



Opioid-Free Anesthesia and Postoperative Cognitive Dysfunction After Minor Urological Surgery: A Case Series Study

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Abstract

Background: Postoperative cognitive dysfunction (POCD) is a complication that mainly occurs in adult patients and refers to a new-onset decline in cognitive function after anesthesia and surgery. The literature lacks evidence regarding opioid-free anesthesia and its impact on mental function postoperatively.

Objectives: The effect of opioid-free anesthesia on POCD following urological surgery has not been previously reported. Accordingly, we present a case series of 15 adult patients undergoing transurethral urological surgery under general anesthesia using an opioid-free protocol with dexmedetomidine, ketamine, and lidocaine.

Methods: Patients that underwent simple transurethral elective urological procedures under general opioid-free anesthesia were included. This case series is part of a prospective clinical study regarding opioid-free anesthesia and served as a pilot sample. The mini-mental state examination (MMSE) test, performed preoperatively and 12 hours postoperatively, was applied to assess POCD.

Results: Fifteen patients with a mean age of 68 years old were included in the study. The opioid-free protocol was associated with non-statistically significant changes of the MMSE test after minor urological procedures.

Conclusions: In our study, an opioid-free protocol of general anesthesia, using a mixture of dexmedetomidine, ketamine, and lidocaine, did not seem to have a negative impact on postoperative cognitive function in patients undergoing transurethral urological surgery. Further studies specifically designed to identify this effect are certainly required to further prove such an effect.

Keywords: Opioid-Free Anesthesia, Postoperative Cognitive Dysfunction, Urological Surgery, Perioperative Care, Cognitive Function

1. Background

Postoperative cognitive dysfunction (POCD) is a complication that mainly occurs in adult patients undergoing surgery and refers to a new-onset decline in cognitive function after anesthesia and surgery (1). This impairment includes various neuropsychological manifestations, such as verbal and visual memory, concentration, attention, executive functioning, and mental flexibility (1). To this day, there are no published studies investigating the impact of opioid-free anesthesia on POCD, an interesting fact to study, especially in the elderly. Opioid-free anesthesia, a relevantly recent anesthetic technique, excludes the use of intraoperative systemic, neuraxial, or intracavitary opioids (2). Intraoperative opioids are avoided using a multimodal approach, which stabilizes the sympathetic nervous system. Agonists of α_2 -adrenergic receptors (dexmedetomidine, clonidine) and local anesthetics (lidocaine, procaine)

are administered intravenously (2). Moreover, low-dose ketamine, magnesium, and dexamethasone are used as part of a multimodal analgesic regimen. However, since all these agents have neuromodulatory effects, their impacts on cognition are still unknown.

2. Objectives

We aimed to investigate the possible effect of opioid-free anesthesia on the cognitive function of a pilot sample of patients undergoing simple elective urological procedures.

3. Methods

From August to September 2019, 15 patients undergoing transurethral urological surgery under general opioid-free anesthesia were included in the study. This case series

is part of a prospective clinical study regarding opioid-free anesthesia and serves as a pilot sample. The Hospital Scientific Committee approved this study and written informed consent was obtained from all patients. The consolidated standards of reporting trials (CONSORT) flow diagram of the study is shown in Figure 1. Inclusion criteria were patients > 18 years old, American Society of Anesthesiologists (ASA) status I-III, and elective minor urological procedure. Exclusion criteria were inability to read or write, known psychiatric disease under medication, dementia, severe liver and/or renal disease with subsequent electrolyte disturbance, known allergy to the drugs used, known cardiac arrhythmia (2nd-3rd atrioventricular block), preoperative mini-mental state examination (MMSE) test < 23, major surgical complications, drug abuse, excessive alcohol intake, history of the same operation, and patient refusal. The demographic status, medical history, and educational level of the patients were documented.

The anesthetic technique was based on the Mulier protocol (2). Induction of anesthesia was performed using a mixture of dexmedetomidine (Dexdor, Orion) 0.1 µg/kg, ketamine (Ketamina Molteni, IFET SA) 0.1 mg/kg, and lidocaine (2% w/v lidocaine injection; BBraun) 1 mg/kg, plus propofol (Propofol-Lipuro 1%; BBraun) 2 mg/kg and rocuronium (Esmeron, MSD) 0.6 mg/kg ideal body weight. Maintenance was achieved with a mixture of dexmedetomidine, ketamine, and lidocaine and an infusion of propofol adjusted accordingly to the bispectral index (BIS; maintained between 40 and 60). Patients received ranitidine (Lumaren, ELPEN) 50 mg, dexamethasone (Dexaton, Vianex) 4 mg, and paracetamol (Aptel, Uni-Pharma) 1 g 15 minutes before the end of surgery. At the end of the procedure, propofol infusion was discontinued, and neuromuscular blockade was reversed with sugammadex (Bridion, MSD) according to train-of-four readings.

Cognitive function evaluation was performed in an undisturbed room. The MMSE test was used to assess cognitive status. Patients completed the test in 2 time frames: 1 day prior to surgery and 12 hours after surgery.

Regarding the statistical analysis, the Shapiro-Wilk test was performed to test for normal distribution of continuous variables. The results are given as mean ± SD or as median and interquartile range (IQR) according to the normality of continuous variables. All qualitative variables are presented as absolute or relative frequencies. Data were analyzed using Stata version 10.1 (Stata Corporation, College Station, TX 77845, USA).

4. Results

Fifteen patients (10 men and 5 women) were included in the study, with a mean age of 68 years old. Regarding

the educational level, 10 patients (66.67%) had received tertiary education. The study group characteristics are listed in Table 1. Seven patients underwent transurethral resection of bladder tumor. The mean duration of surgery was 26 minutes, and the mean time to extubation was 8.66 minutes. Intraoperative data are presented in Table 2. Regarding cognitive assessment, patients had a mean preoperative MMSE score of 28. The mean preoperative and postoperative MMSE test scores are exhibited in Table 3.

Table 1. Somatometric Characteristics

Variable	Results ^a
Age (y)	68 [50 - 76]
Weight (kg)	80.8 (16.51)
Height (m)	1.71(0.09)
BMI (kg/m ²)	27.29(3.93)
Gender (male vs female)	10 (66.67%) vs 5 (33.33%)
ASA (I/II/III)	4(26.67%) 9(60%) 2(13.33%)
^b Educational level (I vs II)	5(33.33%) vs 10 (66.67%)

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

^a Results are presented as mean (SD) or as median (IQR) according to the distribution of continuous variables. Categorical variables are presented as absolute and relative frequencies.

^b Educational level: I, "secondary education"; II, "tertiary education".

Table 2. Intraoperative Data

Variable	Results ^a
Transurethral resection of bladder tumor	7
Ureter lithotripsy	3
Direct vision internal urethrotomy	1
Cystourethroscopy	3
Nephrolithotripsy	1
Duration of surgery (min)	26 [19 - 74]
Duration of anesthesia (min)	48 [39 - 97]
Time to extubation (min)	8.66 (1.67)
BIS at baseline	97.5 [95.5 - 98]
BIS at extubation	81.5 [80 - 84.5]

Abbreviation: BIS, bispectral index.

^a Results are presented as mean (SD) or as median (IQR) according to the distribution of continuous variables.

5. Discussion

POCD was first described in 1980 (3). However, until now, there is no unanimous agreement in the literature regarding the definition of POCD. For instance, POCD does

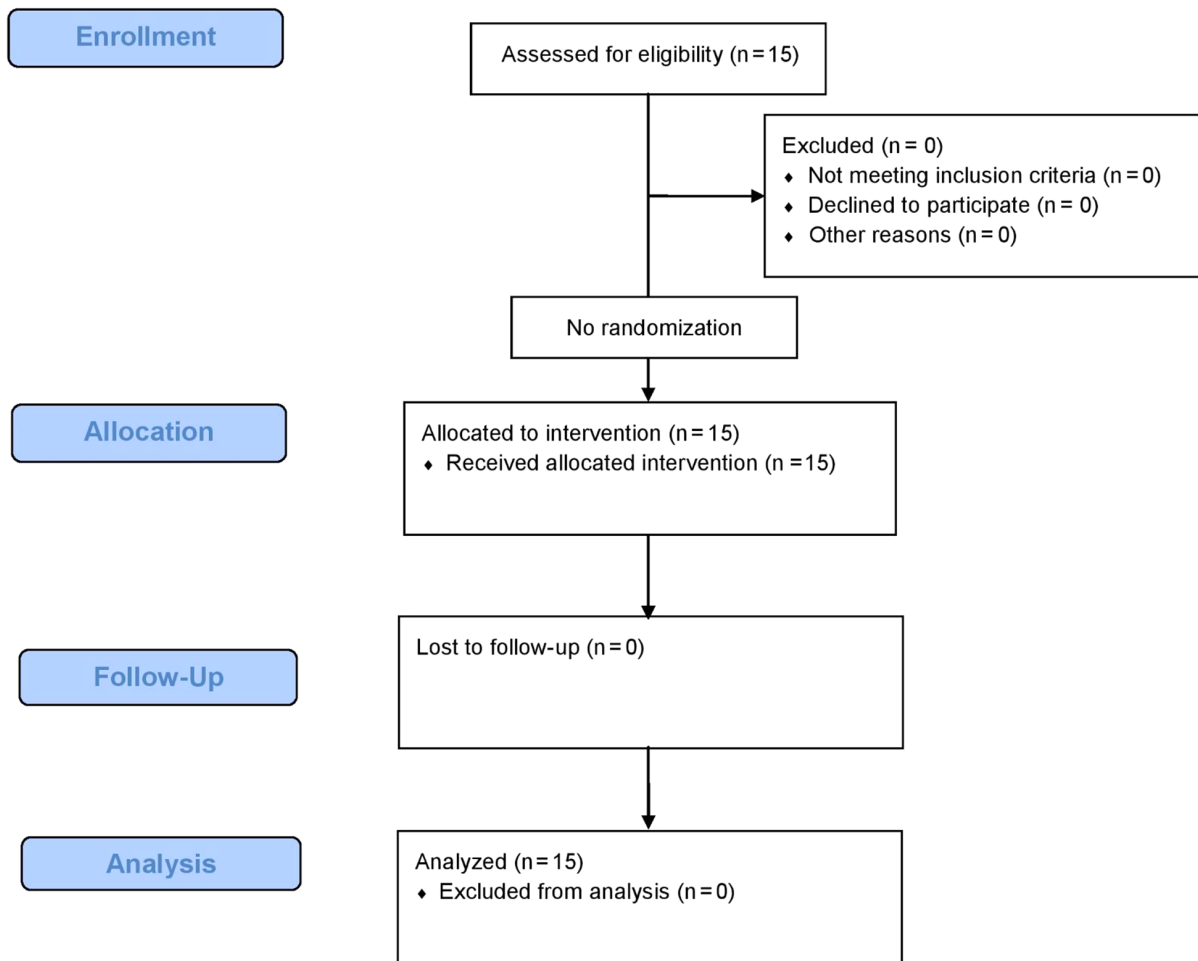


Figure 1. The consolidated standards of reporting trials flow diagram

Table 3. Cognitive Assessment

Variables	Results ^a
MMSE test score (baseline)	28 [26 - 30]
MMSE test score (12th hour)	28.06 (1.75)

Abbreviation: MMSE, mini-mental state examination.
^a Results are presented as median (IQR) or mean (SD).

not appear as a term in the Diagnostic and Statistical Manual of Mental Disorders (DSM). POCD is characterized by subtle changes in neuropsychological tests performed preoperatively and postoperatively. It can have a long-term effect on patients up to 5 years after the surgical procedure (4). Since elderly patients have a higher risk of POCD, they have also attracted major attention among researchers (1).

There are several risk factors associated with POCD. Advanced age is a major risk factor for POCD. Preexisting cere-

bral, cardiac, or vascular disease, preoperative mild cognitive impairment, low educational level, and history of alcohol abuse are some patient-related risk factors for POCD. Furthermore, extensive surgical procedure, intra- or postoperative complications, secondary surgery, long-acting anesthetic, marked disturbance of homeostasis, organ ischemia due to hypoxia and hypoperfusion, intra- or postoperative anesthetic complications have been identified as further risk factors for POCD (5).

The MMSE test is a 30-item measure of global cognition that is used to assess orientation to time and place, related to memory, attention, calculating, recalling, concentration, object naming, reading, writing, and carrying out complex orders. Points are awarded for each correct answer: 28 - 30 for the norm and 24 - 27 for minor cognitive disorders; a score below 24 points suggests dementia syndrome according to the diagnostic criteria (6).

To our knowledge, no study has investigated the effect of opioid-free anesthesia on POCD. This is very important because the pharmacological agents used for opioid-free anesthesia might have several effects on cognition due to their neuromodulatory action, such as ketamine or dexmedetomidine, alone or in combination. Therefore, it is essential to know if this effect exists, especially in the elderly or after long opioid-free procedures.

As a highly selective and potent alpha-2 adrenergic agonist, dexmedetomidine is used to prevent or treat postoperative agitation and delirium and has several advantageous effects such as anxiolysis, analgesia, anesthetic-sparing, and sympatholytic properties with minimal respiratory depression (7-9).

Moreover, our study is consistent with several studies, suggesting that educational status negatively correlates with memory (10). Patients with a higher educational level have been found to be less likely to present with POCD compared with patients with lower educational levels (10).

Previous studies addressing the role of anesthesia on cognitive dysfunction after urological surgery have yielded conflicting results. For instance, the study of Kermany et al. concluded that spinal anesthesia contributed to lower disturbance in cognitive function after surgery than general anesthesia (11). On the contrary, Lertakyamane and Somprakit found no significant difference postoperatively in mental scores after both general and regional anesthesia (12). According to their study, age-but not anesthetic technique-affected mental scores after surgery.

In another study, Wioletta et al. found that POCD was independent of the type and duration of anesthesia (13).

The literature lacks evidence regarding opioid-free anesthesia and its impact on mental function postoperatively. Our findings indicated that an opioid-free anesthetic protocol might have a protective effect on POCD. This is an important observation as the impact of opioid-free anesthesia on POCD has not yet been studied, not only in urological surgery, but in the general surgical population. The exact effect of opioid-free anesthesia on POCD remains to be determined, especially in the elderly, who are more vulnerable to POCD, and in procedures of longer duration (14).

Limitations to our study include that the findings presented in this paper are preliminary data with a relatively small sample size but certainly indicate the necessity for further investigation. Second, ketamine was shown to increase the high-frequency electroencephalogram (EEG) activity, thus making EEG-monitors, including the BIS monitor, unpredictable (15). Ketamine may also change the EEG power spectrum by causing a rise in theta activity, and this influences the manner in which the BIS values are calculated by a commercially secret algorithm (16). On the other

hand, studies have reported that low-dose ketamine had no effect on BIS values (17). This discrepancy between studies indicates the difficulty of interpreting entropy and BIS values with ketamine infusion in clinical practice.

5.1. Conclusions

Overall, this study revealed that an opioid-free protocol of general anesthesia, using a mixture of dexmedetomidine, ketamine, and lidocaine, did not seem to have a negative impact on postoperative cognitive function, as it did not cause a change between preoperative and postoperative MMSE scores. This observation suggests that an opioid-free anesthetic protocol should be further investigated in larger populations and longer operations to prove such an effect, compared to opioid-based general anesthesia and/or regional anesthesia as well.

Footnotes

Authors' Contribution: G. E. conceived the original idea and protocol, designed the evaluation, and wrote the manuscript. C. B. contributed to the development of the protocol, participated in designing the evaluation, performed parts of the statistical analysis, and helped to draft the manuscript. E. S re-evaluated the clinical data, revised the manuscript, and performed the statistical analysis. L. R. collected the clinical data, interpreted them, and revised the manuscript. P.M. was responsible for the critical revision of the manuscript for important intellectual content and supervised the study. All authors read and approved the final manuscript.

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