

## Original Article

# Effect of different depth of anesthesia on postoperative cognitive function after retroperitoneal laparoscopic radical nephrectomy

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**Abstract:** Postoperative cognitive function could be influenced by different depth of anesthesia and different types of abdominal surgery. Laparoscopic partial nephrectomy has become widely used for surgical method of renal cell carcinoma (RCC) in the past few years, and it also led central nervous system complications as well. The objective of the present study was to investigate the effects of different depths of sedation on postoperative cognitive function in patients undergoing retroperitoneal laparoscopic radical nephrectomy. A total of 100 patients undergoing retroperitoneal laparoscopic radical nephrectomy were randomly divided into 3 groups. Anesthesia with the usage of propofol and remifentanyl, which was adjusted to maintain bispectral index (BIS) at  $30 < \text{BIS} \leq 40$  with 32 patients in group I,  $40 < \text{BIS} \leq 50$  with 35 patients in group II, and  $50 < \text{BIS} \leq 60$  with 33 patients in group III. Mini-Mental State Examination (MMSE), Trail-Making Test (TMT) and Clock Drawing Test (CDT) were used to evaluate the cognitive function one day before and after surgery. We found that no significant statistical difference was found in demographic data among patients in the 3 groups ( $P > 0.05$ ). MMSE score in group I was significantly higher than the other 2 groups post-operation ( $P < 0.05$ ). Meanwhile, TMT completion time in group I was also found to have markedly lower than the other 2 groups ( $P < 0.05$ ). Besides, CDT score in group I and group II were significantly higher than that in group III, and no significant difference was found between group I and group II. Thus, we come to a conclusion that  $30 < \text{BIS} \leq 40$  had the minimal influence on postoperative cognitive function after retroperitoneal laparoscopic radical nephrectomy.

**Keywords:** Postoperative cognitive dysfunction, retroperitoneal laparoscopic radical nephrectomy, remifentanyl, anesthesia

## Introduction

Renal cell carcinoma (RCC) is a common malignancy of the urinary system, accounting for 2%~3% of adult malignant tumors and about 80%~90% of renal malignant tumors. RCC is quite specific to patients among 50 to 70 years, and the incidence is increasing around the world [1, 2]. To reduce morbidity caused by radical nephrectomy and to preserve renal function, laparoscopic partial nephrectomy has become more widely used and it has resulted in improving survival rates [3]. Patients often

experience central nervous system complications after retroperitoneal laparoscopic radical nephrectomy, mainly expressed as memory loss, abstract thinking level decrease and disorientation. These changes are called postoperative cognitive dysfunction (POCD) [4, 5].

Generally, central nervous system complications commonly occur in patients with surgery. Different surgical procedures may result in different effects on postoperative cognitive function. Many of the previous studies indicated that depth of anesthesia was also associated

# The depth of anesthesia influences postoperative cognitive function

**Table 1.** Demographic of included patients in the 3 groups

Variable	30 < BIS ≤ 40	40 < BIS ≤ 50	50 < BIS ≤ 60	P value
N (%)	32 (32.0)	35 (35.0)	33 (33.0)	
Age (year)	49.7±7.8	48.2±9.3	51.4±10.5	0.527 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	23.8±3.9	22.9±3.7	23.5±4.1	0.693 <sup>a</sup>
Education (year)	12.9±3.6	11.7±2.8	12.4±3.3	0.751 <sup>a</sup>
ASA Status (I/II)	13/19	14/21	11/22	0.628 <sup>b</sup>
Surgery time (min)	101.6±40.7	98.1±37.9	99.3±35.5	0.554 <sup>a</sup>

<sup>a</sup>P value was obtained from one-way ANOVA, <sup>b</sup>P value was obtained from Chi-square test. BIS: Bispectral index. BMI: Body mass index. ASA: American Society of Anesthesiologists.

with POCD [6, 7]. Bispectral index (BIS) is one of several technologies used to monitor depth of anesthesia, which is used to determine depth of anesthesia. Salova EM et al. pointed out that a lower BIS value remains the most advantageous in surgical disease, such as severe cardiovascular pathology, epilepsy surgery, spinal cord injury and neurosurgery [8]. Shu AH, et al. reported that maintained the BIS in the 40-50 range during the combined intravenous-inhalational anesthesia yielded milder influence on postoperative cognitive function after gynecologic laparoscopic operation [9].

Therefore, it is important to choose a suitable depth of anesthesia to decrease the effect of the anesthetic agent on post surgery cognitive function. To our knowledge, few studies are conducted to investigate the changes of cognitive function in patients undergoing retroperitoneal laparoscopic radical nephrectomy. In this work, we recruited 100 patients to explore the effect of different depths of anesthesia on postoperative cognitive function after retroperitoneal laparoscopic radical nephrectomy.

## Materials and methods

### Patients

The current study was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University. Informed consent was obtained from each participant. Between March 2013 and April 2017, a total of 100 patients aged between 35 and 65 years old with American Society of Anesthesiologists (ASA) physical status I or II, scheduled for retroperitoneal laparoscopic radical nephrectomy were recruited. Patients were randomly divided into 3 groups. The infusion concentration of propofol and remifentanyl was adjusted, and BIS of

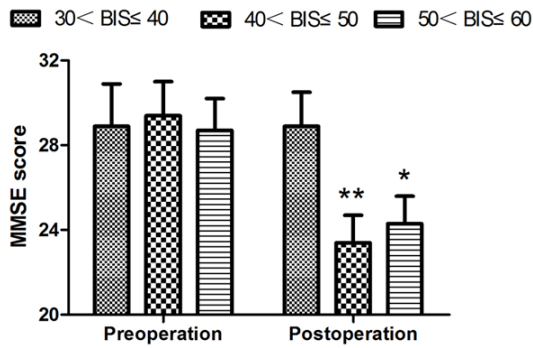
32 patients were maintained at 30 < BIS ≤ 40, 35 patients with 40 < BIS ≤ 50 and 33 patients with 50 < BIS ≤ 60. The inclusion criteria were: 1) patients with no mental illness, endocrine disease or cerebrovascular disease history; 2) no alcohol history and drug use past history; 3) MMSE score > 24; 4) no opioid or anti-psychotic drug use recently;

5) nine years of education. The exclusion criteria were: 1) Suffering from severe liver, cardiovascular or cerebrovascular diseases; 2) Metastasis to distant tissues; 3) The tumor of the kidney was excluded from other metastatic lesions.

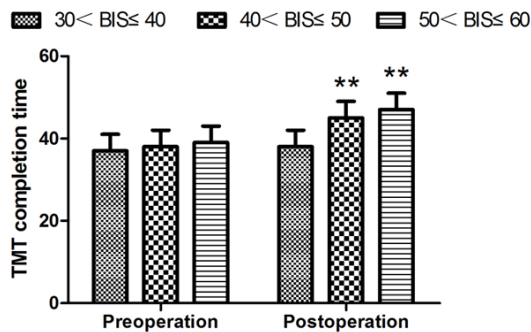
### Treatment protocol

All patients were taken to surgery where the basilic vein was percutaneously cannulated with 20 gauge intravascular catheters. All patients were anesthetized using the same procedure. The heart rate (HR), electrocardiography, respiratory rate, systolic blood pressure (SBP), pulse oximetry, hemoglobin oxygen saturation, and end-tidal CO<sub>2</sub> partial pressure were continuously monitored during the whole process. Anesthesia was induced with sufentanil (2-3 µg/kg, Yichang Renfu Pharmaceutical Company, China), midazolam (0.2-0.4 mg/kg, Jiangsu Jiuxu Pharmaceutical Company, China), and propofol (5 µg/ml, TCI, Guangdong Jiabo Pharmaceutical Company, China). Muscle relaxation was maintained by intermittent (40-60 min) injection of cis-atracurium (0.05 mg/kg, Shanghai Pharmaceuticals Holding Co., Ltd.). Anesthesia was maintained by the total intravenous anesthesia (TIVA) with remifentanyl (0.1-0.15 µg/kg/min, Shenzhen WanLe Pharmaceutical Company, China) and propofol (2-4.5 µg/ml) by TCI. During the anesthesia, the blood concentration of remifentanyl and propofol was regulated to control the depth of sedation. The intraoperative bispectral index (BIS) was maintained at 30-40 in group I, 40-50 in group II, and 50-60 in group III. After the trachea is removed, patients with stable vital signs were sent to a postanesthesia care unit. Endotracheal tubes were removed after full muscle recovery and patients were then moved back to the ward.

## The depth of anesthesia influences postoperative cognitive function



**Figure 1.** Mini-mental state examination (MME) of the patients (Mean ± SD). \* $P < 0.05$ , \*\* $P < 0.01$ , compared with  $30 < \text{BIS} \leq 40$  postoperation group. BIS: Bispectral index.



**Figure 2.** Trail-making test (TMT) completion time of the patients (Mean ± SD). \*\* $P < 0.01$ , compared with  $30 < \text{BIS} \leq 40$  postoperation group. BIS: Bispectral index.

### Outcome measures

Cognitive function was evaluated one day preoperatively and one day postoperatively in a quiet place with only one patient and the experienced psychometrician each time. Both the rate and patient were blinded to the treatment methods and groups. We used the sequentially numbered, opaque, sealed envelopes to conduct allocation concealment and blind outcome assessment. In this study, the mini-mental state examination (MMSE), trail-making test (TMT) and clock drawing test (CDT) were used to assess cognitive function. POCD could be judged that the MME score postoperatively was at least two points lower than that before the operation, or CDT score was reduced by more than one point after operation. TMT completion time is the time required to connect disorderly 1-25 numbers in order, and cognitive dysfunction is positively correlated with TMT

completion time. These 3 scales were validity and reliability for cognitive function. The psychometrician trained in MMSE, TMT and CDT collected, scored, and interpreted the data.

### Statistical analyses

All data obtained were evaluated with SPSS 20.0 packet program (IBM Analytics, Armonk, New York, USA) and expressed as mean ± SD. One-way analysis of variance was used for comparison among groups. If a significant difference was found, a Bonferroni or Tamhane's T2 post-hoc analysis was conducted to determine which group differed significantly according to the equal variance criterion.  $P < 0.05$  was used to determine statistically significant difference.

## Results

### Patients

A total of 100 ASA physical Status I or II patients were included in the study. The detailed information of these patients was presented in **Table 1**. We found that there were no statistically significant differences in age, body mass index, ASA classification, education level, and hospital stay and operation time among the groups ( $P > 0.05$ ).

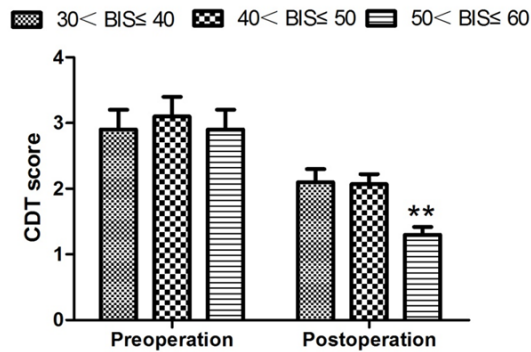
### MMSE score

MMSE was performed at one day preoperatively and one day postoperatively. We found that there was no statistically significant difference among the three groups in preoperative MMSE scores ( $P > 0.05$ ). The average MMSE score in group I was significantly higher than those in the other two groups after surgery ( $P < 0.05$ ), and there was no significant difference between group II and group III. ( $P > 0.05$ ), as shown in **Figure 1**.

### TMT completion time

TMT completion time was performed at one day preoperatively and one day postoperatively. There was no statistically significant difference among the three groups of the preoperative TMT completion time ( $P > 0.05$ ). The average TMT completion time in the first group was significantly less than those in the other two groups after surgery ( $P < 0.01$ ), and there was no significant difference between the second

## The depth of anesthesia influences postoperative cognitive function



**Figure 3.** Clock drawing test (CDT) of the patients (Mean  $\pm$  SD). \*\* $P < 0.01$ , compared with  $30 < \text{BIS} \leq 40$  postoperation group. BIS: Bispectral index.

and the third group ( $P > 0.05$ ), as shown in **Figure 2**.

### CDT score

CDT score was performed at one day preoperatively and one day postoperatively. No statistically significant difference was found among the three groups of the preoperative CDT score ( $P > 0.05$ ). The average CDT score in the third group was significantly less than those in the other two groups after surgery ( $P < 0.01$ ), and there was no significant difference between the first and the second group ( $P > 0.05$ ), as shown in **Figure 3**.

### Discussion

Retroperitoneal laparoscopic surgery exhibits advantages in the treatment of RCC. It may avoid peritoneal violation and reduce interference by abdominal organ. Besides, it may also prevent adhesions and provide a safe minimally invasive option in RCC patients [10, 11]. However, the complications of anaesthesia are inevitable, and POCD occurs frequently following retroperitoneal laparoscopic radical nephrectomy [12]. Therefore, it is necessary to analyze the factors affecting POCD, in order to improve postoperative recovery satisfaction. Many factors contribute to POCD in clinical interventions [13, 14]. The depth of anesthesia is considered to be a risk factor for POCD as the areas of the brain involved in cognitive control overlap. Research demonstrated that POCD could be influenced by different depth of anesthesia in different types of abdominal surgery [8, 9]. However, the relationship between the depth of anesthesia and retroperitoneal la-

paroscopic radical nephrectomy still remains unknown.

MMSE, TMT and CDT were recommended by the International Study of postoperative cognitive dysfunction to assess the cognitive function [15, 16]. The MMSE had a good sensitivity and was easily to operate, and TMT could assess several aspects: Visual attention, visuospatial abilities, task-switching, and psychomotor processing speed [17]. In addition CDT could precisely reflex the semantic memory, visuospatial structure and executive function post-surgery [18]. In this study, all patients obtained some relative training to make sure that they could successfully complete the MMSE, TMT and CDT before the experiment. We found that the average MMSE score in the first group was significantly higher than those in the other two groups after surgery, and there was no significant difference between the second and the third group. Meanwhile, the average TMT in the first group was decreased, which markedly lower than those in the second and third group after surgery. Besides, the average CDT score in the third group was significantly less than those in the second and third group postsurger, and there was no significant difference between the first and the second group. These results indicated the BIS of retroperitoneal laparoscopic radical nephrectomy patients within 30-40 range demonstrated a minimal negative effect on postoperative cognitive function. Many reasons contribute to this phenomenon. Remifentanil, a potent synthetic opioid analgesic drug, which exhibits rapid onset and good controllability without damaging the liver or kidney functions [19]. Besides, the dose of remifentanil could be easily controlled and no redundant accumulation with continuous infusion [20]. In this study, we used a low-dose remifentanil due to its short operative time, and the relationship between remifentanil and POCD still need further study. Several studies have been reported that propofol could potentiate the activity of gamma-aminobutyric acid receptor, and downregulate the channel-closing time [21]. A previous study reported that propofol could effectively contribute to anesthetic action probably via endocannabinoid system [22]. What was more, research indicated that the peripheral innate immune system could be activated by tissue damage induced in the surgery, which might markedly lead to the

## The depth of anesthesia influences postoperative cognitive function

exaggerated release of inflammatory cytokines [23]. It was noteworthy that these inflammatory cytokines could impair postoperative cognitive function in a few days post-surgery [24]. Moreover, studies demonstrated that propofol could suppress the serum level of pro-inflammatory cytokines and improve the postoperative cognitive function in the early stage after surgery [25]. In this study, we found that the depth of sedation in the first group (BIS, 30-40) was the deepest, which indicated that the maximum dose application of propofol in this group. Therefore, we come to a conclusion that the minimal impact on the postoperative cognitive function with the maximum propofol dosage suggested that propofol probably be able to suppress the inflammatory response in central nervous system and eventually lead to POCD improvement.

In conclusion, this study reveals that the depth of sedation ( $30 < \text{BIS value} \leq 40$ ) conduct the minimum influence on postoperative cognitive function for patients experienced retroperitoneal laparoscopic radical nephrectomy. Therefore, we think that depth of sedation ( $30 < \text{BIS value} \leq 40$ ) can be safely used in retroperitoneal laparoscopic radical nephrectomy.

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### Disclosure of conflict of interest

None.

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## The depth of anesthesia influences postoperative cognitive function

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