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Preoperative alcohol consumption, intraoperative bleeding and postsurgical pain may increase the risk of postoperative delirium in patients undergoing radical retropubic prostatectomy

Preoperativno konzumiranje alkohola, intraoperativno krvarenje i postoperativni bol mogu povisiti rizik od nastanka postoperativnog delirijuma kod bolesnika nakon radikalne retropubične prostatektomije

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Abstract

Background/Aim. The incidence of postoperative delirium (POD) after non-cardiac surgery is a problem not often 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 (the American Society of Anestesiology) status II, scheduled to undergo RRP under general anesthesia, in a prospective study. All patients completed MMSE tests (the Folstein Mini Mental State Exam) the evening before, and 48 hours after the surgery. Assessment for the presence and severity of delirium was performed using CAM (the 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 correlation to intraoperative bleeding ($p = 0.036$). The patients with higher pain scores had significant decline in MMSE after the 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 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 resulted in lower postoperative MMSE scores, which highlights the importance of adequate intraoperative treatment of patients during surgery and anesthesia in order to reduce the risk of developing POD.

Key words:
delirium; postoperative complications; alcohol consumption; bleeding; postoperative pain; risk factors; prostatectomy.

Apstrakt

Uvod/Cilj. Postoperativni delirijum (POD) kod bolesnika nakon nekardiohirurških procedura je često neprepoznat od strane anesteziologa. Cilj naše studije bio je procena učestalosti postoperativnog delirijuma (POD) i mogućih faktora rizika od njegovog nastanka kod bolesnika koji su bili u opštoj anesteziji usled hirurškog zahvata kod radikalne retropubične prostatektomije (RRP). **Metode.** Nakon dobijanja dozvole Etičkog komiteta, prospektivna studija

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obuhvatila je 80 bolesnika, ASA (*the American Society of Anestesiology*) skor II, koji su planirani za RRP u opštoj anesteziji. Bolesnici su ispunili MMSE test (*the Folstein Mini Mental State Exam*) preoperativno (veče pred operaciju) i postoperativno (48 sati nakon operacije). U studiji smo ipitivali prisutsvo i težinu delirijuma upotrebom CAM (*the Confusion Assessment Method*), a stepen agitacije i sedacije primenom RASS (*the Richmond Agitation and Sedation Scale*). **Rezultati.** Prosečni preoperativni MMSE skor (28,59 ± 1,04) bio je značajno snižen u postoperativnom periodu (27,74 ± 1,52; $p < 0{,}0001$). Sniženje prosečnog postoperativnog MMSE skora bilo je u korelaciji sa intraoperativnim krvarenjem ($p = 0.036$). Bolesnici sa višim intenzitetom bola imali su značajno snižen postoperativni MMSE skor (28,75 vs. 26,25; $p < 0{,}001$). Kod četiri od pet bolesnika koji su imale delirijum, zabeležen je redovni unos alkohola (> 1 pića dnevno) u preoperativnom periodu ($p < 0{,}0001$). Na osnovu RASS skora, agitacija je registrovana kod 13 (16,3%) bolesnika, i kod svih je zabeleženo značajno veće intraoperativno krvarenje u odnosu na ostatak ispitanika ($p < 0.001$). **Zaključak.** Rezultati naše studije pokazuju da je u preoperativnoj evaluaciji značajno registrovati preoperativnu konzumaciju alkohola, uzevši u obzir da su svi bolesnici 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 skor, što ukazuje na značaj adekvatnog intraoperativnog tretmana bolesnika u toku hirurgije i anestezije u cilju smanjenja rizika od razvoja POD.

Ključne reči:
delirijum; postoperativne komplikacije; alkohol, pijenje; krvarenje; bol, postoperativni; faktori rizika; 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 post-anesthesia care unit (PACU) and intensive care unit (ICU) in the upcoming years [3, 4]. Postoperative delirium in patients undergoing surgical procedures under general anesthesia is very important because it is 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 the 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 et al. [12] 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. 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. In a systematic review of 9 different studies, Orman et al. [14] 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 in order to ensure precise medication titration. This scale has been frequently used in the research and clinical practice settings for delirium assessment. In a prospective cohort study on 510 ICU patients, Vasilevskis et al. [17] 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 (RRP) under general anesthesia.

Methods

This prospective observational study was conducted after receiving approval from Ethical Committee of the Clinical Center of Serbia in Belgrade, Serbia. We consented and enrolled 80 male patients who were scheduled for radical retropubic prostatectomy at the Clinic of Urology, Clinical Center of Serbia. All the 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 were excluded from the study.

All 80 patients underwent radical retropubic prostatectomy under general anesthesia. Half an hour prior to the induction of anesthesia, the 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 *iv* of fentanyl and 2 mg/kg *iv* of propofol for induction of anesthesia, and 0.6 mg/kg *iv* of rocuronium bromide muscle relaxant to facilitate tracheal intubation. General anesthesia was maintained by a mixture of sevoflurane (Fex = 0.8%), nitrous oxide and oxygen (FiO_2 = 40). Neuromuscular antagonism maintenance dose 0.15 mg/kg of 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 *iv* 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 the surgery, residual neuromuscular blockade was reversed by mixture of atropine 0.75 mg *iv* and neostigmine 1.5 mg *iv*.

Upon admission to the ICU, patients received continuous *iv* infusion of tramadol 400 mg/day and diclofenac-Na^+ 75 mg *im* every 12 hours if the pain scores were more than 3 out of 10 on the Numeric Rating Scale (NRS).

We collected the 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), the American Society of Anestesiology (ASA) status, duration of anesthesia, duration of surgery, total blood loss, length of stay in the ICU and total length of stay in the hospital. Furthermore, we collected the MMSE scores preoperatively and postoperatively, and postoperatively CAM, RASS and NRS scores.

Twelve hours before the surgery patients were interviewed, and the Folstein MMSE questionnaire, 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 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 CAM test was used to evaluate the presence and severity of delirium and agitation. This test is easy to perform for the short period of time (5 minutes). The 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 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 the difference in pain scores at $\alpha = 0.05$, power = 0.95, and effect size of 0.36. We considered the difference of 3 in MMSE pain scores to be a 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). The Student's *t*-test and Pearson's Chi-square (χ^2) test were applied for testing differences between variables; as for testing the 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 RRP. The enrolled patient age range was between 44 and 74 years (the average age was 65 ± 6 years). All the patients were assigned ASA II status. The majority of the 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 consumption 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 the 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, $p < 0.0001$). The older patients had lower postoperative MMSE scores, but without any statistical significance (Figure 1). The 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).

The surgery duration was between 97 and 145 minutes (average 125 ± 11 minutes). The average duration of anesthesia was 151 ± 13 minutes (ranging 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 the surgery was 1,058 ± 278 mL. Throughout the entire surgery, hematocrit values were checked regularly, and blood transfusion was initiated if the hematocrit levels were below 0.33. The patients received 1–3 units (equivalent to 300–900 mL) of packed red blood cells (pRBCs). Compared to intraoperative bleeding, there was the mean postoperative MMSE scores decline. Specifically, less intraoperative bleeding was in correlation with the highest postoperative MMSE score ($\rho = 0.5397$), which was expressed as statistically significant $p = 0.036$ (Figure 3).

Postoperatively, patients reported pain scores between 0

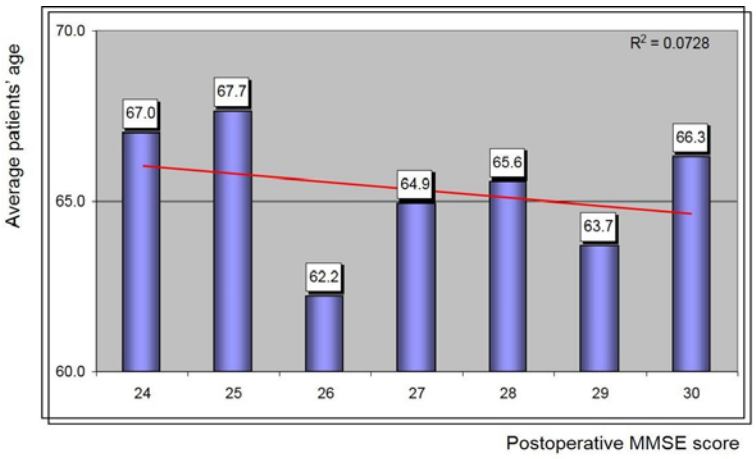

Fig. 1 –Postoperative Mini Mental State Exam (MMSE) scores and average patients' age.

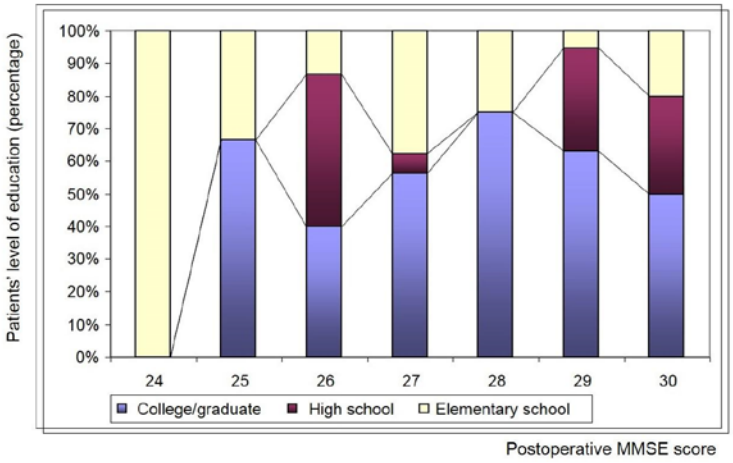

Fig. 2 – Postoperative Mini Mental State Exam (MMSE) scores and patients' level of education.

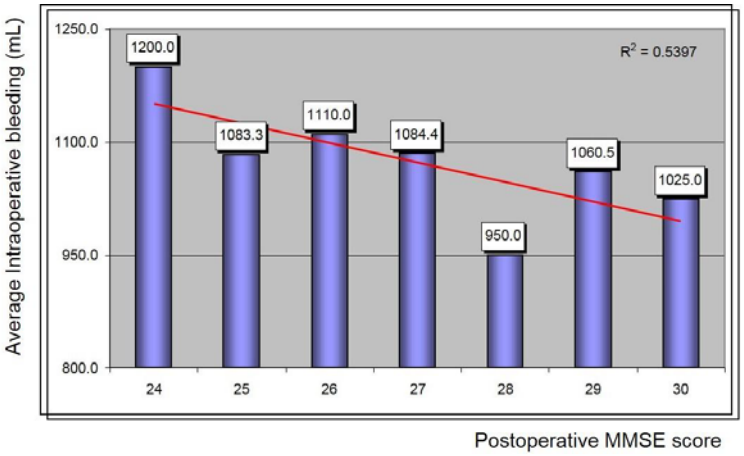

Fig. 3 – Postoperative Mini Mental State Exam (MMSE) scores and average intraoperative bleeding.

and 4 on an 11-point NRS scale (0–10), with an average of 2.33 ± 1.11. The 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 MMSE scores decline after the surgery (28.75 vs. 26.25; $p < 0.001$). Correlation between postoperative pain scores and MMSE scores decline was statistically significant ($p = 0.002$).

The CAM diagnostic algorithm was utilized for all the patients. According to the 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 ($\chi^2 = 63.16$; $p < 0.0001$). 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 the others (1,100 mL and 1,053.7 mL respectively), without statistical significance as well.

The RASS score (score of agitation and sedation) ranged from -2 to +4 for all patients. Most of the patients, 67 (83.7%), were awake, alert and demanding with the RASS score = 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. The patients with the RASS score = 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 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 ($R = 0.044$; $p = 0.881$).

Patients that had POD stayed in the ICU longer (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 stayed in the hospital slightly longer (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 RRP 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 the 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].

In a retrospective database analysis, Fineberg et al. [19] 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) and with the history of alcohol and/or drug abuse, having depression, some neurological or psychiatric disorders, electrolyte, pulmonary or renal abnormalities, anemia or congestive heart failure. 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]. The results of our study, as well as other studies, [19–21] confirmed that physician should emphasize the question regarding alcohol consumption prior to the 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 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] observed 51 patients (average 75.1 years of age) after major abdominal surgeries and showed that 26 of them (51%) developed delirium, and where delirium lasted for more than 3 days there was significantly greater blood loss.

The results of our study showed that patients experiencing more pain had significant MMSE decline after surgery. Leung et al. [26] also found that patients with higher postoperative pain, having received higher doses of opioids, had 3.6 times greater risk for developing POD.

Our patients who developed POD stayed longer in the ICU. Observing 48 patients, Ely et al. [27] studied the relationships between delirium in the ICU and outcomes including length of hospitalization. Multivariate analysis showed that POD was the most important independent factor for the length of hospitalization [27]. When compared to the other patients that have not developed delirium, our patients who developed POD did not stay in the hospital much longer. However, it is well known that these patients usually have prolonged hospitalization, 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. The patients that developed delirium (18.8%) were elderly (average 71 years of age), 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 stayed in the PACU and hospital longer, 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, they 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 the patients at high risk for developing delirium and apply different strategies to prevent delirium occurrence.

In a meta-analysis of 29 randomized controlled studies that reported perioperative interventions and postoperative delirium after non-cardiac surgeries, Moyce et al. [31] showed that perioperative geriatric consultation and lighter anesthesia were associated with the reduced risk of POD.

The limitations of our study are that it was done in a single center, patients were younger than 65 years of age, and certain patients had some form of psychiatric impairment, which could be the reason for relatively low incidence of postoperative delirium.

Conclusion

The 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 adequate intraoperative treatment of patients during surgery and anesthesia in order to reduce the risk of developing postoperative delirium.

Conflict of interest

Nothing to declare.

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