai H. The efficacy and safety of dexmedetomidine in cardiac surgery patients: a systematic review and meta-analysis. *PLoS One.* 2018;13(9):e0202620.
- Turan A, Duncan A, Leung S, Karimi N, Fang J, Mao G, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet.* 2020;396(10245):177-85.
- Artemiou P, Bily B, Bilecova-Rabajdova M, Sabol F, Torok P, Kolarcik P, et al. Melatonin treatment in the prevention of postoperative delirium in cardiac surgery patients. *Kardiologicheskii Zhurnal.* 2015;12(2):126-33.
- van Norden J, Spies CD, Borchers F, Mertens M, Kurth J, Heidgen J, et al. The effect of peri-operative dexmedetomidine on the incidence of postoperative delirium in cardiac and non-cardiac surgical patients: a randomised, double-blind placebo-controlled trial. *Anaesthesia.* 2021;76(10):1342-51.
- Nguyen J, Nacpil N. Effectiveness of dexmedetomidine versus propofol on extubation times, length of stay and mortality rates in adult cardiac surgery patients: a systematic review and meta-analysis. *JBHI Database System Rev Implement Rep.* 2018;16(5):1220-39.
- Mahrose R, ElSerwi H, Maurice A, Elseri M. Postoperative delirium after coronary artery bypass graft surgery: dexmedetomidine infusion alone or with the addition of oral melatonin. *Egyptian Journal of Anaesthesia.* 2021;37(1):62-8.

24. Herman JA, Urman RD, Urits I, Kaye AD, Viswanath O. The effect of a dexmedetomidine infusion on delirium in the ICU. *J Clin Anesth.* 2022;79:110351.

25. Hughes CG, Boncyk CS, Culley DJ, Fleisher LA, Leung JM, McDonagh DL, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint consensus statement on postoperative delirium prevention. *Anesth Analg.* 2020;130(6):1572-90.

26. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLulich AMJ, et al. Delirium. *Nat Rev Dis Primers.* 2020;6(1):90.

27. Han Y, Tian Y, Wu J, Zhu X, Wang W, Zeng Z, et al. Melatonin and its analogs for prevention of post-cardiac surgery delirium: a systematic review and meta-analysis. *Front Cardiovasc Med.* 2022;9:888211.

28. You W, Fan XY, Lei C, Nie CC, Chen Y, Wang XL. Melatonin intervention to prevent delirium in hospitalized patients: a meta-analysis. *World J Clin Cases.* 2022;10(12):3773-86.

29. Majewski P, Zegan-Barańska M, Karolak I, Kaim K, Żukowski M, Kotfis K. Current evidence regarding biomarkers

used to aid postoperative delirium diagnosis in the field of cardiac surgery - review. *Medicina (Kaunas).* 2020;56(10):493.

30. Buratto E, Schulz A, Konstantinov IE. Commentary: delirium prevention in cardiac surgery: simplicity is beauty. *J Thorac Cardiovasc Surg.* 2021:S0022-5223(21)01150-8.

31. Enomoto K, Kosaka S, Kimura T, Matsubara M, Kitada Y, Mieno M, et al. Prevention of postoperative delirium after cardiovascular surgery: a team-based approach. *J Thorac Cardiovasc Surg.* 2021;S0022522321011260.

32. Sosnowski K, Mitchell M, Cooke M, White H, Morrison L, Lin F. Effectiveness of the ABCDEF bundle on delirium, functional outcomes and quality of life in intensive care patients: a study protocol for a randomised controlled trial with embedded process evaluation. *BMJ Open.* 2021;11(7):e044814.

33. Moraes FDS, Marengo LL, Silva MT, Bergamaschi CC, Lopes LC, Moura MDG, et al. ABCDE and ABCDEF care bundles: a systematic review protocol of the implementation process in intensive care units. *Medicine (Baltimore).* 2019;98(11):e14792.

Rad je primljen 12. VII 2022.

Recenziran 19. VIII 2022.

Prihvaćen za štampu 19. VIII 2022.

BIBLID.0025-8105:(2022):LXXV:3-4:133-137.