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Abstract

**Background/Aim.** The incidence of postoperative delirium (POD) after non-cardiac surgery is a problem often not recognized by many anesthesiologists. The objective of our study was to detect POD and its possible cause, in patients undergoing Radical Retropubic Prostatectomy (RRP) under general anesthesia. **Methods.** After Ethical Committee approval, we enrolled 80 patients, ASA status II, in a prospective study, who were scheduled to undergo RRP under general anesthesia. All patients completed MMSE tests (Folstein Mini Mental State Exam) evening before, and 48 hours after surgery. Assessment for the presence and severity of delirium was performed using CAM (Confusion assessment method), and an assessment of the degree of agitation and sedation using RASS (The Richmond Agitation and Sedation Scale). **Results.** The average preoperative MMSE score (28.59±1.04) significantly decreased following the surgery (27.74±1.52) (p<0.0001). The average postoperative MMSE score trend descended in comparison to intraoperative bleeding (p=0.036). Patients with higher pain scores had significant decline in MMSE after surgery (28.75 vs 26.25; p<0.001). Five patients were considered positive for delirium, and four of them reported regular alcoholic drinks intake (>1 drink per day) preoperatively (p<0.0001). Based on RASS score, 13 patients (16.3%) were agitated or sedated, and they had statistically significantly higher intraoperative bleeding (p<0.001). **Conclusion.** Results of this study emphasize the importance of proper preoperative evaluation; especially regarding the alcohol consumption since all patients that developed POD reported moderate alcohol consumption. Furthermore, greater intraoperative bleeding and postoperative pain scores did not influence the occurrence of delirium, but resulted in lower postoperative MMSE scores, which highlights the importance of proper intraoperative management from both surgery and anesthesia to lower risk for developing POD.

**Keywords:**
postoperative delirium, alcohol consumption, intraoperative bleeding, postoperative pain, radical retropubic prostatectomy.
Apstrakt

Uvod/Cilj. Postoperativni delirijum (POD) kod pacijenata nakon nekardiohirurških procedura je često neprepoznato od strane anesteziologa. Cilj naše studije je procena učestalosti postoperativnog delirijuma (POD) i mogućih faktora rizika za njegov nastanak kod pacijenata koji su bili u opštoj anesteziji usled hirurškog zahvata kod radikalne retropubične prostatektomije (RRP). Metode Nakon dobijanja dozvole Etičkog Komiteta, prospektivna studija obuhvatila je 80 pacijenata, ASA skor II, koji su planirani za RRP u opštoj anesteziji. Pacijenti su ispunili MMSE test (Folstein Mini Mental State Exam) preoperativno (veče pred operaciju) i postoperativno (48 sati nakon operacije). U studiji smo ipitivali prisutstvo i težinu delirijuma upotrebom CAM (Confusion assessment method), a stepen agitacije i sedacije primenom RASS (The Richmond Agitation and Sedation Scale). Results Prosečni preoperativni MMSE skor (28.59±1.04) je bio značajno snižen u postoperativnom period (27.74±1.52) (p<0.0001). Prosečan postoperativni MMSE skor bio je niži u poredjenju sa intraoperativnim krvarenjem (p=0.036). Pacijenti sa višim intenzitetom bola imali su značajno snižen postoperativni MMSE skor (28.75 vs 26.25; p<0.001). Kod četiri od pet pacijenata koji su imali delirijum, zabeležen je redovni unos alkohola (>1 pića dnevno) u preoperativnom periodu (p<0.0001). Na osnovu RASS skora, agitacija je registrovana kod 13 pacijenata (16.3%), i kod svih je zabeleženo značajno veće intraoperativno krvarenje u odnosu na ostatak ispitanika (p<0.001).

Zaključak. Rezultati naše studije ukazuju da je u preoperativnoj evaluaciji značajno registrovati preoperativnu konzumaciju alkohola, uzvodi u obzir da su svi pacijenti koji su u postoperativnom period razvili POD, preoperativno konzumirali alkohol u većoj količini. Iako veće intraoperativno krvarenje i postoperativni bol višeg intenziteta nisu uticali na učestalost pojave delirijuma, snižavali su MMSE skorovi, što ukazuje na značaj adekvatnog intraoperativnog tretmana pacijenta u toku hirurgije i anestezije u cilju smanjenja rizika za razvoj POD.

Ključne reči: postoperativni delirijum, konzumiranje alkohola, intraoperativno krvarenje, postoperativni bol, radikalna retropubična prostatektomija.
Introduction

The incidence of postoperative delirium after non-cardiac surgery in patients older than 18 years of age could range between 19 and 44.5%. (1, 2) This problem is often underestimated and not recognized by many anesthesiologists. Postoperative delirium is more frequent in the elderly but is also perceived in younger patients as well. Since the world population over the age of 65 is increasing, this would be a more commonly observed problem in the PACU and ICU in the upcoming years. (3, 4) Postoperative delirium in patients undergoing surgical procedures under general anesthesia are very important because they are associated with poor outcomes, increased mortality rate, increased length of stay in the PACU and overall hospital stay as well. (5, 6)

Pathogenesis of delirium is poorly understood. In several attempts, researchers tried to develop predictor model to identify postoperative risk for delirium by looking at severe illness, visual impairment, cognitive impairment, nitrogen/creatinine ratio, neurological impairments, and social habits (smoking, ethanol abuse). (7-9) However, none of these parameters direct significant sensitivity toward delirium determination. On the other hand, delirium could have iatrogenic etiology triggered by anesthetic medications. Sieber et al. (10) in a randomized study showed that use of light propofol vs. deep sedation could reduce the prevalence of postoperative delirium by 50% in patients undergoing hip fracture repair under spinal anesthesia.

Different screening tools have been used in hospitalized patients for the screening of delirium. (11) The Mini Mental State Exam (MMSE), initially described by Folstein in 1975 is recommended as a simple tool in the early detection of cognitive impairment and state of delirium. Even though it cannot have a final diagnostic accountability, it can serve in screening for mental state function validation. (12) Sensitivity and specificity for delirium/dementia are 87% and 82%, respectively, calculated when 24 out of 30 were used as cut-off score. (13) The Confusion Assessment Method (CAM) test was designed to be used by clinicians that are not mental health professionals. Gusmao-Flores et al. (14) in a systematic review of 9 different studies showed very high sensitivity and specificity of this test in several studies (80% and 95.9%, respectively). Furthermore, CAM scale has the highest level of compatibility with the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) classification, which is now considered to be the gold standard in the diagnosis of delirium. (15) The Richmond Agitation and Sedation Scale (RASS) is a 10-
point scale that was developed in collaboration with critical care physicians, nurses, and pharmacists. (16) It was initially developed to assess the level of agitation or sedation to ensure precise medication titration. This scale has been frequently used in the research and clinical practice settings for delirium assessment. Vasilevskis et al. (17) in a prospective cohort study on 510 ICU patients showed that RASS in combination with CAM is a sustainable and reliable measure of delirium and sedation along a bedside.

The objective of our study was to detect postoperative delirium using pre- and postoperative MMSE, postoperative CAM and RASS, as well as possible risk factors in male patients undergoing Radical Retropubic Prostatectomy under general anesthesia.

Methods

This prospective observational study was conducted after receiving approval from Ethical Committee Clinical Center of Serbia. We consented and enrolled 80 male patients who were scheduled for Radical Retropubic Prostatectomy at Urology Hospital, Clinical Center. Excluded from the study were all patients who had clinically significant cardiovascular, respiratory, hepatic, renal, neurological diseases or psychiatric disorders, those who had history of benzodiazepine abuse or those who had undergone a general anesthesia 30 days before screening.

All 80 patients underwent Radical Retropubic Prostatectomy under general anesthesia. Half-hour prior to induction of anesthesia, patients were pre-medicated with midazolam 5 mg IM and atropin 0.5 mg IM. Common methods of balanced general anesthesia were applied. All patients received 1.5 μg/kg of fentanyl and 2 mg/kg of propofol for induction of anesthesia, and 0.6 mg/kg of rocuronium bromide muscle relaxant to facilitate tracheal intubation. General anesthesia was maintained by mixture of sevoflurane (Fex=0.8%), nitrous oxide and oxygen (FiO₂=40). Neuromuscular antagonism maintenance dose 0.15 mg/kg rocuronium bromide was administered when 2 responses to TOF (“Train of Four”) stimulation were present. Analgesia was maintained by intravenous injection of opioids that included 0.5-1.0 μg/kg fentanyl bolus injection. Intraoperative monitoring for all patients included continuous recording of five-lead electrocardiogram (ECG) with special attention to ST segment, oxygen saturation by pulse oximetry, and noninvasive blood pressure, airway gas analysis, capnography and TOF stimulation. At the
end of surgery, residual neuromuscular blockade was reversed by mixture of atropine 0.75 mg IV and neostigmine 1.5 mg IV.

On arrival in the Intensive care unit patients received continuous IV infusion of Tramadol 400 mg/day and Diclofenac-Na+ 75 mg IM every 12 hours if pain scores were more than 3 out of 10 on the Numeric Rating Scale (NRS).

We collected following variables: demographic information (age, height, weight, education level), comorbidity (detailed medical history with emphasis on neuropsychiatric disorders), as well as alcohol consumption (number of drinks per day), ASA status, duration of anesthesia, duration of surgery, total blood loss, length of stay in the intensive care unit (ICU) and total length of stay in the hospital. Furthermore, we collected the Mini Mental State Exam (MMSE) scores pre-operatively and postoperatively; postoperative Confusion Assessment Method (CAM) and Richmond Agitation and Sedation Scale (RASS) scores; as well as Numeric Rating Pain scores (NRS).

Twelve hours before the surgery patients were interviewed, and Folstein Mini Mental State Exam questionnaires (MMSE) written in Serbian language were completed. The MMSE is an 11-question assessment tool that can be completed within 5-10 minutes, with the maximum test score of 30. This test is a global assessment of many domains including: orientation of time and place, registration of 3 words, attention and calculation (recall of 3 words, language and visual construction), which allows for detection of mood changes, abnormal mental experiences and thought process impairment.(12) Reassessment of cognitive status using MMSE score was performed 48 hours after the surgery.

The Confusion Assessment Method (CAM) test was used to evaluate for the presence and severity of delirium and agitation. This test is easy to perform in short period of time (5 minutes). The Richmond Agitation and Sedation Scale (RASS) was used to assess the level of sedation. This 10-point scale has one level to denote a calm/alert state (0), five levels of sedation (-1 to -5) and four levels to detect anxiety or agitation (+1 to +4). These two scales, CAM and RASS, were collected 48 hours after the surgery. One person interviewed patients and collected all MMSE, CAM and RASS scores to prevent any inconsistency.

Pain scores were recorded on an 11-point Numeric Rating Scale-NRS (0-10), every 6 hours postoperatively in the first 48 hours after the surgery.
**Statistical analysis**

The sample size estimated for this study was 78, based on a difference in pain scores at $\alpha=0.05$, power=0.95, and effect size of 0.36. We considered a difference of 3 in MMSE pain scores to be clinically significant improvement. Statistical analysis included measures of central tendency (the statistical variability of the series, the interval of variation, mean with standard deviation and weighted average). Student’s T-test and Pearson Chi-square test were applied for testing differences between variables, and for testing correlation between variables we used the Pearson’s correlation coefficient. A $p$ value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 20.0 software (IBM Corporation, Armonk, NY).

**RESULTS**

The study included 80 hospitalized patients who underwent Radical Retropubic Prostatectomy. Enrolled patient age range was between 44 and 74 years old (the average age was 65±6 years). All patients were ASA II status. The majority of patients, 48 of them (60%), had a normal body mass index (BMI). Regarding the level of education, most of them 46 (57.5%) had high level of education (college degree or graduate degree). Only 4 patients (5%) reported regular consummation of more than one drink per day.

The average preoperative MMSE score of 28.59±1.04 was within normal score range, in accordance to patient’s age and level of education, whereas score measured 48h after surgery was 27.74±1.52. When MMSE values were compared with the preoperative baseline, the mean MMSE scores decreased significantly following the surgery ($T$ test=4.602, $p<0.0001$). Older patients had lower postoperative MMSE scores, but without statistical significance ([Figure 1](#)). Patients with lower level of education showed higher cognitive deterioration postoperatively according to MMSE scores, however, the difference was not statistically significant ($p>0.05$) ([Figure 2](#)).

**Figure 1.**

**Figure 2.**

The surgery duration was between 97 and 145 minutes (average 125±11 minutes). The average duration of anesthesia was 151±13 minutes (range from 121 to 171 minutes). There was no correlation between postoperative delirium and duration of surgery or anesthesia ($p>0.05$).

On average, the blood loss during surgery was 1058±278 ml. Throughout the entire surgery, hematocrit values were checked regularly, and blood transfusion was initiated if
the hematocrit levels were below 0.33. Patients received 1-3 units (equivalent to 300-900 mL) of packed red blood cells (pRBCs). When compared with intraoperative bleeding the average postoperative MMSE score was in descending trend. Specifically, less intraoperative bleeding was in correlation with the highest postoperative MMSE score ($p=0.5397$), which was expressed as statistically significant $p=0.036$ (Figure 3).

**Figure 3.**

Postoperatively, patients reported pain scores between 0 and 4 on an 11-point NRS scale (0-10), with an average of 2.33±1.11. Majority of patients had pain scores 3/10 (57.5%), and only 4% of them had 4/10. Patients with higher pain scores had significant decline in MMSE after surgery (28.75 vs 26.25; $p<0.001$). Correlation between postoperative pain scores and decline in MMSE was statistically significant ($p=0.002$).

CAM diagnostic algorithm was utilized for all patients. According to CAM scale, five patients were considered positive for delirium. Four out of 5 patients were classified as moderate alcohol consumers because they were consuming up to 2 drinks per day preoperatively ($x^2= 63.16$, $p<0.0001$). Patients that developed delirium were a few months older (65.75 years) when compared to those that did not develop delirium (64.40 years), which had no statistical significance. The patients that developed delirium had lower MMSE scores preoperatively (27.80), compared to those that did not develop delirium (28.64), and that was without significant difference. Additionally, these patients also had greater blood loss compared to others (1,100 ml and 1,053.7 ml respectively), without statistical significance as well.

RASS score (score of agitation and sedation) was in the range of -2 to +4 for all patients. Most of the patients, 67 (83.7%), were awake, alert and demanding with RASS=0 and 13 patients (16.3%) were agitated or sedated. Three out of 5 patients with delirium had mixed delirium, 1 patient had hypoactive and 1 patient had hyperactive delirium. Patients with RASS=0 had less intraoperative bleeding (average 1,004.03±211.03 ml) then patients that were agitated or sedated (average, 1,244.44±391.41 ml) ($F=11.91$, $p<0.001$).

Furthermore, there was a statistically significant correlation between preoperative MMSE scores and postoperative RASS ($R=0.552$; $p=0.018$). RASS scores have increased postoperatively for most of the patients with low preoperative MMSE. However, postoperative MMSE descending score was related to lower RASS, but without statistical significance as well ($R=0.044$; $p=0.881$).
Patients that had POD stayed longer in the ICU (average 95±19 hours) than patients without POD (average 49±11 hours) and this difference was statistically significant (p=0.0411). Furthermore, patients with POD had slightly longer length of stay in the hospital (10±3 days) than patients without POD (8±2 days); however, this difference was not statistically significant (p>0.05).

**Discussion**

Our results revealed that only 6.25% of patients developed delirium after Radical Retropubic Prostatectomy under general anesthesia, which is significantly lower incidence than observed (21.23%) in a study by Tai et al.(18); however, our patients were, on average, six years younger than patients in their study. Studies that followed incidence of delirium for patients after other (non-urological) types of surgeries showed the incidence ranging from 0.84% up to 51%.(19-21)

Results of our study pointed out that the risk factors for developing delirium in our patient population were moderate alcohol consumption, intraoperative bleeding, and postoperative pain. Based on CAM scale, four out of 5 patients that developed delirium reported use of more than one drink per day which fits into criteria for moderate alcohol consumption per Dietary Guidelines for Americans 2015-2020.(22) The other authors found that alcohol abuse was one of the predictors for the development of delirium as well.(19),(20),(23)

Fineberg et al.(19) in a retrospective database analysis showed the incidence of postoperative delirium of 0.84% in patients undergoing spine surgical procedures. They found that patients who developed delirium were elderly (≥65 years), had depression, alcohol and/or drug abuse, some neurological or psychiatric disorders, electrolyte, pulmonary or renal abnormalities, anemia or congestive heart failure.(19) They also found that delirium was associated with 7.6 times increased mortality rate.(19)

Shah et al.(20) showed that 11.5% of 774 study patients undergoing major resection of head and neck squamous carcinoma developed delirium. They showed that older age (≥69 years), preexisting cognitive impairment, surgery duration (longer than 6 hours) and alcohol consumption are predictors for developing delirium.(20) It was found that asking the patients whether they have ever been advised on cutting back on drinking alcohol or
abstained for at least a week in the past year could help in postoperative delirium risk identification.(20)

Hudetz et al.(23) conducted a prospective study with 28 patients over the age of 55 with self-reported alcohol abuse, and the same number of matched non-consuming alcohol controls, undergoing elective surgery under general anesthesia. Even though experimental patients’ group did not consume alcohol for 5 weeks prior to the surgery, they had a higher incidence of postoperative delirium due to impaired executive (frontal lobe) functions even without neurological defects.(23) Results from our study, as well as other studies,(19-21) confirmed that physician should emphasize the question regarding alcohol consumption prior to surgery.

We excluded patients with clinically significant cardiovascular, respiratory, hepatic, renal, neurological and psychiatric diseases, yet confirmed that cognitive impairment is an important predictor for post-operative delirium, as shown by many other authors.(9, 24, 25) The etiology of cognitive impairment observed in elderly patients is multifactorial. When dealing with elderly patients in the preoperative anesthesia clinic, anesthesiologists should assess the cognitive function and identify all risk factors that might be associated with cognitive dysfunction.(24)

Several already existing models are able to identify patients with predisposing factors for developing postoperative delirium.(9, 25) Marcantonio et al.(25) developed a set of scores for patients undergoing elective non-cardiac surgery including factors such as: age, poor cognitive and functional status, significantly abnormal preoperative levels of glucose, sodium and potassium levels, as well as self-reported alcohol abuse.

It is important to recognize that even intraoperative management may play a role in the development of POD. Results of our study showed that patients that had more intraoperative bleeding had lower postoperative MMSE scores than the RASS scores, which revealed either agitation or sedation. Olin et al.(21) followed 51 patients (average age of 75.1 years) after major abdominal surgeries and showed that 26 of them (51%) developed delirium, and those whose delirium lasted more than 3 days had significantly greater blood loss.

Results of our study showed that patients experiencing more pain had significant decline in MMSE after surgery. Leung et al.(26) also found that patients with higher
postoperative pain, and who received higher doses of opioids, had 3.6 times greater risk for developing POD.

Our patients who developed POD had longer stay in the ICU. Ely et al.(27) studied relationships between delirium in the intensive care unit (ICU) and outcomes including length of stay in the hospital following 48 patients. Multivariate analysis showed that POD was the most important independent factor for the hospital length of stay.(27) When compared to other patients that have not develop delirium, our patients who developed POD did not stay much longer in the hospital. However, it is well known that these patients usually have prolonged hospital stay, which is related to increased morbidity and mortality.(5, 19, 28)

Veiga at al.(29) evaluated the incidence and determinants for delirium development during the immediate postoperative period in 680 adult PACU patients. Patients that developed delirium (18.8%) were elderly (median age of 71 years), had higher ASA physical status, were more likely to have emergency surgery, and were more severely ill (hypertension, hyperlipidemia, ischemic heart disease, congestive heart disease, cerebrovascular disease, or previous renal insufficiency). They also had a longer length of stay in the PACU and hospital, and also received higher volume of intraoperative fluids. They showed that POD was an independent determinant for hospital mortality and post 6-month follow-up mortality.(29)

Witlox et al.(28) conducted a meta-analysis of 42 studies that investigated delirium in elderly patients and showed that it is associated with poor outcomes, increased risk of death, institutionalization, and dementia. However, it also showed that delirium was independent of other confounders such as age, sex, comorbid illness or illness severity, or the presence of dementia at baseline. Delirium can be prevented in some cases; nevertheless, once present, management of delirium has very limited results in improving long-term mortality.(30) The most important is to identify patients at high risk for delirium and apply different strategies to prevent delirium occurrence.

Moyce et al.(31) in a meta-analysis of 29 randomized controlled studies that reported perioperative interventions and postoperative delirium after non-cardiac surgeries, showed that perioperative geriatric consultation and lighter anesthesia were associated with reduced risk of POD.
Limitations of our study included that it was based in a single center, patients were younger than 65 years, and certain patients had some form of psychiatric impairment, which could be the reason for relatively low incidence of postoperative delirium.

Conclusion
Results of this study emphasize the importance of proper preoperative evaluation, encouraging physicians to spend more time interviewing patients and getting details from their medical and social history, especially regarding the alcohol consumption, since all the patients that developed POD reported moderate alcohol consumption. Furthermore, greater intraoperative bleeding and postoperative pain scores did not influence the occurrence of delirium, but rather resulted in lower postoperative MMSE scores, which highlights the importance of proper intraoperative management from both surgery and anesthesia side in order to lower the risk for developing postoperative delirium.

Conflict of Interest: Nothing to disclose.

LEGENDS
Figure 1. Postoperative MMSE and average patients’ age
Figure 2. Postoperative MMSE and patients’ level of education
Figure 3. Postoperative MMSE and average intraoperative bleeding (ml)

REFERENCES


Average patients' age

Postoperative MMSE score

R² = 0.0728
Average Intraoperative bleeding (mL)

Postoperative MMSE score

$R^2 = 0.5397$

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