Sedation in Regional Anesthesia: Remifentanil and Propofol Infusions

REJYONEL ANESTEZİDE SEDASYON: PROPOFOL VE REMİFENTANİL İNFÜZYONLARI

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Summary

We compared the safety and effectiveness of remifentanil and propofol infusions used for sedation in bladder or prostate cancer patients undergoing TUR with spinal anesthesia in this study

ASA I-II (aged 50-82 years), 42 male patients were randomly allocated into two groups, Propofol (n=22) and Remifentanil (n=20). Patients received 0.5 mg/kg propofol bolus followed by 3 mg/kg/h infusion in Propofol group and 0.5 μg/kg remifentanil bolus followed by 6 μg/kg/h infusion in Remifentanil group. Arterial blood pressure, heart rate, respiratory rate and oxygen saturation were recorded. Sedation level was followed by 'Observer's Assessment of Alertness/Sedation Scale'. When oversedation or safety end-points are reached, infusion rates were reduced by steps of 0.75 mg/kg/h for propofol and 1.5 μg/kg/h for remifentanil. Spinal block was performed by using 2 ml of 0.5 % hyperbaric bupivacain. Intraoperative and postoperative adverse effects were observed and treated as needed.

More infusion rate decreases were needed in Propofol group to obtain required sedation level ($p<0.05$). Hemodynamic parameters were lower in Propofol group. Mean time to return to alertness was found 4.7 ± 2.7 min in Propofol group, 2.8 ± 2.0 min in Remifentanil group ($p<0.05$). Intraoperative bradycardia incidence was higher in Propofol group ($p<0.05$). Intraoperative respiratory depression and desaturation were both found to be more in Remifentanil group. One patient in Propofol group, 6 patients in Remifentanil group were desaturated in the postoperative period ($p<0.05$). Intraoperative nausea and postoperative nausea-vomiting incidences were higher in Remifentanil group ($p<0.05$). The patient and anesthetist satisfaction were similar in both techniques.

Remifentanil and propofol can be used for sedation during spinal anesthesia, but high incidences of respiratory depression, nausea and vomiting at sedative doses may restrict the clinical use of remifentanil.

Key Words: Regional anesthesia, Sedation; Remifentanil, Propofol

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Özet

Bu çalışmada, spinal anestezi ile transüretral rezeksiyon uygulanacak hastalarda, sedasyon sağlamak amacı ile kullanılan propofol ve remifentanil infüzyonlarının etkinliği ve güvenilirliği karşılaştırıldı.

ASA I-II, 50-82 yaşları arasında 42 erkek hasta rastgele iki gruba ayrıldı: Propofol (n=22) ve Remifentanil (n=20). Çalışmaya, Propofol grubunda 0.5 mg/kg bolus ve 3 mg/kg/sa infüzyon dozu, Remifentanil grubunda 0.5 μg/kg bolus ve 6 μg/kg/sa infüzyon dozu ile başlandı. Kan basıncı, kalp atım hızı, solunum sayısı ve oksijen saturasyonu değerleri takip edilerek kaydedildi. Sedasyon seviyesi 'Gözlemcinin Uyanıklık / Sedasyon Değerlendirme Skalası' ile izlendi. Güvenlik sınırlarına ulaşıldığında, infüzyon hızı propofol için 0.75 mg/kg/sa, remifentanil için 1.5 μg/kg/sa olmak üzere basamaklar halinde azaltıldı. Spinal anestezi, 2 ml %0.5 hiperbarik bupivakain kullanılarak uygulandı. İntraoperatif ve postoperatif yan etkiler gözlenerek tedavi edildi.

İstenilen düzeyde sedasyon sağlayabilmek için, Propofol grubunda daha fazla infüzyon hızı azaltmasına gerek duyuldu ($p<0.05$). Hemodinamik parametreler Propofol grubunda daha düşük seyretti. Uyanma zamanı Propofol grubunda ortalama 4.7 ± 2.7 dk, Remifentanil grubunda 2.8 ± 2.0 dk bulundu ($p<0.05$). İntraoperatif bradikardi insidansı Propofol grubunda daha fazlaydı ($p<0.05$). İntraoperatif bulantı ve postoperatif bulantı-kusma Remifentanil grubunda daha fazla bulundu ($p<0.05$). İntraoperatif solunum depresyonu ve desatürasyon da Remifentanil grubunda daha fazlaydı. Propofol grubunda bir, Remifentanil grubunda altı hastada postoperatif desaturasyon görüldü ($p<0.05$). Hasta ve hekim memnuniyeti her iki teknikte de benzerdi.

Remifentanil ve propofol infüzyonları, spinal anestezide sedasyon amacıyla kullanılabilir, fakat sedasyon dozlarında belirgin solunum depresyonu yapması, daha yüksek oranda bulantı ve kusma görülmesi remifentanilin klinik kullanımını sınırlayabilir.

Anahtar Kelimeler: Rejyonel anestezi, Sedasyon; Remifentanil, Propofol

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Regional anesthetic techniques are becoming increasingly popular because of its advantages to general anesthesia including reduced risk of pulmonary aspiration and thromboembolic complications, good intraoperative and postoperative analgesia (1,2). However, many patients are apprehensive about remaining fully conscious and aware of events during operation. As positioning and performance of block also increase the stress and anxiety of patient, additional supplement of sedation in order to improve patient acceptability and comfort is required.

Table 1. Observer's Assessment of Alertness Scale

Assessment Categories				Composite Score (Level)
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	**Composite Score(Level)**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no pitosis	**1** (Alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild pitosis (less than half the eye)	**2**
Responds only after name is called loudly and repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked pitosis (half the eye or more)	**3**
Responds only after mild prodding or shaking	Few recognizable words	-	-	**4**
Does not respond to mild prodding or shaking	-	-	-	**5**

Opioids are often administered in premedication to avoid physical or psychological discomfort and to supplement insufficient analgesia from the regional block. When opioids are used for sedation, their adverse effects on ventilation must be carefully observed and a patent airway with protective reflexes should be maintained. Remifentanil, a new opioid derivative, provides a short and predictable duration of analgesia without accumulation, a dose related sedation and easily titrable infusion doses by its pharmacokinetic and pharmacodynamic properties (3).

Propofol is widely used for comfort and sedation during regional anesthesia. Propofol infusion at subanesthetic doses has shown to provide good sedation and recovery properties, but it may depress ventilatory response to hypoxia and oxygen support may be needed (4).

In this study, we compared the safety and effectiveness of remifentanil and propofol infusions used for sedation in bladder or prostate cancer patients undergoing TUR with spinal anesthesia.

Methods and Materials

After obtaining approval of local ethics committee and written informed consent of patients, ASA I-II (aged between 50-82 years), 42 male patients were anticipated in this open randomized study. Patients who have chronic use of analgesics, antidepressants and anxiolytic drugs were excluded.

No premedication was administered and the patients were randomly allocated into two groups, Propofol (n=22) and Remifentanil (n=20). On arrival at the operating room, an antecubital intravenous cannula was placed and 8 ml/kg 0.09 % NaCl infusion was administered in half an hour. The basal values of noninvasive arterial blood pressure, heart rate (HR) with electrocardiogram monitorization, respiratory rate (RR) and oxygen saturation (SpO_2) were recorded. Sedation level was followed by 'Observer's Assessment of Alertness/Sedation Scale' (OAA/S). (Table 1). Patients received 0.5 mg/kg propofol bolus followed by 3 mg/kg/h infusion in Propofol group and 0.5 μg/kg remifentanil bolus followed by 6 μg/kg/h infusion in Remifentanil group. The study drugs were administered from the same intravenous cannula. A simple syringe-infusion pump system was used for the administration of drug infusions (Becton Dickenson Infusion Systems, Program 2, France). When oversedation (OAA/S > 2) or safety end-points are reached, infusion rates were reduced by steps of 0.75 mg/kg/h for propofol and 1.5 μg/kg/h for remifentanil (Table 2). Infusion rates were increased by the same steps if OAA/S scale was < 2, until adequate sedation level was obtained. Study drug infusions were continued until the end of operation and this was recorded as infusion time.

When adequate level of sedation (OAA/S ≥ 2) was produced, spinal block was performed from L_{2-3} or L_{3-4} intervertebral space in the lateral decubitus position by using a 22 or 25 gauge spinal needle. 2 ml of 0.5 % hyperbaric bupivacain was injected after a successful puncture. The effectiveness of spinal anesthesia was assessed by pin-prick test. Vital signs and OAA/S scale were assessed at 1st, 3rd and 5th minutes from the beginning of infusion and by 5 minute intervals until the end of operation. Observation of vital signs and sedation levels were continued by two hours after the operation. The time to return of alertness (OAA/S score 1) was recorded.

All patients received 3 L/min nasal oxygen. Intraoperative and postoperative adverse effects were observed and treated as needed. Hypotension, systolic

Table 2. Safety End-points to Reduce Infusion Rate

Safety end-point
OAA/S scale > 2
Respiratory rate ≤ 8 breaths/min
SpO_2 < 95% (While administering O_2)
Heart rate < 55 beats/min
Systolic heart pressure < 80 mmHg

Table 3. Demographic Characteristics of Patients (mean ± SD)

	Propofol (n=20)	Remifentanil (n=20)
Age (years)	63.8 ± 7.1	64.1 ± 9.7
Weight (kg)	69.5 ± 11.1	68.7 ± 14.4
Gender (F / M)	0 / 20	0 / 20
ASA (I / II)	17 / 3	18 / 2

Table 4. Times to Block Performance, Beginning of Operation, Duration of Operation and Infusion (mean ± SD)

	Propofol (n=20)	Remifentanil (n=20)
Time to block performance (min)	16.0 ± 8.5	15.2 ± 7.0
Time to beginning of operation (min)	22.4 ± 6.9	22.7 ± 7.4
Duration of operation (min)	39.7 ± 23.1	37.4 ± 17.2
Duration of infusion (min)	62.3 ± 24.8	60.1 ± 18.0

blood pressure < 80 mmHg, was controlled by fluid administration and infusion rate decreases. 0.5 mg atropine was used for treatment of bradycardia (HR < 55 beats/min) and 10 mg metoclopramide for nausea and vomiting. When respiratory depression and desaturation occurred, patients were stimulated and infusion rates were decreased. Oxygen administration via mask was applied when needed.

The patients and the anesthetists were asked to evaluate their overall surgical experience by using a 4-point rating scale (1=Poor, 2=Moderate, 3=Good, 4=Excellent) at the end of the study.

Statistical Analysis

Mean and standard deviation values are used for comparison of the groups. Blood pressure, heart rate, respiratory rate, SpO_2 variables are compared with Student *t* test. Mann Whitney *U* test is used when the data are not appropriate to use Student *t* test. Chi-Square test is used to compare adverse effects. A p value <0.05 is considered as statistically significant.

Results

There was no significant difference between groups in demographic properties, time to performance of block, time to beginning of operation, duration of operation and infusion. Two patients, one underwent to open prostatectomy and the other given general anesthesia because of prolonged operation time, were withdrawn from the study (Table 3, Table 4).

All of the patients were sedated enough for performance of spinal anesthesia in the first 10 minutes. The average of time to performance of block was recorded as 16 min in Propofol group and 15.2 min in Remifentanil group.

The average of infusion rate to achieve adequate level of sedation during operation was found 2.3 ± 1.0 mg/kg/hr (0.0-4.25 mg/kg/hr) in Propofol group and 5.7 ± 1.6 µg/kg/hr (1.5-9 µg/kg/hr) in Remifentanil group.

No infusion rate adjustments were needed for 5 patients (25%) in Propofol group and for 9 patients (45%) in Remifentanil group. More decreases were needed in propofol infusion rate to obtain required sedation level. 17 patients in Propofol group, 11 patients in Remifentanil group showed signs of oversedation and infusion rates were decreased ($p<0.05$). Although there was no statistical significance, more increases of infusion rate were needed in Remifentanil group.

Mean arterial blood pressure MBP and HR values of patients are shown at Figures 1, 2. Hemodynamic parameters were lower in Propofol group without any statistical significance (Figure 1, Figure 2).

Intraoperative and postoperative adverse effects of study drugs and time to return to alertness are shown at Table V. Mean time to return to alertness was found 4.7 ± 2.7 min (1-10 min) in Propofol group, 2.8 ± 2.0 min (1-7 min) in Remifentanil group ($p<0.05$). 7 patients in Propofol group and one patient in Remifentanil group had intraoperative bradycardia ($p<0.05$). Although there was no statistically significant difference between groups, intraoperative respiratory depression and desaturation were both found to be more in Remifentanil group. One patient in Propofol group, 6 patients in Remifentanil group were desaturated in the postoperative period ($p<0.05$) (Table 5).

500 µg alfentanil was administered to control the complaint of pain in 4 patients in Propofol group. Only one patient had mild pain during surgery in Remifentanil group and infusion rate increase was enough to overcome.

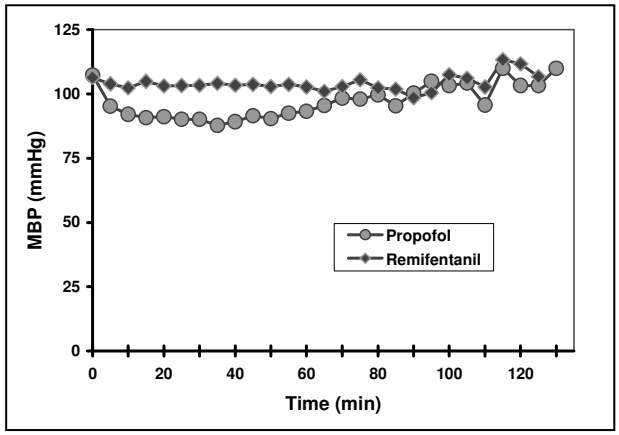

Figure 1. Mean Blood Pressures (MBP) During Propofol and Remifentanil Infusions.

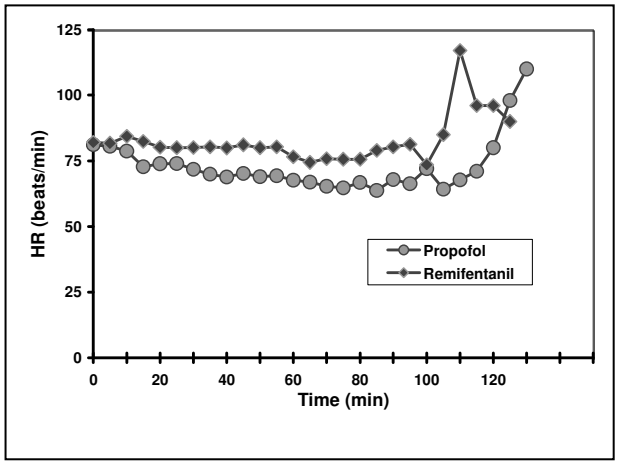

Figure 2. Heart Rates (HR) During Propofol and Remifentanil Infusions

The patient and anesthetist satisfaction were similar in both techniques (Table 6).

Discussion

We used 0.5 μg/kg bolus, 6 μg/kg/hr infusion rate of remifentanil and 0.5 mg/kg bolus , 3 mg/kg/hr infusion rate of propofol for sedation in this study. All of the patients were sedated at the required level in the first 10 minutes. In a recent study, it was suggested that the use of a remifentanil infusion (0.05-0.15 μg/kg/min) was an acceptable alternative to a propofol infusion (25-75 μg/kg/min) during ambulatory surgery procedures performed under local anesthesia. It was stated in the same study that decreases in the infusion rates were frequently required after approximately 15 to 20 minutes, so the 'effect site' concentrations of the drugs were obviously continuing to increase during the early infusion period (5). We also thought that it would be possible to achieve a steady-state effect concentration more rapidly by administering a loading dose prior to maintenance infusion and administered a bolus loading dose in our study.

Although there are many reports suggesting that the opioid analgesic, remifentanil, is enough to provide sedation, some authors find concurrent administration of 2 mg IV midazolam necessary to achieve enough sedation, amnesia and analgesia (6). However, in another study, it was found that in midazolam premedicated patients, a bolus dose of remifentanil could produce clinically significant respiratory depression in the absence of surgical stimulation (5). Similar to the respiratory depression produced by the combination of midazolam and fentanyl, the respiratory depression observed in that study was due in part to the interaction between midazolam and remifentanil and was directly proportional with the increasing doses of midazolam (5-7).

A mean infusion rate of 2.3 mg/kg/h for propofol and 5.7 μg/kg/h for remifentanil were used throughout the operation in order not to reach an OAA/S scale over 2 and a safety end-point occur. Although oversedation was observed more frequently in Propofol group, sedative properties were better than remifentanil. Oversedation was easily controlled by infusion rate adjustments and stimulation of patient.

We used OAA/S scale to assess sedation during infusion. This scale was developed to measure the level of alertness in subjects who are sedated and was found to be both reliable and valid (8). The sedation level of patients can be affected by some factors other than the drug concentrations; such as the level of regional anesthesia, a

Table 5. Time to Return to Alertness and Adverse Effects

	Propofol (n=20)	**Remifentanil (n=20)**
Time to return alertness (min)	4.7 ± 2.7	2.8 ± 2.0*
Intraoperative adverse effects		
Oversedation	17 /20	11 / 20 *
Hypotension	0 / 20	1 / 20
Bradycardia	7 / 20	1 / 20 *
Respiratory depression	2 / 20	5 / 20
Desaturation	9 / 20	13 / 20
Nausea	1 / 20	7 / 20*
Vomiting	0 / 20	0 / 20
Arrhythmia	0 / 20	0 / 20
Postoperative adverse effects		
Hypotension	0 / 20	0 / 20
Bradycardia	5 / 20	3 / 20
Respiratory depression	0 / 20	1 / 20
Desaturation	1 / 20	6 / 20*
Nausea	2 / 20	9 / 20*
Vomiting	1 / 20	8 / 20*
Arrhythmia	0 / 20	0 / 20

* $p<0.05$

Table 6. Patient and anesthetist satisfaction (%)

	Propofol(n=20)		**Remifentanil**(n=20)	
	Anesthetist	Patient	Anesthetist	Patient
Poor (%)	-	-	5	-
Moderate(%)	5	-	10	-
Good(%)	40	15	40	20
Excellent(%)	55	85	45	80

noisy operation room, the spontaneous sleep of patient, high motivation to remain alert and observer. In this study, we tried to diminish the observer dependent differences by making the same observer assess the sedation scale of each patient.

Propofol and remifentanil cause respiratory depression in a dose dependent manner. For this reason, close observation of respiratory system, SpO_2 monitoring and supplemental O_2 administration is needed while using propofol or remifentanil infusion for sedation (4,5,9). Propofol depresses ventilatory response to hypoxia but this effect is minimal at doses used for sedation. The remifentanil dose needed for sedation is very close to dose that causes respiratory depression. The patients that received remifentanil in this study had more intraoperative respiratory depression and desaturation, although they were less sedated. Respiratory depression may occur also in the postoperative recovery period. Only one patient had postoperative desaturation in Propofol group while one patient had respiratory depression and 6 desaturation in Remifentanil group. From those, one patient in Propofol group and 3 in Remifentanil group were found to have low O_2 saturation before infusion of drugs. Neither of the patients needed naloxone and respiratory depression was rapidly managed by infusion rate decreases and stimulation of patients.

Remifentanil, when used as a supplement for local or regional anesthesia, has some adverse effects like other μ opioid receptor agonists. Studies have shown that remifentanil causes respiratory depression due to a decrease in tidal volume and respiratory rate (6,10-12). But unlike the other opioids, remifentanil dependent respiratory depression can be resolved in a few minutes by reducing infusion rate and stimulation as a result of its short elimination half life.

While making sedation with remifentanil during ophthalmic block, respiratory depression episodes were found to occur after the remifentanil bolus administration and their incidence was not enhanced by the adjunction of an infusion (13). Respiratory depression is directly related with the blood concentration and peak concentrations of drugs can be avoided by slow administration. Therefore, it is suggested that bolus doses of remifentanil must be administered slowly over 30-60 s to minimize the risk of respiratory depression.

Arterial blood pressures remained stable in both groups throughout the study, with lower values in Propofol group. Bradycardia incidence was higher in Propofol group. There are studies showing that propofol has minimal effects on cardiovascular system when used at subanesthetic doses for sedation (1,14-16). In another study that compared remifentanil and propofol used for sedation, propofol significantly decreased MAP and HR, whereas remifentanil produced minimal effects on the cardiovascular system for similar degrees of sedation (3). Remifentanil infusion causes significant depression on hemodynamic parameters when used as a component of general anesthesia (17,18), but hemodynamic stability is well preserved at sedative doses (3,9). In a study where propofol sedation is used with central blockade, hemodynamic changes were found to be related to the onset of the central neuraxis block and did not appear to be exacerbated by even the highest propofol infusion rate (4 mg/kg/h) (16). The local or regional anesthetic techniques used with drug infusions may be responsible from these different clinical results. We obtained a low level anesthesia with a low amount of hyperbaric local anesthetic. Sensorial blockade did not rise above T_{10} level in any patient. This restriction in sympathetic blockade and hydration of patients before spinal anesthesia led to stability at blood pressure. Thus, it is not possible to explain the high incidence of bradycardia in Propofol group by sympathetic blockade. In this study, heart rates below 55 beats/min were regarded as bradycardia because of high incidences of bradycardia during administration of remifentanil in general anesthesia. This might have been misleading. We suggest that a lower heart rate value can be used as safety end point for sedative infusions of propofol and remifentanil.

We found the incidences of nausea and vomiting higher in Remifentanil group. Studies have shown that remifentanil, like other μ opioid receptor agonists, may cause nausea and vomiting during its infusion or early postoperative period (6,10-12). Propofol is known to have antiemetic properties (19). Subhypnotic doses of propofol have been used for treatment of nausea and vomiting (20). Although the incidence of nausea and vomiting was higher in Remifentanil group, patient satisfaction was similar between the groups. 85% of patients in Propofol group and 80% of patients in Remifentanil group defined the anesthetic technique as excellent.

An infusion rate of 6-9 μg/kg/h remifentanil is reported to provide adequate sedation and analgesia in minor surgical procedures (21). In this study, 4 patients in Propofol group and one patient in Remifentanil group had complaint of pain during the operation. The patients in Propofol group were treated with alfentanil while the one in Remifentanil group was treated by only infusion rate increase as the sedation level was also decreased.

The time to return to alertness after cessation of drug infusions was shorter in Remifentanil group. This is due to its short elimination half-life and rapid metabolic clearance that is different from other opioids. Return to alertness was later in Propofol group, but it was also favorable for a drug used for sedation and had no clinical importance.

A syringe-pump delivery system was used for infusion of drugs in this study. This is thought to be enough for infusion of both study drugs. During propofol infusion, a better correlation has been found between dose and effect than blood concentration and effect (22). Given the pharmacokinetic profile of remifentanil, complex drug delivery systems do not seem to provide any clinically significant advantages over the simple variable rate syringe pump delivery system used in this study (23).

None of the patients developed TURP syndrome, but it must be taken into consideration that additional sedation and analgesia can mask the initial symptoms of TURP syndrome in our study group.

In this study, we concluded that the titrated doses of remifentanil and propofol for a required level of sedation can be used safely with spinal anesthesia by respiratory system monitorization and selection of suitable patients. But high incidences of respiratory depression, nausea and vomiting at sedative doses may restrict the clinical use of remifentanil.

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