

## Original Research Article

# Effect of target-controlled infusion of remifentanil in combination with propofol on anesthesia and endotracheal intubation response in patients undergoing surgical aneurysm clipping

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## Abstract

**Purpose:** To investigate the effect of target-controlled infusion of remifentanil in combination with propofol on anesthesia and endotracheal intubation response in patients undergoing surgical aneurysm clipping.

**Methods:** The clinical data of 106 patients undergoing surgical aneurysm clipping at the Central Hospital of Wuhan, Wuhan City, China from September 2020 to December 2022 were retrospectively analyzed. Subjects in control group were given fentanyl intravenous infusion anesthesia while study group was treated with target-controlled infusion anesthesia of remifentanil combined with propofol. Hemodynamics and blood-gas indices were evaluated before anesthesia (T1), immediately after endotracheal intubation (T2) and at extubation (T3). The incidence of anesthesia-related complications was determined.

**Results:** In study group, the agitation score was decreased compared to that of control group, while the Ramsay sedation score was increased ( $p < 0.05$ ). The incidence of cough during endotracheal catheter indwelling and extubation was 7.27% in study group, which was less than 21.57% in control group ( $p < 0.05$ ). The cough score of study group was also reduced ( $p < 0.05$ ). There were no significant differences in the SpO<sub>2</sub> and PetCO<sub>2</sub> values between the two groups at different times ( $p > 0.05$ ). Furthermore, the mean arterial pressure at T2 and T3 was upregulated and heart rate (HR) was downregulated in study group ( $p < 0.05$ ). Recovery time of spontaneous respiration, time of eye-opening and extubation in study group were decreased compared to control group ( $p < 0.05$ ).

**Conclusion:** Target-controlled infusion of remifentanil in combination with propofol improves anesthetic effect in patients undergoing surgical aneurysm clipping, reduces tracheal intubation reaction, maintains hemodynamic stability and improves recovery quality of patients. Future study will be required to evaluate the efficacy and optimal effective concentration in a diverse population.

**Keywords:** Surgical aneurysm clipping, Remifentanil, Propofol, Target-controlled infusion, Anesthesia effect, Tracheal intubation response

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## INTRODUCTION

Due to the extended duration of surgical aneurysm clipping, drug accumulation during general anesthesia is prone to occur, impacting the quality of patient recovery. Moreover, the intensity of intraoperative stimulation may change at any moment, necessitating continuous anesthesia adjustments to ensure a seamless procedure. Clinical data show that the ideal general anesthetic drug for surgical aneurysm clipping should have the advantages of stable induction, rapid onset, anesthetic effect, preservation of the blood-brain barrier, absence of neurotoxicity, etc [1]. Remifentanyl has an ester bond that non-specific esterases readily metabolize, resulting in an ultra-short-duration analgesic effect. While its analgesic potency is comparable to that of fentanyl, remifentanyl increases the control of anesthesia and better regulates the depth of anesthesia to meet the needs of surgical operations [2]. Propofol is the most commonly used drug for target-controlled infusion. It is a fast and powerful general anesthetic, which has the advantages of quick effect, short duration and low adverse reactions. It has been widely used in various clinical departments for anesthesia and sedation of severely ill patients.

Studies have indicated that target-controlled infusion of anesthetic drugs during surgical aneurysm clipping enhances smooth operation and improves the quality of postoperative recovery of patients [3]. Based on the theory of pharmacokinetics, target-controlled infusion organically integrates anesthesia and drug metabolism more objectively and reasonably, maintains constant plasma concentration, monitors sedation and analgesia of patients and better maintains hemodynamic stability [4]. Based on this, this study aimed to investigate the effects of target-controlled infusion of remifentanyl and propofol on the anesthetic effect and endotracheal intubation response of patients undergoing surgical aneurysm clipping and to provide a reference for the selection of safe, reasonable and effective neurosurgical anesthesia methods.

## METHODS

### Patients

The clinical data of 106 patients undergoing surgical aneurysm clipping from September 2020 to December 2022 were collected and retrospectively analyzed. Subjects were randomly grouped into control group (n = 51) and study group (n = 55). This study was approved

by the Ethics Committee of Central Hospital of Wuhan, (approval no. 20191163W). All procedures were conducted in compliance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki [5].

### Inclusion criteria

The included patients were those who were undergoing surgical aneurysm clipping in The Central Hospital of Wuhan from September 2020 to December 2022; patients who met the criteria specified in the American Society of Anesthesiologists (ASA) grade I-II; patients who provided signed, informed consent form.

### Exclusion criteria

The study excluded patients falling within the following categories: Patients with severe cardiac, liver and renal dysfunction; patients with cardiovascular and cerebrovascular diseases; patients with a history of mental illness; patients with abnormal airway structure; patients with a history of long-term use of sedative opioids; patients with a combination of hearing or intellectual disabilities.

### Treatments

Both groups were administered 2 mg of midazolam and 0.5 mg of atropine via intramuscular injection 30 min before anesthesia (opioids were not used). Upon entering the operating room, the patient's electrocardiogram, blood pressure and pulse oxygen saturation were initially monitored. Peripheral venous access was established in the upper limb and local anesthesia was administered for venipuncture in the right internal jugular vein. Double central venous catheters were inserted for central pressure monitoring and an infusion was maintained. Subsequently, a left radial artery puncture was performed for continuous monitoring of arterial blood pressure. Study group was given target-controlled infusion of remifentanyl (Yichang Humanwell Pharmaceutical Co. Ltd. batch number: H20030200) combined with propofol (Guangdong Jiabo Pharmaceutical Co. Ltd. batch number: H20051843). In contrast, control group was given intravenous fentanyl infusion anesthesia.

In study group, body weight, age and drug concentration of patients were recorded using anesthesia control instrument. Then, the drugs were administered in the intravenous anesthesia control instrument based on pharmacokinetic parameters. In accordance with the relevant parameters reported in the literature [6], the dose

of propofol and remifentanyl in anesthesia induction and anesthesia operation was maintained at 3 ~ 6 mg/L and 2.5 ~ 4.5 ng/minutes, respectively. When the patient became unconscious, succinylcholine (Hanfeng Pharmaceutical Co. Ltd, batch no. H20054745) was administered intravenously at a dose of 1.5 mg/kg. After tracheal intubation, vecuronium was injected intravenously at a dose of 0.8 mg/kg (Organon, Netherlands, batch number: H20100383). The concentrations of target-controlled infusion of propofol in combination with remifentanyl, according to intraoperative conditions, prevent discomfort caused by shallow anesthesia. Half-dose vecuronium bromide was added approximately every 50 minutes and muscular administration was stopped 1.5 hours before the completion of the operation. Patients in control group were administered midazolam (NHWA Co. Ltd. batch number: H20143222) at 0.05 mg/kg. Sufentanil (Yichang Humanwell Pharmaceutical Co. LTD. batch number: H20054256), administered intravenously at a dose of 0.5 µg/kg, was diluted with normal saline to 0.1 µg/mL and slowly injected into the vein within 60 seconds. Attrikuramide (SUNCADIA Co. Ltd. batch number: H10970367) was injected into the vein at a dose of 0.4 ~ 0.6 mg/kg. Endotracheal intubation was performed when the desired effect of muscle relaxation injection was achieved and mechanical ventilation was administered to the patient with anesthesia.

During the operation, an intravenous infusion of remifentanyl at a rate of 0.2 µg/kg was performed by fine-tuning the administration concentration based on the actual situation of intraoperative hemodynamic indices. The supply of the muscle relaxant atracurium was stopped 15 minutes before the surgery's conclusion, and the infusion of propofol and remifentanyl was terminated 10 minutes before the surgery's conclusion.

## Evaluation of parameters/indices

### **Agitation score**

A comparison was made between intraoperative agitation scores (0 – 3-point scale) and Ramsay sedation scores (6-point scale) [7]. The Agitation Score was categorized as follows: 0 (quiet cooperation), 1 (complains of discomfort without accompanying behavioral reactions), 2 (frequent complaints of discomfort), and 3 (behavioral reactions such as limb movements).

### **Ramsay's sedation score**

The classification of Ramsay's sedation score is as follows: 1 (irritability), 2 (quiet cooperation), 3 (lethargy but able to follow commands), 4 (sleeping but able to be awakened), 5 (slow response to calls), and 6 (deep sleep and wakefulness).

### **Airway intubation response**

A comparison was made between the incidence of coughing and cough scores (0 - 2-point scale), which evaluated cough occurrences during endotracheal catheter insertion and extubation [8] viz: 0 (regular breathing during endotracheal catheter insertion, and slight/ no coughing during endotracheal catheter extubation), 1 (regular breathing during endotracheal catheter insertion, occasional coughing, coughing during endotracheal catheter extubation), 2 (severe coughing, irregular breathing, unable to extubate).

### **Blood gas analysis**

The Pulse Oximeter Oxygen Saturation (SpO<sub>2</sub>) as well as end-tidal carbon dioxide (PetCO<sub>2</sub>) levels were determined at different time intervals using the Philips MP monitor.

### **Hemodynamics**

The multifunctional monitor of Space Labs monitored the Mean arterial pressure (MAP) and heart rate of patients before anesthesia induction (T1), immediately after endotracheal intubation (T2) and during extubation (T3).

### **Recovery quality**

The recovery times for spontaneous respiration, time of eye-opening and extubation were determined and compared.

### **Sedation score**

The recovery of patients was evaluated using the Observer's Assessment of Alertness/Sedation score (OAA/S) [9] as follows: 5 (appropriate response to normal name calling), 3 (apathy to normal name calling or response only to loud or repeated name-calling); 2 (response only to tapping or shaking), 1 (unresponsive to tapping or shaking).

### **Anesthesia-related complications**

The incidence of per-operative anesthesia-related complications including bradycardia, nausea, vomiting and chills was evaluated.

**Statistical analysis**

The SPSS 22.0 software was used to process the data. The enumeration data was expressed as percentage (%), and compared using  $\chi^2$  test. Measurement data was expressed as mean  $\pm$  standard deviation (SD) after normality test and compared using *t*-test.  $P < 0.05$  was considered significant.

**RESULTS**

**Basic patient data**

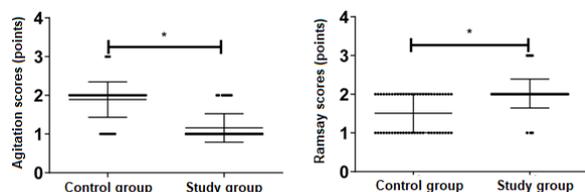
The basic data of the patients are represented in Table 1. Clinical characteristics, including gender, age, body weight and ASA grade did not differ significantly between the two groups ( $p > 0.05$ ).

**Table 1:** Clinical characteristics of patients in both groups

Classification	Study group	Control group
Gender		
Male	31	30
Female	24	21
Age (years)	51.85 $\pm$ 6.03	51.31 $\pm$ 5.85
Body weight (kg)	53.19 $\pm$ 5.37	54.02 $\pm$ 6.14
ASA grade		
I	29	30
II	26	21

**Agitation and Ramsay sedation scores**

In patients receiving remifentanyl and propofol (study group), the agitation score was significantly lower, while Ramsay's sedation score was significantly higher than control group (Figure 1;  $p < 0.05$ ).

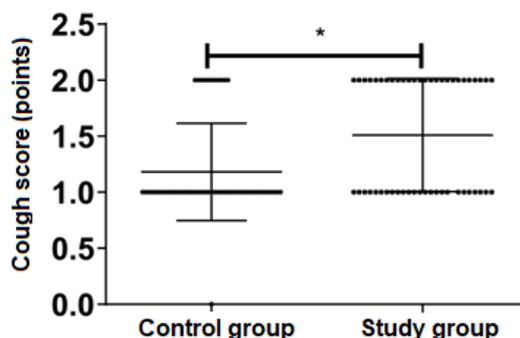


**Figure 1:** Comparison of the Agitation score and Ramsay sedation score between groups.  $*P < 0.05$  vs. control group

**Tracheal intubation response**

The incidence of cough during endotracheal catheter indwelling and extubation was 7.27 % under anesthesia with remifentanyl and propofol (study group), which was lower than 21.57 % under sufentanil anesthesia ( $p < 0.05$ ). The

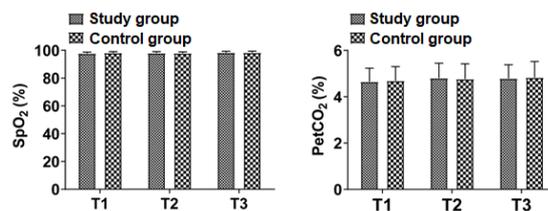
cough score in patients with combined anesthesia was significantly lower than that of patients with sufentanil anesthesia (Figure 2;  $p < 0.05$ ).



**Figure 2:** Comparison of cough scores between groups.  $*P < 0.05$  vs. control group

**Blood gas analysis indices**

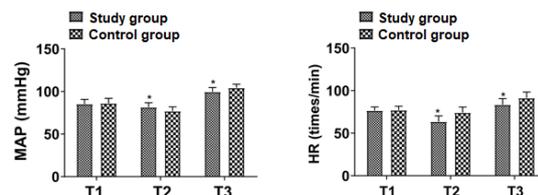
No significant differences were seen in SpO<sub>2</sub> and PetCO<sub>2</sub> levels at different periods under different anesthesia methods (Figure 3;  $p > 0.05$ ).



**Figure 3:** Levels of blood gas indices compared between both groups

**Hemodynamic indexes**

The MAP and HR showed no significant differences ( $p > 0.05$ ) at T1. However, MAP was higher and HR was lower at both T2 and T3 in patients with remifentanyl + propofol anesthesia than those with sufentanil anesthesia (Figure 4;  $p < 0.05$ ).

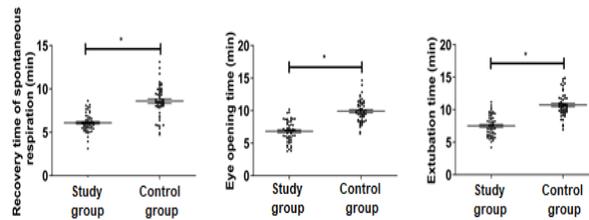


**Figure 4:** Hemodynamic indices.  $*P < 0.05$  vs. control group

**Quality of recovery**

The effectiveness of remifentanyl and propofol

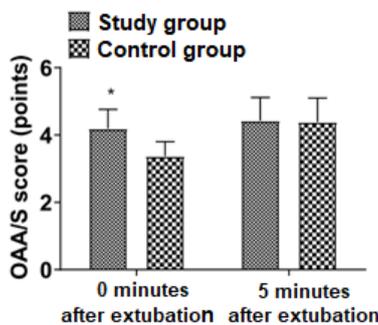
anesthesia in shortening the recovery time for spontaneous respiration, eye-opening and extubation was demonstrated in comparison to sufentanil anesthesia. (Figure 5; \* $p < 0.05$ ).



**Figure 5:** Quality of recovery. \* $P < 0.05$  vs. control group.

**OAA/S score**

As shown in Figure 6, patients in study group had higher OAA/S scores immediately after extubation than those in control group ( $p < 0.05$ ). The two anesthesia methods caused no difference in OAA/S score 5 minutes after extubation ( $p > 0.05$ ).



**Figure 6:** OAA/S scores after extubation. \* $P < 0.05$ , vs. control group

**Incidence of anesthesia-related complications**

As shown in Table 2, remifentanil + propofol contributed to a lower incidence of agitation compared to sufentanil ( $p = 0.034$ ).

**Table 2:** The incidence of anesthesia-related complications in both groups

Group	Bradycardia	Nausea and vomiting
Study	4 (7.27)	1 (1.82)
Control	7 (13.73)	3 (5.88)
$\chi^2$	1.185	1.204
P-value	0.276	0.273

**DISCUSSION**

Clinical data have shown that the ideal requirements for surgical aneurysm clipping

anesthesia are rapid induction of anesthesia, sufficient analgesia, reduction of intracranial pressure, rapid wakefulness without agitation, respiratory depression and residual drug effects [10]. The selection of appropriate and effective anesthesia methods is crucial for the smooth operation of surgical aneurysm clipping [11]. Target-controlled infusion is a novel intravenous administration method rooted in pharmacokinetics that ensures a stable blood concentration.

Remifentanil, an ultra-short-acting  $\mu$  receptor agonist, offers a quick onset, short duration of action and rapid elimination, and its metabolism remains unaffected by plasma cholinesterase, anticholinesterase drugs, patient liver/kidney function and body weight. It is primarily metabolized by non-specific esterase hydrolysis in both plasma and tissue, eventually excreted through urine [12]. As a result, remifentanil is well-suited for continuous intravenous infusion in clinical settings. Propofol is the most commonly used drug in target-controlled infusion, leading to a substantial enhancement in the anesthetic outcome.

This study found that Remifentanil and Propofol reduced the agitation score effectively and increased Ramsay's sedation score, indicating that target-controlled infusion of remifentanil and propofol significantly improved the anesthetic effect of patients undergoing surgical aneurysm clipping. This is because remifentanil rapidly establishes a patient's blood-brain equilibrium after administration. Propofol enhances chloride ion channels, resulting in cellular hyperactivation and playing the role of nervous system inhibition. The combined administration of these two drugs synergistically enhances the anesthetic effect. Moreover, target-controlled infusion flexibly adjusts drug concentration and accurately and rapidly administers drugs, so that patients have a higher degree of consciousness, reduce drug residue, and promote postoperative recovery [13].

During surgical aneurysm clipping, most inhalational anesthetics lead to cerebral vascular dilation and increased intracranial pressure. The **Chills, Agitation** is commonly considered that total intravenous anesthesia may be an ideal anesthesia method in clinic [14]. Propofol is often combined with other opioid analgesics to achieve a satisfactory anesthetic state. Remifentanil is a commonly used opioid in anesthesia maintenance, known for its rapid onset, short duration and potent analgesic effects. Under prolonged administration, remifentanil does not cause a delay in the recovery of patients and it

provides surgeons with excellent surgical conditions [15]. Clinical data show that the combination of propofol and remifentanyl is the most promising anesthesia method for surgical aneurysm clipping at present [16]. However, the conventional intravenous infusion approach encounters challenges in the real-time adjustment or sustenance of the essential blood concentration. As a result, the study implemented the target-controlled infusion method during surgical aneurysm clipping. As observed in our study, propofol and remifentanyl led to a decrease in the time for spontaneous respiration recovery, eye-opening time and time for extubation, increased the OAA/S score immediately after extubation and reduced the cough score, indicating that target-controlled infusion of remifentanyl in combination with propofol improves the quality of recovery.

The use of target-controlled infusion of propofol in combination with remifentanyl anesthesia in surgical aneurysm clipping not only makes the anesthesia reach a certain depth but also reduces the cardiovascular response during endotracheal intubation, effectively inhibits the stress response caused by traumatic stimuli and maintains intraoperative hemodynamic steady-state [17]. It is widely accepted that maintaining hemodynamic stability is a prerequisite for smooth operation. Remifentanyl, being a receptor agonist, offers advantages such as effective pain relief, rapid onset and excellent controllability, among other benefits. On the other hand, propofol is a well-recognized antioxidant, which reduces oxidative stress damage of brain tissue during surgery [18].

This study showed that there were minimal alterations in intraoperative hemodynamic parameters following the administration of propofol and remifentanyl. This suggests that the anesthesia approach contributes to the preservation of the body's hemodynamic stability. This phenomenon could be attributed to the effective controllability of remifentanyl and the reduction in intraoperative stress response resulting from the combined anesthesia [19]. However, it should be noted that remifentanyl excites the vagus nerve and inhibits the sinoatrial node. The incidence of slow heart rate is high in patients after administration of remifentanyl, so it is crucial to monitor the dosage and infusion rate carefully in elderly patients or those with sinoatrial node dysfunction.

### **Limitations of this study**

This study utilized a small sample size. In future

studies, more qualified subjects for study need to be recruited. The concentration, and dosage of remifentanyl in combination with propofol may affect the accuracy of the outcomes. Therefore, more high-quality RCTs are necessary to further evaluate the efficacy and safety.

## **CONCLUSION**

Target-controlled infusion of remifentanyl in combination with propofol improves patients' anesthetic effect during surgical aneurysm clipping, reduces tracheal intubation reaction, maintains hemodynamic stability, and improves the quality of recovery of patients. A large study is needed in the future to further evaluate the efficacy and the optimal effective concentration.

## **DECLARATIONS**

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### **Funding**

None provided.

### **Ethical approval**

None provided.

### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **Conflict of Interest**

No conflict of interest associated with this work.

### **Contribution of Authors**

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Shijie Yang and Yaqin Wu conceived and designed the study, and drafted the manuscript. They contributed equally to this work. Shijie Yang, Yaqin Wu, Jingli Chen and Shenghua Li collected, analyzed and interpreted the experimental data. Jingli Chen and Shenghua Li revised the manuscript for important intellectual content. All authors read and approved the final manuscript for publication.

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