

## Comparison of Sedative and Hemodynamic Effects of Remifentanil and Propofol in Patients with Pulmonary Disease Requiring Mechanical Ventilation in Intensive Care Unit

Lida Fadaizadeh <sup>1</sup>, Shideh Dabir <sup>2</sup>, Badiolzaman Radpay <sup>3</sup>

<sup>1</sup> Telemedicine Research Center, <sup>2</sup> Tracheal Disease Research Center, <sup>3</sup> Lung Transplantation Research Center, NRITLD, Shahid Beheshti University M.C., TEHRAN-IRAN.

### ABSTRACT

**Background:** ICU hospitalized patients usually need sedation. Common sedatives include benzodiazepines, opioids, barbiturates and etc. This study was conducted to compare the sedative, hemodynamic and respiratory effects of propofol and remifentanil in pulmonary disease patients requiring intubation and mechanical ventilation in intensive care unit of Masih Daneshvari Hospital during the years 2005-2007.

**Materials and Methods:** This study was conducted as a randomized controlled clinical trial. All patients with pulmonary disease requiring mechanical ventilation in the ICU were randomly divided into two groups. The first group was given an initial 10 µg /kg/min infusion of propofol and the second group received an infusion of remifentanil starting with 0.05 µg /kg and the doses sequentially increased to reach a sedation state of 3-4 according to Ramsay sedation scale. The regimen was continued for 48 hours, during which blood pressure, heart rate, and respiratory rate were monitored every 3 hours. Data was analyzed using SPSS version 11 software.

**Results:** A total of 40 patients with a mean age of 58.67±18.57yrs (range 21-85 yrs) including 27 (67.5%) males and 13 (32.5%) females entered the study. The mean time to optimal sedation was 17.9±13.9 min and 20.16±16.11 min for remifentanil and propofol groups, respectively (p=0.09). The mean systolic and diastolic blood pressures of each group showed a small decrease after initiation of infusion but this decrease was not statistically significant (p= 0.26 for remifentanil and p=0.12 for propofol group). The heart rate and respiratory rate showed no dramatic change during the infusion period.

**Conclusion:** Both remifentanil and propofol are suitable drugs for sedating patients with pulmonary disease and neither of them induces dramatic hemodynamic changes. Therefore, using each of them is effective for optimal sedation of patients.

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**Key words:** Sedation, Propofol, Remifentanil, Mechanical ventilation

Correspondence to: Radpay B

Address: NRITLD, Shaheed Bahonar Ave, Darabad, TEHRAN 19569,

P.O:19575/154, TEHRAN- IRAN

Email address: bradpay@nritld.ac.ir

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## INTRODUCTION

ICU hospitalized patients require sedation. Common sedatives include benzodiazepines, opioids, barbiturates and etc (1-3). Opioids are especially at the center of attention because of their optimal analgesic and sedative effects. Among them, morphine is specifically known as the drug of choice for induction of sedation. However, morphine is not a good choice for ICU hospitalized patients suffering from insufficiency of various organs because upon administration, it is converted to active metabolites that are 46 times more potent than the drug itself. These metabolites accumulate in the body in patients with renal insufficiency. For this reason, today the main focus is on employing short acting drugs with the lowest metabolic burden. Quick onset and rapid recovery of propofol have led to its widespread use for sedation and anesthesia among available short-acting sedatives. However, its long-term use is not recommended because of the metabolic burden that it imposes on the blood lipid profile of ICU hospitalized patients. On the other hand, long-term use of propofol results in tolerance which limits the duration of usage (4). In comparison, remifentanil is a short-acting, synthetic opioid with an ester linkage which undergoes rapid hydrolysis by non-specific tissue and plasma esterases. Remifentanil has sedative effects as well; therefore, its administration decreases the need for other sedative medications (5-8). However, further investigation is required on the efficacy of this drug for induction of adequate sedation in ICU patients and accelerating their recovery. This study aimed to evaluate the hemodynamic and respiratory effects and level of sedation induced by remifentanil compared to that of propofol in pulmonary disease patients requiring mechanical ventilation in the intensive care unit.

## MATERIALS AND METHODS

This was a randomized controlled clinical trial conducted in the ICU of Masih Daneshvari Hospital

during 2005-2007.

Under study enrolled patients were adults suffering from pulmonary diseases in the age range of 18-90 yrs who were admitted to the ICU for respiratory care and mechanical ventilation. This study was approved by the Ethical Committee of Masih Daneshvari Hospital.

The inclusion criteria were as follows:

1. Pulmonary disease patients requiring intubation and mechanical ventilation
2. Age range of 18-90 years
3. Patients who could not tolerate tracheal tube and required IV sedation

The exclusion criteria were:

1. An underlying condition such as hepatic or renal insufficiency, an underlying heart disease (cardiac insufficiency, valvular disease, etc) or drug addiction (according to patients' medical files and past medical history)
2. Hemodynamic instability and blood pressure drop (blood pressure under 90/60 mmHg)

First, a blood sample was taken from all patients in order to evaluate their liver function (ALP, SGOT, SGPT, BILTG, and cholesterol) and renal function (BUN, Cr). Afterwards, patients' level of sedation was assessed using the Ramsay Sedation Scale. Patients were already intubated and connected to the respiratory support device. They were randomly divided into 2 groups of remifentanil and propofol (alternately). The first group received minimum dosage of remifentanil which was 0.05µg/kg/min as intravenous infusion while the patients in the 2<sup>nd</sup> group were given minimum dosage of propofol that was 10µg/kg/min intravenously. It should be mentioned that none of the patients received bolus dosage for induction of sedation.

Level of sedation for patients was controlled by Ramsay Sedation Scale and the dosage required for reaching level 3-4 of this scale was calculated. Ramsay Sedation Scale is a widely used applied assessment of the level of sedation of a hospitalized

patient. The scale, from 1 to 6, describes a patient as follows:

1. anxious, agitated, restless
2. co-operative, oriented, and tranquil
3. responsive to commands only
4. asleep, exhibiting brisk response to stimulus
5. asleep, exhibiting a sluggish response to stimulus
6. unarousable

If the desired level of sedation was not achieved by the minimum dosage of remifentanil or propofol, dosage increased every 5 minutes as titrated in order to reach the desired clinical effect. Both regimens were continued for 48 hours and blood pressure, heart rate, electrocardiogram and respiratory rate of patients were monitored every 3 hours during this time period. Blood pressure was measured using automatic Siemens blood pressure monitor. Respiratory rate was recorded according to the figure shown on the ventilator monitor. After 48 hours, the time to optimal sedation, the mean dosage of the sedative used and patients' general condition were evaluated and their treatment continued.

In order to calculate the sample size, first 10 patients (5 from each group) were evaluated experimentally and after that the actual sample size was calculated to be 20 patients in each group by analyzing the obtained results.

Patients were assessed in 16 phases and the mean of each variable was calculated in phase 1 (before the administration of drug), phase 2 (after the administration of drug and reaching the optimal level of sedation) and phases 3-16. Student's t-test was used for analyzing the statistical correlations.

## RESULTS

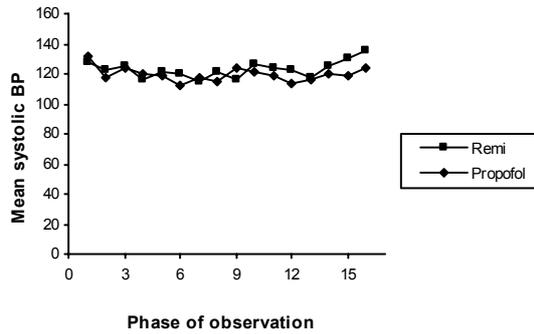
A total of 40 patients suffering from pulmonary diseases including chronic obstructive pulmonary disease (COPD) (18%), pneumonia (10.3%), malignancy (10.3%), acute respiratory distress syndrome (ARDS) (5.1%), idiopathic pulmonary

fibrosis (IPF) (7.7%) and etc. (48%) were evaluated. They were divided into 2 groups (20 patients each). Remifentanil was administered for the first group and in the second group, patients were given propofol. The mean age of all understudy patients was  $58.67 \pm 18.57$  yrs. The mean age of the remifentanil and propofol groups was  $56 \pm 21.48$  and  $61.20 \pm 15.26$  yrs, respectively.

A total of 27 males (67.5%) and 13 females (32.5%) entered the study out of which, 11 males (55%) and 9 females (45%) were in the remifentanil and 16 males (80%) and 4 females (20%) were in the propofol groups. The mean time to sedation (Ramsay scale 3 or 4) was  $17.9 \pm 13.9$  min in the remifentanil group and  $20.16 \pm 11.16$  min in the propofol group. The minimum dosage required for sedation with remifentanil was  $0.11 \pm 0.15 \mu\text{g}/\text{kg}/\text{min}$  which was 2.2 times the initial dose. This dosage was  $16.5 \pm 9.1 \mu\text{g}/\text{kg}/\text{min}$  for propofol which was 1.6 times the initial dose of drug. The mean primary systolic blood pressure of all patients was  $129.40 \pm 23.19$  mmHg. This number was  $127.3 \pm 17.33$  mmHg for the remifentanil and  $131.50 \pm 28.18$  mmHg for the propofol groups ( $p=0.57$ )(Table 1). During 48 hours, blood pressure (BP) was taken 16 times. Table 1 shows the mean of BP alterations. Figure 1 shows the mean of BP alterations in the 2 groups of remifentanil and propofol.

**Table 1.** Comparison of the mean systolic blood pressure among first and second phases and the mean of phases 2-16 of observation.

Period of observation/ drug	Mean systolic pressure(mmHg)	P value (between first and other phases)
First Remifentanil	$127.30 \pm 17.33$	
Second Remifentanil	$122.85 \pm 22.30$	0.26
Mean(2-16) Remifentanil	$121.22 \pm 16.32$	0.85
First Propofol	$131.50 \pm 28.18$	
Second Propofol	$117.75 \pm 29.49$	0.12
Mean(2-16) Propofol	$118.63 \pm 12.57$	0.04



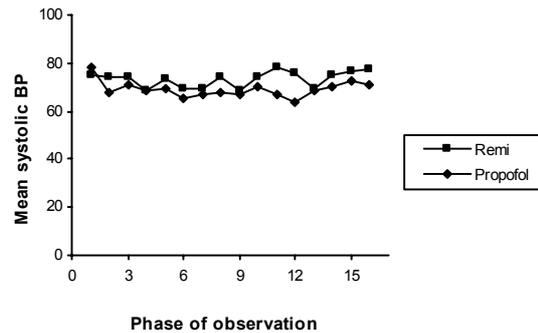
**Figure 1.** Alterations in the mean systolic blood pressure of patients in various phases of observation.

Although at first, no significant difference was found in the mean diastolic BP between the 2 groups ( $75.15 \pm 14.98$  mmHg in the remifentanyl and  $78.2 \pm 19.4$  in the propofol groups,  $p=0.17$ ), the drop of diastolic BP between the phases 1 and 2 in the propofol group was greater than that in the remifentanyl group. However, this difference was not statistically significant ( $p=0.07$ ). Such a considerable decrease was not seen in the remifentanyl group ( $p=0.81$ ).

Considering the diastolic BP changes between phase 1 and the mean of next 15 phases, it was revealed that BP changes in the remifentanyl group were insignificant ( $p=0.33$ ) whereas, dramatic changes were observed in this regard in the propofol group ( $p=0.01$ ) which were statistically significant (Figure 2).

At first, the mean heart rate was almost similar in both groups and no significant difference was detected in this regard (105.5 in the remifentanyl and 97.5 in the propofol group,  $p=0.44$ ). After the administration of drug, heart rate decreased in both groups. However, this decrease was not statistically significant ( $p=0.08$  for the remifentanyl group and  $p=0.15$  for the propofol group). Heart rate had a descending trend in both groups (Table 2 and Figure 3). No significant difference was observed between the 2 groups in terms of the respiratory rate (29 in the remifentanyl compared to 24 in the propofol groups,  $p=0.28$ ). Comparison of the respiratory rate at first

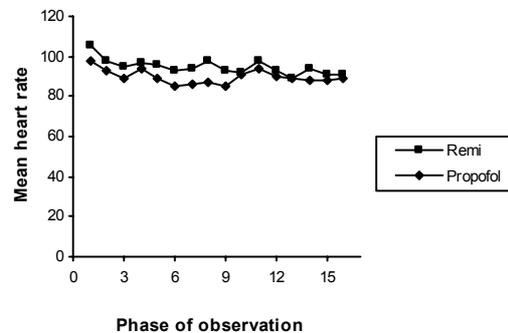
and in phase 1 after the administration of drug showed that respiratory rate decreased in both groups in a stable fashion and this decrease in both groups was statistically significant ( $p=0.02$  for the remifentanyl and  $p=0.05$  for the propofol groups). This trend was almost similar in both groups (Figure 4).



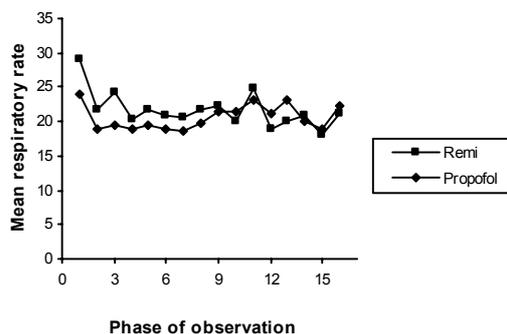
**Figure 2.** Alterations in the mean diastolic blood pressure of patients in various phases of observation.

**Table 2.** Comparison of the mean heart rate among first and 2nd phases and the mean of phases 2-16 of observation

Period of observation/ drug	Mean heart rate/min	P value (between first and other phases)
First Remifentanyl	105.50±17.39	
Second Remifentanyl	98.10±16.99	0.08
Mean(2-16) Remifentanyl	94.90±16.33	0.00
First Propofol	97.55±25.84	
Second Propofol	93.25±27.40	0.15
Mean(2-16) Propofol	89.13±23.79	0.01



**Figure 3.** Alterations in the mean heart rate of patients in various phases of observation.



**Figure 4.** Alterations in the mean respiratory rate of patients in various phases of observation.

## DISCUSSION

This study aimed to evaluate and compare the hemodynamic, respiratory and sedative effects of propofol and remifentanyl, their effective dosage and their onset of action in mechanically ventilated patients in the ICU. Our study results demonstrated that the quality and level of sedation induced by these 2 drugs were almost similar and both could successfully induce a sedation level of 3-4 according to Ramsay Sedation Scale. But our main focus in this study was on the mean time to sedation, minimum required dosage to reach the desired level of sedation (Ramsay scale 3-4) and the pharmacodynamics of the sedative medications and their effect on patients' hemodynamic and respiratory state.

The mean time to sedation was equal in both remifentanyl and propofol groups. This was in accord with pharmacokinetics of these drugs and other studies' findings (9-11). Remifentanyl and propofol are both known as ultra short-acting medications (12-17).

In terms of the effective dosage of remifentanyl, it was detected that by using about 2.2 times the initial dosage, the optimal level of sedation was achieved. This rate was 1.6 times the initial dosage for propofol. This dosage of remifentanyl was similar to that reported by other studies (10,11,16). Therefore, the minimum dosage of drug per se is efficient for

inducing optimal sedation and no bolus dosage is required. This was also true about propofol and adjunct sedatives were not required.

In terms of the effect of these drugs on hemodynamic and respiratory status of patients, remifentanyl and propofol both caused hemodynamic changes in patients in phase 1 before the patients' condition stabilized. As seen in Figures 1 and 2, BP changes occurred in both remifentanyl and propofol groups. However, these alterations were not sudden or out of control. Various studies have considered remifentanyl as a drug with little interference with hemodynamic stability (5,6,13). They have mostly mentioned hypotension as a side effect of this drug, but not an adverse one and no report is available on dramatic BP drop in the first phase following administration of drug (10,11,13,18). Blood pressure drop has always been an issue in the first phase following administration of propofol. BP drop in both groups seems to be associated with the administration of initial bolus dosage. However, our study showed that the mean BP in phases 2-16 was significantly lower than that in the first phase but this difference was not profound. As mentioned earlier, alterations in systolic and diastolic blood pressures were not sudden or severe and the pattern of decrease was relatively stable.

Tachycardia is a sign of patients' anxiety or pain and even under general anesthesia it is considered as a sign of feeling pain by the patient. By relieving the pain and anxiety, tachycardia resolves or improves. In our study, we used tachycardia as an indicator for the quality of sedation. The results showed that both drugs were successful in decreasing the initial heart rate and causing optimal sedation. Remifentanyl and propofol both caused a gradual continuous decrease in heart rate resulting in complete sedation. In both groups, starting drug infusion resulted in an initial significant decrease in heart rate which continued throughout the infusion.

Similar studies did not mention anything regarding the trend of alterations in heart rate but it is considered as a factor indicative of hemodynamic stability. However, no significant difference has been mentioned in this regard in comparison with other drugs (10,13).

Another sign of sedation is decreased respiratory rate in patients which is usually caused by sedatives. In our study, both drugs decreased the respiratory rate of patients and the difference between phase 1 and next phases in this regard was statistically significant in both groups. No data is available in this respect from other studies and therefore, making a comparison was not possible. However, in recent studies it has been mentioned that both propofol and remifentanyl decrease the duration of intubation and mechanical ventilation which were not evaluated in this study and further investigations are required in this regard (19-21).

## CONCLUSION

Remifentanyl is an ultra short-acting sedative medication which unlike other synthetic opioids is not hepatically or renally metabolized. This means that accumulation does not occur with remifentanyl and therefore it is a potent drug for inducing sedation in ICU patients.

Propofol is another short-acting drug used for sedation in ICU patients.

This study indicated that low dose administration of these drugs had no adverse effect on the hemodynamic status of patients with respiratory problems and each of these 2 drugs can efficiently induce optimal sedation.

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