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# Effect of Low Dose Ketamine on Postoperative Cognitive Dysfunction in Geriatric Patients Undergoing Abdominal Surgery

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**Abstract:** We aimed to investigate the effect of low dose ketamine on cognitive functions in geriatric patients undergoing elective abdominal surgery under general anesthesia. Forty patients aged 65 and older planned for elective abdominal surgery were randomly divided into two groups. While 5 ml saline was administered to the control group, ketamine group received iv 0,5 mg/kg ketamine 5 minutes before induction. Hemodynamic variables, BIS, $etCO_2$ and ET-Sevo were measured every 15 min until the end of the operation. Furthermore, extubation time, time to spontaneous eye opening and Aldrete Scores were measured. Mini Mental State Examination (MMSE), Trieger Dot Test (TDT) and Clock Drawing Test (CDT) were performed 24 hours prior to the operation and repeated 1 and 6 hours after the operation. There were not statistical differences in terms of demographic characteristics ($p>0.05$). Total remifentanil consumption in control group was significantly higher than ketamin group ($p<0.001$).There were no differences between two groups with respect to the extubation time, time to eye opening and Aldrete Scores at 2$^{nd}$ and 5$^{th}$ minutes. ($p>0.05$). MMSE, TDT, CDT values measured preoperatively didn't vary statistically between the groups ($p>0.05$) but results at the postoperative 1$^{st}$ and 6$^{th}$ hours were higher in ketamine group ($p<0.01$). Results at postoperative 1$^{st}$ hour were lower in the control group, whereas results at the 6$^{th}$ hour increased although they didn't return to the preoperative values. Results at postoperative 1$^{st}$ hour in ketamine group were significantly different and lower than the preoperative and postoperative values ($p<0.001$). We concluded that low dose ketamine had positive effects on cognitive functions in geriatric patients undergoing elective abdominal surgery under general anesthesia.

**Key words:** Ketamine, cognitive function, geriatric patient, abdominal surgery

## INTRODUCTION

The postoperative psychomotor deterioration is defined as the postoperative cognitive dysfunction (POCD) and its postoperative incidence is very high among the geriatric patients undergoing major surgery (1). The psychomotor function disorder may be associated with the anesthetic agents, known to have dosage and time dependent effects on the cognitive functions, as well as the physiological changes resulting from the anesthesia (2,3). Postoperative deterioration in cognitive functions and psychomotor capabilities is usually temporary and transient. It has been demonstrated that these symptoms can be presented even under a very short-term anesthesia (2-4).

Ketamine is a sedative, hypnotic, amnestic and analgesic potent agent that has been shown to play an effective role in the balanced anesthesia and to reduce the need for anesthetics (5). When administered at normal doses, ketamine deteriorates the functions of the brain and affects the cognitive functions. The sub-anesthetic doses of ketamine administered before induction have been shown to have positive effects on recovery and cognitive functions (6).

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The aim of this study was to investigate the effects of sub-anesthetic doses of ketamine administered before induction on postoperative recovery and cognitive functions in geriatric patients undergoing elective abdominal surgery under general anesthesia.

## MATERIALS and METHODS

After the Ethics Committee approval (Clinical Drug Trials Ethics Advisory Board of the Ministry of Health on 27 June 2012, EC.2012/45 ) was obtained, this prospective, randomized, double-blind, placebo-controlled study comprised 40 geriatric patients aged 65 and older who were at least literate, ASA physical status I-II were planned to undergo elective abdominal surgery involved after written informed consent was taken. Total Abdominal Hysterectomy was planned for 25 of the patients, while 15 patients were to be operated due to inguinal hernia.

Patients who had significant coronary, pulmonary, renal, hepatic diseases, neuropsychiatric diseases affecting the CNS and cognitive functions, fever and infection, metabolic and endocrinal diseases, malnutrition and dehydration, low levels of vitamin B12 and folate; those who took medications that affected CNS, who were alcohol and substance addicts, smokers, urgent cases, patients in the risk group of ASA III and above, patients younger than 65, those who scored 23 and lower in the MMSE performed one day before the operation were excluded from the study.

One day before the operation, MMSE, Trieger Dot Test (TDT), Clock Drawing Test (CDT) were performed for the patients involved in the study to determine the normal cognitive functioning levels. Patients drew the closed envelopes in which the group names were written and they were randomly assigned to the control group and ketamine group. Premedication was not administered to avoid any impact on the cognitive functions. Peripheral vascular access was established with a 20G cannula in the operating theatre and they received 500 ml 0.9% NaCl solution until the induction of anesthesia. Electrocardiogram (ECG), peripheral oxygen saturation ($SpO_2$), noninvasive arterial pressure (NIBP) monitoring (Datex-Ohmeda S/5 Aisys®, Sweden), BIS (BIS VISTA™ Monitoring System, USA), neuromuscular monitoring (NMT) (TOF-Watch S®, Organon, Ireland) were performed. Heart Rate (HR), Systolic Pressure (SAP), Diastolic Pressure (DAP), Mean Arterial Pressure (MAP), BIS and $SpO_2$ were measured and recorded as basal values, after induction and intubation, at 15, 30, 45, 60, 75 and 90$^{th}$ minutes of the operation, at the 5$^{th}$ minute of extubation and intubation. Patients were exposed to preoxygenation with 100% $O_2$ for 5 minutes. Five minutes before the induction of anesthesia; iv 5 ml of saline solution was administered to the control group, while patients in the ketamine group received 0.5 mg/kg (diluted with saline solution to 5 ml) R-Ketamine (Ketalar® Pfizer, Turkey). A remifentanil (Ultiva® GlaxoSmithKline, Italy) infusion was started at a rate of 0.5 µg/kg/min to induce anesthesia and 2-3 mg/kg propofol (Propofol® 1%, Fresenius Kabi, Austria) was administered intravenously. After the spontaneous breathing disappears, rocuronium was administered at a dose of 0.6 mg/kg (Esmeron®, Merck Sharp Dohme, USA) for muscle relaxation. The patients were intubated orotracheally 3 minutes after the administration and they started receiving mechanical ventilation. Anesthesia maintenance was achieved by 0.5-1 MAC sevoflurane administration and 0,1-0,3 µg/kg/min remifentanil infusion with 50% $O_2$ + 50% air. Patients were ventilated with a tidal volume of 6-8 mL/kg and respiratory rate of 10-14 /min to achieve an $EtCO_2$ of 30-35 mmHg.

Anesthetics and analgesics were regulated to keep MAP and HR values within ±20% of the basal value and BIS value within the range of 40 to 60 during the operation. An increase of 20% in the MAP of the patients and/or HR value of > 90 beat/min and/or BIS value of > 60 was considered as surface anesthesia, thus remifentanil dose was increased by 25%. When the increased remifentanil dose was not adequate, the dose of the general anesthetic agent was increased. A decrease of 20% in the MAP value and/or HR value of < 50 beat/min and/or BIS value of < 40 was considered as deep anesthesia, thus remifentanil dose was reduced by 25%. When the reduction of remifentanil dose was not adequate, the dose of the general anesthetic agent was decreased.

General anesthetic agent was discontinued at the start of skin closure, while remifentanil infusion was terminated at the completion of skin closure. When patients had BIS values of 80 and greater and minimum TOF value of 75%, they were extubated. To provide postoperative analgesia, patients were given iv Tramadol HCl (Contramal® Abdi İbrahim, Turkey) 1.5 mg/kg. Analgesia was standardized by administering 75 mg im diclofenac to all patients if they had pain in the first six hours.

Time to extubation, time to eye opening, Aldrete Recovery Scores at the 2nd and 5th minutes following extubation were recorded. Patients having Aldrete Recovery Score of 9 were followed up in the postanesthesia care unit. After recovery from anesthesia, MMSE, TDT (patients were asked to unite the dots to draw a figure composed of dots and the dots that were missed were recorded), CDT ( patients were asked to draw a clock shape on a blank piece of paper and mark the hours accurately, and then place the hour and minute hands to show ten past eleven) were performed at postoperative 1st and 6th hours to evaluate the cognitive functions.

***Statistical Analysis***

It was agreed to assign 20 people to each group according to the sample size calculated in SPSS software with $\alpha$ reliability of 95% and β reliability (power of the test) of 80% based on the findings of previous studies (6). The data of the study was recorded in SPSS 16.0 (SPSS IL 16.0 Chicago, USA) software package.

For homogeneity of the groups, gender and ASA rates of the groups were assessed and compared with Chi-square test, mean age with Mann Whitney U test, differences between vital findings and medicine use with Mann Whitney U test and time-dependent differences of each group with Friedman analysis. When significant differences were found in Friedman analysis, Wilcoxon Signed Ranks with Bonferroni correction was used among the post-hoc double tests. $p<0.05$ was considered to be statistically significant.

## RESULTS

There were no statistically significant differences between the groups in terms of demographic data, ASA, surgery and anesthesia duration and hemodynamic data ($p > 0.05$) (Table 1).

Statistically significant differences were found between both groups with respect to the total remifentanil consumption ($p<0.001$) (Table 2). Significant differences were not found between the groups in terms of time to extubation, time to eye opening and Aldrete Scores ($p>0.05$) (Table 2).

There wasn't any significant difference between the preoperative MMSE average scores of the groups ($p>0.05$), except at the 1st and 6th hours ($p<0.01$). Patients in the ketamine group had a higher average score than those in the control (Table 3).

The MMSE scores decreased at the postoperative 1st hour and MMSE score increased at the 6th hour; nevertheless, it didn't reach to the preoperative level in the both groups. The significant difference in the ketamine group was found at the 1st hour, while it was also found that MMSE scores at the 1st hour decreased significantly compared to both preoperative and postoperative values ($p<0.001$) (Table 3).

There wasn't any significant difference between the preoperative average of TDT scores in the control and ketamine groups (p>0.05). However, there were significant differences at the 1st hour and 6th hour postoperatively (p<0.001) (Table 4).

There wasn't any significant difference between the control and ketamine group with respect to preoperative CDT average scores (p>0.05). However, significant differences were found between the CDT average scores at the postoperative 1st hour (p<0.01) (Table 5). The CDT scores decreased at the postoperative 1st hour and increased at the 6th hour although they did not reach up to the preoperative levels (p<0.05). It was also found that there was a significant difference at the postoperative 1st hour within the ketamine group (p<0.001) (Table 5).

## DISCUSSION

The aim of assessing the cognitive functions is to determine not only the degree of recovery from anesthesia but also the residual effects of surgery and anesthesia. While these modifications might be caused by the anesthetic agent, physiological changes due to anesthesia might also be the underlying cause. The aim is to enable the patients to perform as in the preoperative period as soon as possible and prevent any permanent cognitive dysfunction in addition to the smooth induction and maintenance of anesthesia. (7-11).

A good recovery and analgesia should be provided for the patients who will undergo abdominal surgery in order to relax the anterior abdominal wall musculature, suppress the sympathetic and hemodynamic reflex responses to the surgical stimulants, prevent heat loss and dehydration and minimize the postoperative complications in addition to the fulfillment of basic principles of general anesthesia (12). Therefore, strong opioids combined with inhalation anesthetics in abdominal surgery are used confidently in order to maintain intraoperative analgesia and hemodynamic stability especially during painful surgical interventions (13,14). Moreover, the opioid to be selected should provide a good intraoperative analgesia; have a short-acting property and a good recovery profile in order to eliminate the long-acting adverse effects of opioid on cognitive functions. In our study, remifentanil, a short-acting opioid that possessed the abovementioned properties, was selected and it was found that intraoperative average remifentanil consumption was lower within the ketamine group.

Postoperative cognitive dysfunction is characterized with the deterioration of memory and concentration and has a very high incidence among the geriatric patients undergoing major surgery. It leads to postoperative delirium, increased morbidity, delayed functional recovery and extended length of stay among geriatric patients (15). The incidence of transient postoperative cognitive dysfunction is very high ranging from 44% to 61% among the geriatric patients undergoing different types of surgery. Therefore, the use of those anesthetic agents with high clearance and low level of metabolism might be advantageous for cognitive functions among the geriatric patients (1).

Following the surgical nociception, central sensitivity occurs due to the stimulation of NMDA receptors and partially the neorokinin receptors. For that reason, a pain-free postoperative period can be provided with preemptive analgesia by administering NMDA receptor antagonists such as ketamine, blocking the nociceptive stimulation and preventing the central sensitivity. Ketamine that we used in our study as a NMDA receptor antagonist prevents not only the peripheral afferent stimulation but also the central sensitivity of the nociceptors. When administered in sub-anesthetic dose (0.1-0.5 mg/kg), ketamine blocks NMDA channels; thus we think that ketamine effects the postoperative cognitive functions positively thanks to its neuroprotective effect. Aydın et al. (16) showed in their study that 0.5 mg/kg of ketamine didn't affect the time to extubation and time to eye opening, which is consistent with our findings. Solano et al. (17) demonstrated in their study that administration of ketamine in dogs reduced the MAC value of isoflurane; in our study, however, Sevoflurane consumption didn't decrease, whereas time to extubation, eye opening and orientation was similar. We believe that this was due to the preoperative administration of ketamine at a sub-hypnotic dose because awakening from general anesthesia is delayed as the dose of ketamine is increased.

Postoperative cognitive dysfunction is common among geriatric patients undergoing a major surgery (4). The mechanism of POCD is not fully known. Predisposition of the patient, postoperative factors, anesthetic agents and adjuvant drugs administered during anesthesia, old age, anemia, infections, alcohol addiction, electrolyte imbalance, existing cognitive dysfunctions and type of surgery, duration of surgery, genetic factors, long-term hypertension and hypotension, hormone levels, preoperative medication, postoperative infection and respiratory complications, postoperative pain are the risk factors for POCD (18). The patients in our study didn't posses any of the above mentioned risk factors for POCD except for old age. Anesthetic agent choice might also affect POCD because the residual levels of volatile anesthetics might lead to modifications in the CNS activity. For this reason, those anesthetic agents with high elimination rate and low level of metabolism might be advantageous for this patient population. Kalman et al. (19) reported that they found postoperative psychomotor dysfunction among patients undergoing major abdominal surgery under isoflurane anesthesia. Çobanoğlu et al. (20) compared the effects of desflurane and sevoflurane on the early postoperative cognitive dysfunction among the geriatric patients and concluded that neither of the anesthetic agents were superior to one another. Similarly, Hudetz et al. also found that the MMSE, TDT, CDT scores of the patients in the ketamine group were significantly higher at the postoperative 1st hour than the values in the control group.

There is limited information about POCD after a non-cardiac surgery (4). Postoperative cognitive dysfunction is a very common condition that is characterized with the deterioration of memory and concentration especially among geriatric patients undergoing major surgery (15). However, the association between the time to recovery from general anesthesia and cognitive dysfunction has not been well established. It is known that cognitive functions might not return to the preoperative levels although awakening from general anesthesia and recovery are achieved and it might take months to return to these levels (4, 21 ). In our study, the values of three tests performed preoperatively were observed to decline at the postoperative 1st hour significantly in both groups although the patients recovered.

In another study, peripheral oxygen saturation was compared with cognitive functions and it was found that the cognitive functions deteriorated when the peripheral oxygen saturation fell below 80%. Cognitive functions improved when the peripheral oxygen saturation was raised above 90% (22). Similarly, in our study, a positive correlation was found in both groups between the peripheral oxygen saturation and MMSE scores recorded at all hours. None of the patients had a SpO2 value lower than 90%. In another prospective study, low blood pressure was found to be positively associated with the declined and impaired cognitive functions. This association was explained with two reasons: Either the problems that started in the brain led to low blood pressure or long-term low blood pressure led to the reduction of blood flow in the brain and eventually deteriorated the cognitive functions (23). In our study, blood pressure of the patients was stable on the whole, none of the patients had a long-term hypotension or hypertension and no correlation was found in the tests performed.

In conclusion, administration of ketamine at sub-anesthetic dose among geriatric patients for anesthesia not only achieved a stable hemodynamic state but also reduced the need for intraoperative opioid administration and had a positive impact on the postoperative cognitive functions. We believe that determination of agents that have positive effects on the cognitive functions as well as the factors that deteriorate the cognitive functions after general anesthesia and the assessment methods will provide secure information about the postoperative cognitive dysfunction and reduce its prevalence and severity through certain measures to be taken.

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**Table 1.** Demographic datas of patients and durations of surgery and anesthesia (Mean± SD)

| | **Control Group (n=20)** | **Ketamine Group (n=20)** | **P** |
|---|---|---|---|
| Age (years) | 69.20±3.00 | 68.10±3.88 | 0.077 |
| Weight (kg) | 74.95±10.48 | 75.00±8.58 | 0.881 |
| Height (cm) | 166.75±6.71 | 166.80±7.09 | 0.860 |
| Gender (Female/Male) | 12/8 | 13/7 | 1.000 |
| Operation Time (min) | 88.55±6.1 | 88.65±5.01 | 0.978 |
| Anesthesia Time (min) | 105.65±6.08 | 107.30±5.71 | 0.277 |
| ASAI/II | 3/17 | 2/18 | 0.633 |

**Table 2.** Total anesthetic doses and postoperative evaluation (Mean ± SD)

| | **Control Group (n=20)** | **Ketamine Group (n=20)** | **P** |
|---|---|---|---|
| Total remifentanil (μg) | 1445.75±168.56 | 1092.50±116.47 | <0.001* |
| Average $E_T$ sevoflurane (%) | 1.29±0.17 | 1.29±0.15 | 0.839 |
| Extubation time (min) | 7.04±1.20 | 6.89±1.54 | 0.136 |
| Time to eye opening (min) | 8.64±1.36 | 8.26±1.56 | 0.198 |
| Aldrete score at 2$^{nd}$ min. | 7.10±0.71 | 7.30±0.65 | 0.247 |
| Aldrete score at 5$^{th}$ min. | 9.10±0.64 | 9.30±0.47 | 0.318 |

* p< 0.001 indicates significant difference.

**Table 3.** SMMT results and comparison between preoperative SMMT values and values at Postoperative 1st and 6th hours (Mean ± SD)

| | Control Group (n=20) | Ketamine Group (n=20) | Mann Whitney U (P) | WilcoxonSigned | |
|---|---|---|---|---|---|
| | | | | Control group P | Ketamine group P |
| SMMT Preop | 26.10±1.33 | 26.35±1.50 | 0.571 | | |
| SMMT Postop1st Hour | 18.55±1.32 | 21.85±1.46 | < 0.001* | | |
| SMMT Postop 6th Hour | 24.65±.81 | 26.10±1.17 | < 0.001* | | |
| SMMT Preop-SMMT Postop 1st hour | | | | < 0.001* | < 0.001* |
| SMMT Preop-SMMT Postop 6th hour | | | | <0.01# | 0.282 |
| SMMT Postop 1.Saat-SMMT Postop 6th hour | | | | < 0.001* | < 0.001* |

*p < 0.001 indicates very significant difference

#p<0.01 indicates significant difference

**Table 4.** TDT results and comparison between Preoperative TDT values and values at Postoperative 1st hour and 6th hour (Mean ± SD)

| | Control Group (n=20) | Ketamine Group (n=20) | Mann Whitney U (P) | WilcoxonSigned | |
|---|---|---|---|---|---|
| | | | | Control group P | Ketamine group P |
| TDT Preop | 2.60±1.64 | 2.50±1.40 | 0.956 | | |
| TDT Postop 1st hour | 10.45±2.33 | 7.10±1.52 | < 0.001* | | |
| TDT Postop 6th hour | 3.35±1.14 | 2.15±1.42 | 0.004# | | |
| TDT Preop-TDT Postop 1st hour | | | | < 0.001* | < 0.001* |
| TDT Preop-TDT Postop 6th hour | | | | 0.056 | 0.343 |
| TDT Postop 1st hour -TDT Postop 6th hour | | | | < 0.001* | < 0.001* |

*p < 0.001 indicates very significant difference

#p<0.01 indicates significant difference

**Table 5.** CDT results and comparison between CDT values and values at Postoperative 1st hour and 6th hour (Mean ± SD)

| | **Control Group (n=20)** | **Ketamine Group (n=20)** | **Mann Whitney U (P)** | **WilcoxonSigned** | |
|---|---|---|---|---|---|
| | | | | **Control group P** | **Ketamine group P** |
| CDT Preop | 3.70±0.47 | 3.75±0.44 | 0.727 | | |
| CDT Postop 1st hour | 1.50±0.95 | 2.35±0.99 | 0.008# | | |
| CDT Postop 6th hour | 3.35±0.75 | 3.50±0.83 | 0.375 | | |
| CDT Preop-CDT Postop 1st hour | | | | < 0.001* | < 0.001* |
| CDT Preop-CDT Postop 6th hour | | | | 0.088 | 0.206 |
| CDT Postop 1st hour - CDT Postop 6th hour | | | | < 0.001* | 0.005# |

*p < 0.001 indicates very significant difference

#p<0.01 indicates significant difference