Ann Med Res 2021;28(6):1201-5

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.09.920

Original Article

The effects of sedation with propofol and propofol-ketamin combination on postoperative cognitive function in elderly patients undergoing spinal anesthesia

Yusuf Ziya Colak[1], Ulku Ozgul[1], Duygu Demiroz Aslan[1], Hatice Birgul Cumurcu[2], Cemil Colak, Mahmut Durmus[1]

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Inonu University, Malatya, Turkey
[2]Department of Psychiatry, Faculty of Medicine, Inonu University, Malatya, Turkey
[3]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Inonu University, Malatya, Turkey

Abstract

Aim: Elderly patients frequently require surgery. Postoperative cognitive dysfunction (POCD) is an adverse event and reduces the patient's quality of life. We aimed to compare the effects of sedation applied with propofol or propofol-ketamine (ketofol) combination on hemodynamics and POCD during spinal anesthesia in elderly patients undergoing urological surgery.

Materials and Methods: Study was performed on 60 ASA I-III patients over 65 years of age. Before the operation (standardized Mini Mental Test) sMMT was applied by a blind researcher. The cases were randomly divided into two groups as propofol (Group P, n=30) and ketofol (Group K, n=30). ECG, SpO_2, Bispectral Index (BIS), noninvasive blood pressure (NIBP) was monitored. After spinal anesthesia, group P received propofol 0.5 mg/kg IV bolus and then 1.5 mg/kg/hour infusion. Group K received propofol 0.4 mg/kg and ketamine 0.1 mg/kg IV bolus and then propofol 1.2 mg/kg/hour and ketamine 0.3 mg/kg/hour infusion. Hemodynamic and respiratory data were recorded. The sedation level was monitored by RAMSAY sedation score. sMMT was repeated by the researcher who performed the initial test at postoperative first 24 hours and postoperative 3rd day.

Results: Significant decreases were observed for heart rate, SAP, and MAP in both groups compared with baseline values. No statistically significant difference was detected between the groups in sMMT values at postoperative 1st and 3rd days. Within-group comparisons revealed significant differences between preoperative sMMT and postoperative 1st day sMMT and between postoperative 1st and postoperative 3rd day sMMT ($p< 0.001$). No difference was detected between preoperative and postoperative 3rd day sMMT ($p< 0.25$). In Group P, there was statistically significantly higher injection pain ($p<0.05$).

Conclusion: In this study we found that the recovery period of the patients was longer and BIS values were higher in group K, but no significant difference could be found in hemodynamic and cognitive functions.

Keywords: Cognitive dysfunction; elderly patient; ketamine; propofol; spinal anesthesia

INTRODUCTION

With the growing number of the elderly population, the need for anesthesia increases due to the rise in procedures requiring surgery (1). Regional anesthesia plays an essential role in these patients, both during surgery and for pain management (2).

There is a growing awareness that sedation is required for the successful and safe application of regional blocks in elderly patients. However, caution should be exercised in the sedation of elderly patients, due to pharmacokinetic and pharmacodynamic changes that occur with age and result in increased sensitivity to many sedatives (3). Benzodiazepines, intravenous anesthetic agents, or opioids are used for sedation to reduce the stress of the patient during the operation period, increase the adaptation to the environment, and provide a lowered level of awareness or amnesia that patients need during surgery (4).

Postoperative cognitive dysfunction (POCD) is the change in cognitive function that may last for months, sometimes be permanent, and evaluated with neuropsychological tests. Factors such as the type of surgery, the duration of the operation, the premedication applied, and the depth of anesthesia affect the cognitive functions (5,6).

Received: 07.09.2020 **Accepted:** 19.11.2020 **Available online:** 24.06.2021
Corresponding Author: Yusuf Ziya Colak, Department of Anesthesiology and Reanimation, Faculty of Medicine, Inonu University, Malatya, Turkey **E-mail:** yzcolak@gmail.com

Severe hypotension due to spinal anesthesia is due to arterial dilatation as well as ponding in the venules that cannot maintain tone. Circulatory changes deviate around 15% in healthy people with good fluid balance. In situation of dehydration and hypovolemia, the blood pressure drop becomes more pronounced. Decreased water ratio, cardiac reserve and baroreceptor response increase the risk of hypotension. Therefore elderly patients under spinal anesthesia are at greater risk of hypotension. The underlying pathophysiology of POD or POCD is multifactor and complicated. Immutable risk factors, such as surgery types, age and baseline cognitive function have been identified. Although the definitive preventive or therapeutic measure of POD or POCD is still unknown, there are increasing studies shows that hypoperfusion of the brain caused by hypotension during the surgery may be one pathogenic mechanism (7).

Benzodiazepines, propofol, clonidine, ketamine, opioids, and propofol-ketamin combination are used for sedation. Even low doses of sedation can lead to severe respiratory depression, hemodynamic instability, and changes in consciousness. The effects of sedative agents on cognitive functions in the elderly have not been fully elucidated.

The aim of this study was to compare the effect of sedation applied with propofol or propofol-ketamine combination on hemodynamics and cognitive functions during spinal anesthesia in elderly patients undergoing urological surgery.

MATERIALS and METHODS

The study included 60 ASA I - III patients at or above 65 years who would undergo elective urological surgery under spinal anesthesia, with the approval of the Ethics Committee (Malatya Clinical Research Ethic Committee-2012/95).

Patients who have neuropsychiatric disorders, alcohol and drug addiction, chronic opioid and sedative drug use, Alzheimer's or Parkinson's disease, history of allergy to study drugs, and contraindications to spinal anesthesia were not included in the study.

Patients were divided into two groups, using the sealed envelope method, as the propofol group (Group P, n=30) and the propofol-ketamine combination group (Group K, n = 30). sMMT was applied to the patients who did not receive premedication before the operation by a researcher blinded to the groups. A sMMT score of 23 or less was considered as cognitive dysfunction. Standard monitorization was provided to the patient in the operation room with electrocardiography (ECG), peripheral oxygen saturation (SpO_2), noninvasive blood pressure (NIBP), and bispectral index (BIS, A-2000 Bispectral Index, Aspect Medical Systems). An intravenous IV line was performed, and hydration was performed with a 10 mL/kg Ringer Lactate solution. Spinal anesthesia was performed by administering 2-2.2 mL 0.5% hyperbaric bupivacaine (Marcaine® Spinal Heavy 0.5%) to the subarachnoid area with a 25 gauge spinal needle through the L3-L4 or L4-L5 intervertebral space in the sitting position. The patients were placed in a supine position with their heads up 30o. Sensory block was evaluated with pinprick test using a 22 gauge hypodermic needle, and motor block was evaluated with modified Bromage scale (Bromage scale; 0= no paralysis at all, free movement of legs and foot, 1= unable to raise hip, 2= unable to raise hip and knee, 3= unable to raise hip, knee and foot).

In patients with sensory block levels of T10 and above, sedation was initiated, surgery was allowed, and oxygen was given through a face mask throughout the procedure. In Group P, propofol was infused at a rate of 1.5 mg/kg / hour after 0.5 mg/kg IV bolus. In Group K, propofol 0.4 mg/kg and ketamine 0.1 mg/kg were given as IV bolus, then propofol 1.2 mg/kg/hour and ketamine 0.3 mg/kg / hour infusion were administered. It was planned to halve the infusion dosages when the respiratory rate was less than 10/minute and SpO_2 was less than %94 and to stop the infusion completely when the respiratory rate was less than 8/minute and SpO_2 was less than %90.

Sedation was evaluated with Ramsay sedation score. We tried to keep Ramsay sedation score around three. Ramsay sedation score was as follows: 1=awake; 2=drowsy, easily awakened by verbal stimulation; 3=awakened by verbal stimulation; 4=sleeping, not responding to verbal and physical stimulation. Drug infusion stopped at the end of the surgical procedure.

Hemodynamics, respiratory rates, sedation scores, and BIS values of the patients were recorded before the operation, after spinal anesthesia, after sedation, and every 5 minutes during the operation. A decrease of 20% or more in mean arterial pressure than the baseline value was considered hypotension, and 250 mL of fluid infusion and 5 mg ephedrine were administered, when necessary. No matter what systolic arterial pressure was, 0.5 mg atropine was administered when heart rate (HR) was <45 beats / min and when low blood pressure did not improve with ephedrine. When nausea-vomiting developed, it was treated with 10 mg IV metoclopramide. After the cessation of sedation, follow-up of the cases was continued at the postoperative care unit until the Modified Aldrete Score reached 9, and this period was recorded. The sMMT was repeated by the researcher who performed the first test within the first 24 hours and on the third postoperative day postoperatively. Injection pain (the intensity of pain was graded using a verbal rating scale), nausea, vomiting, and hallucination complaints of the patients were recorded.

SPSS 20.0 package program was used for the statistical analysis of the data. The normal distribution of the data was analyzed with the Shapiro-Wilk test. Independent samples T-test was used to evaluate the difference between the groups for quantitative variables. Friedman test was used for the repeated measurements for MMT scores and hemodynamics. The Wilcoxon test with

Bonferroni correction was used for multiple comparisons. Pearson Chi-square test, Yates corrected chi-square test, and Fisher's exact chi-square test were used to compare categorical variables between the groups. Descriptive statistics were mean ± standard deviation (mean ± SD), median (the lowest – the highest), or frequency (n). P<0.05 was accepted as significant for all evaluations.

RESULTS

Demographic data, anesthesia, and surgery times of the groups were similar (Table 1).

Table 1. Demographic datas, operation time (mean±SD)

	Group P (n=30)	Group K (n=30)
Age (year)	70.46 ± 4.63	70.60 ± 5.19
Weight (kg)	76.36 ± 8.82	75.50 ± 12.68
Height (cm)	168.70 ± 4.19	168.00 ± 5.29
Operation time (min)	37.5 ± 17.20	44.00 ± 21.90

No statistically significant difference was found between the groups for HR (p> 0.05) (Table 2). Significant differences were found in HR at 5., 10., 15., 20., and 25. minutes after sedation compared with baseline values in group P (p< 0.05). Significant differences were found in HR at 10., 15., 20., and 25. minutes after sedation compared with baseline values in group K (p< 0.05).

Table 2. HR Values of the Cases (Median (min-max), bpm)

	Group P (n=30)	Group K (n=30)
Baseline	73.500 (50 - 120)	78.000 (49 - 126)
After spinal anesthesia	73.500 (53 - 127)	74.500 (46 - 120)
After sedation	69.500 (50 - 112)*	75.500 (51 - 120)
5. min	68.500 (47 - 109)*	72.000 (48 - 122)
10. min	66.000 (49 - 103)*	67.000 (45 - 116)*
15. min	63.500 (49 - 99)*	68.000 (46 - 115)*
20. min	65.000 (49 - 96)*	67.500 (49 - 116)*
25. min	63.500 (50 - 96)*	66.000 (50 - 114)*

*Within group comparisons, HR compared with baseline, p< 0.05

No statistically significant difference was found between the groups in systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP). Within-group comparisons statistically significant decreases were found in MAP compared with baseline at 5., 10., 15., 20., and 25. minutes after sedation in groups P and K (p< 0.05).

There was no difference between sensory and motor block levels. No statistically significant difference could be found between the groups in the Ramsay sedation score (Figure1).

Table 3. MAP Values of the cases. Median (min-max, mmHg)

	Group P (n=30)	Group K (n=30)
Baseline	114.5 (84 - 141)	106.500 (86 - 139)
After Spinal Anesthesia	106.000 (80 - 152)	106.500 (76 - 135)
After Sedation	90.500 (75 - 130)*	99.500 (75 - 134)*
5. min	87.000 (64 - 153)*	94.500 (68 - 130)*
10. min	91.500 (67 - 137)*	94.000 (67 - 136)*
15. min	90.000 (63 - 120)*	92.000 (69 - 134)*

*Differences in MAP compared with baseline values in within group evaluations, p< 0.05

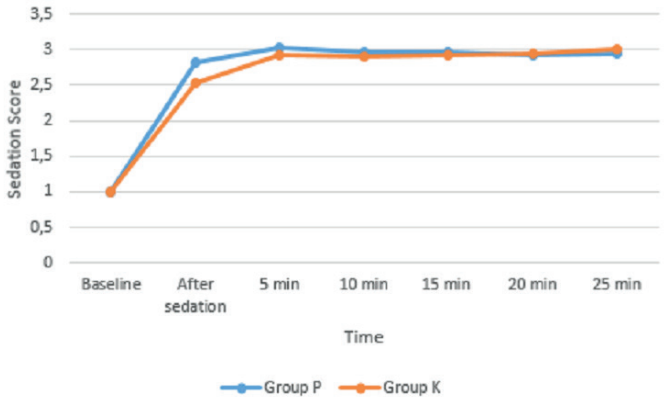

Figure 1. The ramsay sedation score values of the groups

There was a statistically significant difference between the groups in the Modified Aldrete Recovery score (p< 0.05). The time to reach 9 points in the Modified Aldrete Score was 2.56 ± 0.50 minutes in Group P and 3.76 ± 0.85 minutes in Group K.

No statistically significant difference could be found between the groups in sMMT values at the preoperative period and postoperative 1. and 3rd days (p>0.05) (Table 4). Within-group comparisons revealed significant differences between preoperative sMMT values and postoperative 1st day sMMT values and between postoperative 1st day and postoperative 3rd day sMMT values in both groups (p<0.001). No difference could be found between preoperative sMMT and postoperative 3rd day sMMT values.

Table 4. sMMT values. Median (the lowest- the highest)

	Group P (n=30)	Group K (n=30)
sMMT 1	24 (18-29)	24 (20-29)
sMMT 2	23 (16-28)*	22 (18-27)#
sMMT 3	24 (18-29)*	24 (20-29)#

sMMT 1; preoperative sMMT values, sMMT 2; postoperative 1. day sMMT values, sMMT 3; postoperative 3rd day values. *Within-group evaluations (Group P), comparison between sMMT1 and sMMT2, p<0.05
Within group evaluations (Group K), comparison between sMMT2 and sMMT3, p< 0.05

In Group P, there was statistically significantly higher injection pain (p<0.05). No patient developed nausea-vomiting, increased secretions, or hallucinations.

Statistically significant differences were found in BIS values at 5., 10., 15., 20., and 25. minutes after sedation (p< 0.05) (Figure 2).

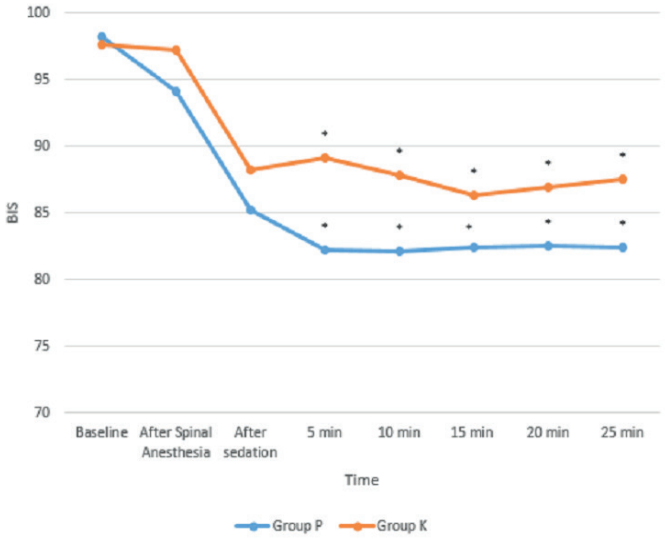

Figure 2. BIS values of the groups *Between groups BIS values, p< 0.05

DISCUSSION

In this study, we compared propofol and propofol-ketamin combination in elderly patients undergoing urological surgery under spinal anesthesia. Patients who received propofol-ketamin combination had longer recovery times and higher BIS values. No differences could be found in hemodynamics and cognitive functions.

Sedation applied during regional anesthesia was found to decrease fear and anxiety and increase patient tolerance and comfort (8). Yaddanapudi et al. (9) infused propofol at 3 mg/kg/hour for sedation to patients above 60 years of age undergoing spinal anesthesia. They reported that propofol was titrated better than midazolam, it achieved adequate sedation, but it caused hypotension requiring sedation. We used lower propofol (1.5 mg/kg/hour) infusion rates (1.5 mg/kg/hour) in the propofol group than Yaddanapudi et al. Although lower blood pressure values were observed than baseline, hypotension requiring treatment was not recorded.

Propofol-ketamine combination has been used in adult and pediatric patients during spinal anesthesia and has been shown to maintain hemodynamic stability compared to propofol sedation. We also used propofol-ketamin combination at doses used by Singh et al. (10) and Frizelle et al. (11) for elderly patients during spinal anesthesia. However, unlike previous studies, lower values were measured in blood pressure compared to baseline in our study. We suggest that this difference may be due to age-related changes in cardiac functions (12).

POCD is a clinical condition that can occur as a result of central nervous system impairment, can occur in different periods and degrees, and can vary from concentration difficulty to delirium (13). It is common in the elderly after non-cardiac surgery. Risk factors for early POCD include age, duration of anesthesia (general and regional anesthesia), low education level, recurrent operation, postoperative infection, and respiratory complications (14). Although the frequency of POCD is expected to be lower in regional anesthesia compared with general anesthesia, studies yield conflicting results (15). Some studies reported no significant difference (16), while others reported better cognitive functions in the early period in regional anesthesia (17). In a study investigating delirium developing after urological surgery in elderly patients, intraoperative hypotension developed in the majority of patients and intraoperative hypotension was a risk factor for POCD (18). Therefore, we used ketamine, which is known to protect hemodynamics well, in combination with propofol. In our study, a similar decrease was observed in MAP compared to baseline in both groups. However, these MAP levels didn't pose a risk of developing POCD.

Liang et all. evaluated the effects of adding ketamine to propofol on cognitive functions in adult patients undergoing sedation for colonoscopy. Compared to baseline, the performance on detection and identification tasks were significantly impaired after the procedure in both group and MAP was high in propofol-ketamine group. Similarly, in our study, the sMMT test in both groups decreased compared to baseline values but there was no statistically significant difference in hemodynamic values between groups. This may be because the dose of ketamine added to propofol was lower than in the study above (19).

BIS is used to monitor conscious sedation. A good correlation was found between sedation scores and BIS in patients deeply sedated with propofol. Although there are studies showing higher BIS levels than expected with ketamine, other studies demonstrated no effect with ketamine (20). In our study, BIS values were significantly higher in the propofol-ketamine combination compared to the propofol group at similar Ramsay sedation levels. This result is consistent with studies showing higher than expected BIS levels with ketamine.

Sieber et al. reported that mild propofol sedation, which they applied during spinal anesthesia with a BIS value above 80, decreased postoperative delirium frequency by 50% compared to deep sedation in which BIS was below 50 (21). In our study, we tried to keep Ramsay sedation score around three and BIS values were above 80 in both groups. We did not have any cases of postoperative delirium.

Casati et al. (22) compared cognitive functions between sevoflurane anesthesia and spinal anesthesia, and found that MMT scores in both groups were lower than the baseline values. Similarly, in our study, MMT scores

decreased significantly on the postoperative 1st day compared to the preoperative period in both groups, it reached the baseline values on the postoperative 3rd day, and there was no difference between the groups in terms of cognitive functions.

Celik et al. compared the effects of propofol-ketamine and propofol-fentanyl combination on recovery after total intravenous anesthesia, and reported that recovery time was longer with propofol-ketamine combination (23). Recovery times in our study were much shorter than this study because our study subjects only received sedation. However, similar to this study, the recovery time after sedation with the propofol-ketamine combination was significantly longer than it was in the propofol group.

The analgesic effect of ketamine has been well studied. It has been reported to reduce injection pain (24). Similarly, in our study, injection pain was statistically significantly lower in group K.

CONCLUSION

In conclusion, this study demonstrated that propofol and propofol-ketamine combination used for sedation had similar effects on hemodynamic and cognitive functions in elderly patients undergoing spinal anesthesia.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Malatya Clinical Research Ethics Committee 2012/95.

REFERENCES

1. Erden IA, Uzun S, Turgut HC et al. Anesthesia in elderly patients. Akad Geriatri 2009;3;162-6.
2. Ozatamer O, Alkis N, Batislam Y et al. Current issues in anesthesia. Nobel Matbaacılık 2002;197-202.
3. Carole L, Curtis D, Ban CHT. Practical regional anesthesia guide for elderly patients. Drugs Aging 2019;36;213-34.
4. Mackenzie N. Sedation during regional anaesthesia: indications, advantages and methods. Eur J Anaesthesiol 1996;13;2-7.
5. Ramaiah R, Lam AM. Postoperative cognitive dysfunction in the elderly. Anesthesiol Clin 2009;27;485-96.
6. Canet J, Raeder J, Rasmussen LS, et al. Cognitive dysfunction after minor surgery in the elderly. Acta Anaesthesiol Scand 2003;47;1204-10.
7. Xiaojin F, Jialing H, Fuzhou H, et al. The correlation of intraoperative hypotension and postoperative cognitive impairment: a meta-analysis of randomized controlled trials. BMC Anesthesiol 2020;20;193
8. Hu P, Harmon D, Frizelle H. Patient comfort during regional anesthesia. J Clin Anesth 2007;19;67-74.
9. Yaddanapudi S, Batra YK, Balagopal A, et al. Sedation in patients above 60 years of age undergoing urological surgery under spinal anesthesia: comparison of propofol and midazolam infusions. J Postgrad Med 2007;53;171-75.
10. Frizelle HP, Duranteau J, Samii K. A comparison of propofol with a propofol-ketamine combination for sedation during spinal anesthesia. Anesth Analg 1997;84;1318-22.
11. Singh R, Batra YK, Bharti N, et al. Comparison of propofol versus propofol-ketamine combination for sedation during spinal anesthesia in children: randomized clinical trial of efficacy and safety. Paediatr Anaesth 2010;20;439-44.
12. Sielenkamper AW, Booke M. Anaesthesia and the elderly. Lippincott Williams & Wilkins, Inc 2001;14;679-84.
13. Monk TG, Price CC. Postoperative cognitive disorders. Curr Opin Crit Care 2011;17;376-81.
14. Hartholt KA, Van der Cammen TJ, Klimek M. Postoperative cognitive dysfunction in geriatric patients. Z Gerontol Geriatr 2012;45;411-6.
15. Bryson GL, Wyand A. Evidence-based clinical update: general anesthesia and the risk of delirium and postoperative cognitive dysfunction. Can J Anaesth 2006;53;669-77.
16. Wu CL, Hsu W, Richman JM, et al. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. Reg Anesth Pain Med 2004;29;257-68.
17. Rasmussen LS, Johnson T, Kuipers HM, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003;47;260-66.
18. Tognoni P, Simonato A, Robutti N, et al. Preoperative risk factors for postoperative delirium (POD) after urological surgery in the elderly. Arch Gerontol Geriatr 2011;52;166-9.
19. Tian L, Luan H, Zhu P, et al. A randomized controlled trial for measuring effects on cognitive functions of adding ketamine to propofol during sedation for colonoscopy. Medicine. 2020;99;36-21859.
20. Höhener D, Blumenthal S, Borgeat A. Sedation and regional anaesthesia in the adult patient. Br J Anaesth 2008;100;8-16.
21. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc 2010;85;18-26.
22. Casati A, Aldegheri G, Vinciguerra E, et al. Randomized comparison between sevoflurane anaesthesia and unilateral spinal anaesthesia in elderly patients undergoing orthopaedic surgery. Eur J Anaesthesiol 2003;20;640-66.
23. Celik N, Bombaci E, Colakoglu S, et al. Propofol-ketamin ve propofol-fentanil ile yapılan total intravenöz anestezide hemodinami ve derlenmenin karşılaştırılması. J Kartal TR 2000;11;801-4.
24. Kalindi AD. Pain on propofol injection: Causes and remedies. Indian J Pharmacol 2016;48;617-23.