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Full Length Research Paper

Dexmedetomidine and Remifentanil as Adjunct to Regional Anesthesia, a Randomized Clinical Trial

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Spinal anesthesia is one of the required methods for orthopedic surgery. It is of quite importance to decrease anxiety of awake patient during an operation under spinal anesthesia. Plenty of drugs have been used for this purpose. We aimed to compare dexmedetomidine and remifentanil administered for sedation and evaluate it by OAA/S and BIS. Patients aged 18-65 years undergoing orthopedic knee surgery under spinal anesthesia were divided into two groups. Group D received dexmedetomidine 1 µg/kg bolus, then 0.2 µg/kg/h infusion; group R received remifentanil 0.5 µg/kg bolus, then 3 µg/kg/h infusion. Hemodynamic variables and respiratory parameters were recorded. Sedation level was measured by OAA/S and BIS. There was no marked difference in hemodynamic parameters between the two groups, but group D had higher OAA/S and lower BIS scores. Although respiration was depressed more in group R, recovery time was shorter in group D. Both remifentanil and dexmedetomidine can be used for sedation provided that the respiratory parameters are monitored. While faster recovery was provided by remifentanil, deeper sedation was achieved by dexmedetomidine.

Keywords: BIS, dexmedetomidine, remifentanil, sedation, OAA/S.

INTRODUCTION

Spinal anesthesia which has advantages such as allowing awake, spontaneously breathing patient and protecting swallowing and coughing reflexes is a frequently preferred anesthetic technique in orthopedic surgery (Valentin et al., 1986). Furthermore, it has advantages of early mobilization in postoperative period, minimal respiratory complications, continued analgesia and shorter hospital stay. However, consciousness of

patient during operation may lead the patient to feel fear, anxiety, stress and discomfort. This condition can be seen even more in orthopedic operations due to surgical technique and using of various instruments. The most proper way to take away this unwanted condition is administering sedation to the patient. The sedation administered during operation should lessen patient's anxiety and fear while improving comfort and increase quality of regional anesthesia (Barash et al., 2001).

Agents been used for sedation include inhalational anesthetics, benzodiazepines, opioids, propofol, ketamine, non-steroidal anti-inflammatory drugs, steroids, hypnotics, acetaminophen, adenosine, β-blockers and

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α_2 -agonists (Turan et al., 2004).

Dexmedetomidine is a novel α_2 -receptor agonist in our country. It has been shown in trials that, α_2 -receptor agonists have sympatholytic and dose-related analgesia and sedation effects and can suppress neuroendocrine and hemodynamic responses to surgery and anesthesia. These properties make dexmedetomidine theoretically appropriate agent to be used in anesthesia (Turan et al., 2004). Moreover, decreasing need for opioids without respiratory depression is an advantage of dexmedetomidine in monitored anesthetic care (Salengross et al., 1998).

Risks due to sedation are related to the sedation level and can be prevented by following the sedation levels. For this purpose, sedation scales such as, Ramsay Sedation Scale (RSS), Observer's Assessment of Alertness/Sedation Scale (OAA/S) and EEG monitoring like Bispectral Index (BIS) can be used (Burrow et al., 2001).

In our study we aimed to compare the efficacies, hemodynamic responses, adverse reactions and recovery times of dexmedetomidine and remifentanyl administered for sedation in patients undergoing arthroscopic knee surgery under spinal anesthesia.

MATERIALS AND METHODS

After the approval of Clinical Trials Local Ethics Committee; 30 patients of ASA I-II physical status aged 18-35 years, undergoing elective arthroscopic knee surgery were included in the study. All patients were informed and written informed consents were taken separately before the procedure.

Patients having advanced stage cardiac and pulmonary disease, neurological disease and obstructive sleep apnea syndrome history; those with anxiolytic, antidepressant, analgesic, α_2 -receptor agonist, reserpine drug use and those having contraindications for spinal anesthesia and psychomotor functional disorder were excluded from the study.

Patients were randomly allocated into two groups as Remifentanyl (Group R, n=15) and Dexmedetomidine (Group D, n=15) by closed envelope method. In Group R, 2 mg lyophilized powder of remifentanyl HCL (Ultiva[®] 2 mg, lyophilized powder flacon, Glaxo Smith Kline, Istanbul) was diluted into 50 mL of 0.9 % saline to make 50 mL of solution at a concentration of 40 μ g/mL. In Group D, 2 mL of dexmedetomidine (Precedex[®] 200 μ g, 2 mL flacon, Abbot Lab, Istanbul) and 48 mL of 0.9 % saline were mixed to make 50 mL of solution at a concentration of 4 μ g/mL. In both groups study drug dilutions were prepared by the main researcher. The prepared study drugs were placed into infusion pump (Eczacıbaşı, Colleague 3 volumetric infusion pump, USA)

after passing through a standard set (REF VMC9626 Baxter, Colleague) of the infusion pump. Patients were not premedicated before the operation.

Routine monitoring included standard electrocardiography (ECG), noninvasive blood pressure (NIBP), peripheral oxygen saturation (SpO₂), nasal end-tidal carbon dioxide pressure (pETCO₂) and respiratory rate (RR) monitoring. Patients were also monitored by BIS (Aspect Medical Systems A-2000 Bispectral index, USA) to measure sedation level. OAA/S values were recorded before, during and after the operation.

After vascular access was provided by a 20 gauge intravenous (iv) catheterization through patient's dorsal side of right/left hand, isotonic saline solution at a rate of 8 mL/kg/h was infused. 3 L/min 100 % oxygen was given via face mask and was continued during anesthesia induction and maintenance.

Spinal anesthesia was performed with 25 gauge spinal needle inserted at L₃₋₄ or L₄₋₅ space in sitting position using 10-15 mg 0.5% hyperbaric bupivacaine. After determining block level at T₁₀ dermatome, sedative infusion was started and the surgery was permitted to begin. In Group D, a bolus administration dose of 1 μ g/kg dexmedetomidine in 10 minutes was followed by an infusion rate of 2 μ g/kg/h until the end of the procedure. In Group R, a bolus administration dose of 0.5 μ g/kg remifentanyl in 10 minutes was followed by an infusion rate of 3 μ g/kg/h until the end of the operation. Spinal anesthesia application times, times to reach sensorial block to T₁₀ and surgery starting times were recorded.

Heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), respiratory rate (RR), end-tidal CO₂ (pETCO₂), peripheral oxygen saturation (SpO₂), BIS and OAA/S values were recorded before intrathecal drug injection; throughout the operation at the 1st minute and later at every 5 minutes of sedative infusion; after the operation in recovery room at 1st minute and later at every 10 minutes.

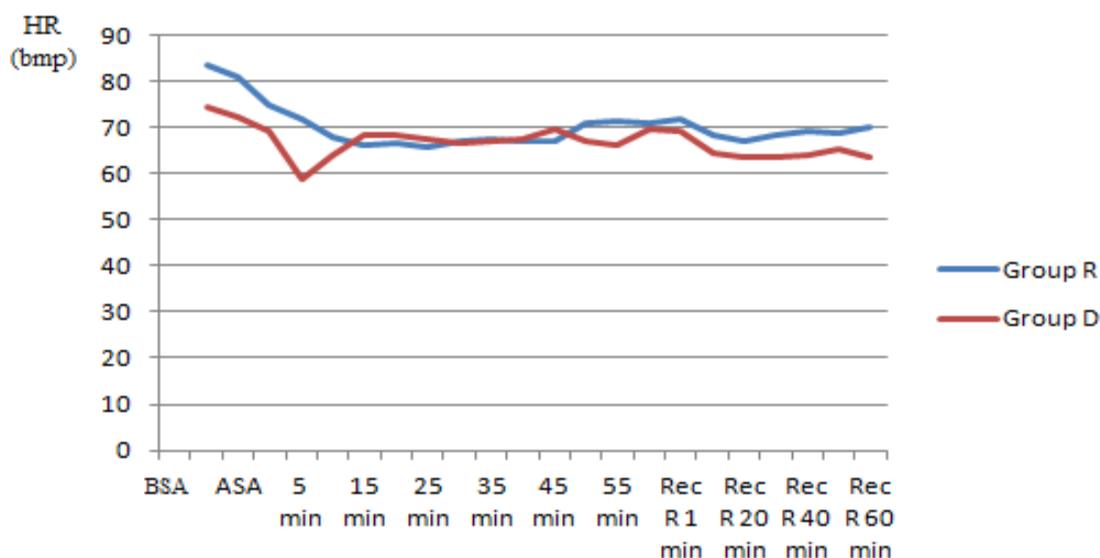
Recovery times of patients were recorded. Recovery time was determined as the time which starts from the cessation of sedative drug infusion until the patient's absolute awakesness, BIS >85 and OAA/S value of 1.

Intraoperative and postoperative hypotension, bradycardia, desaturation, nausea, vomiting, shivering and other adverse reactions were all recorded.

Statistical data analysis was made using SPSS 17.0 software. In evaluation of values; frequency ranges, means, standard deviations, percentages, cross tables were used. Categorical comparisons were made with Chi-Square or Fisher's Exact Test. Mann Whitney U Test was used to compare whether any difference was existed or not between the groups and in independent groups t-test was used. P<0.05 was accepted as significant.

Table 1. Demographical Properties, Anesthesia and Surgery Durations

	Group R (n=15)	Group D (n=15)	P
Age (year)	44.67 ± 12.37	44.33 ± 11.70	0.940
Height (cm)	167.20 ± 10.18	165.13 ± 7.79	0.537
Body weight (kg)	73.60 ± 11.70	74.80 ± 14.98	0.809
Gender	Male	8 (53.3%)	6 (40.0%)
	Female	7 (46.7%)	9 (60.0%)
ASA	I	2 (13.33%)	1 (6.67%)
	II	13 (86.77%)	14 (93.33%)
Anesthesia duration (min)	45.27 ± 10.47	40.47 ± 9.93	0.208
Surgery duration (min)	52.47 ± 10.68	50.07 ± 9.02	0.512

**Figure 1.** Comparison of HR between the Groups

BAS: Before sedative agent, **ASA:** After sedative agent, **Rec R:** Recovery room, **HR:** Heart rate, **bpm:** beats per min.

RESULTS

The demographical data, anesthetic and surgical durations are shown at Table 1; there were no significant differences between the groups ($p > 0.05$).

At the 5th minute of sedative infusion and 60th minute of recovery room, HR values of group D were significantly lower than those in group R ($p < 0.05$), (Figure 1). This difference was clinically unimportant. There was no significant difference in HR values measured at the other times ($p > 0.05$).

MAP values measured at corresponding times from 5th minute of sedative infusion to 20th minute of recovery room were not significantly different ($p > 0.05$); whereas MAP values measured before spinal anesthesia, after spinal anesthesia, at 1st minute of sedative infusion, at recovery room 30th, 40th, 50th and 60th minutes were significantly lower in group D than those in group R ($p < 0.05$), (Figure 2). However, this difference was not important clinically.

After spinal anesthesia, SpO₂ values measured at the 1st and 5th minutes of sedative infusion and at 50th minute of recovery room were significantly lower in group R than those in group D ($p < 0.05$), however this difference was not significant clinically.

After spinal anesthesia, pETCO₂ values measured at the 1st, 40th and 45th minutes of sedative infusion were significantly higher in group R than those in group D; though this difference was not significant clinically ($p < 0.05$).

Respiratory rate values measured at all times of the study were statistically lower in group R than those in group D ($p < 0.05$), (Figure 3). Although this difference was significant quantitatively, it was not important clinically.

OAA/S values measured at the 5th, 15th, 25th, 30th, 35th, 40th, 45th and 50th minutes of the sedative infusion and at the 1st, 10th, 20th and 30th minutes of recovery room were significantly higher in the group D than the group R ($p < 0.05$), (Figure 4).

While there was no significant difference in BIS values

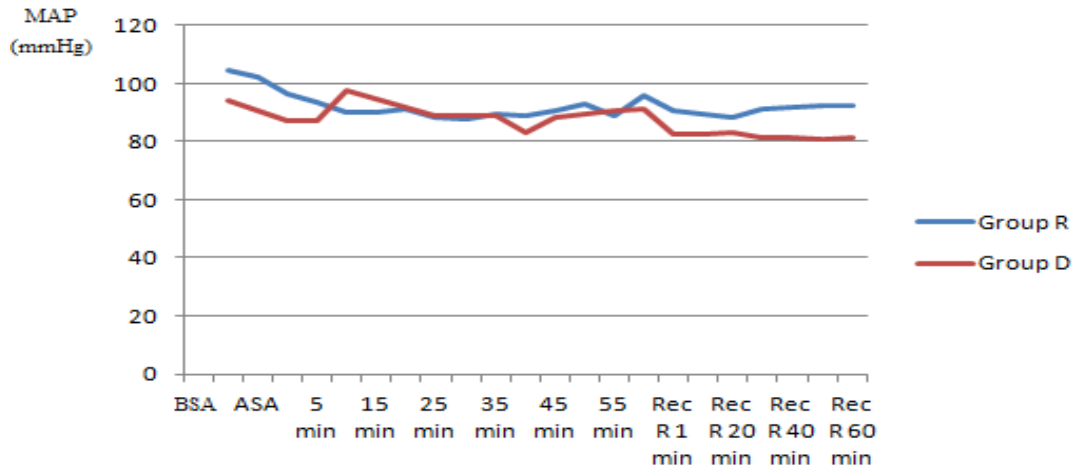


Figure 2. Comparison of Mean Arterial Pressure between the Groups
BAS: Before sedative agent, **ASA:** After sedative agent, **Rec R:** Recovery room, **MAP:** Mean arterial pressure.

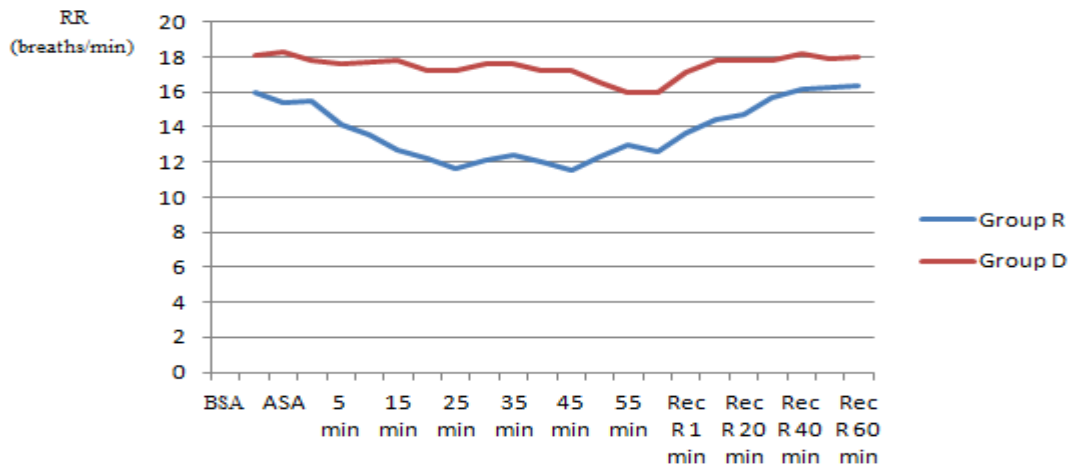


Figure 3: Comparison of Respiratory Rates between the Groups
BAS: Before sedative agent, **ASA:** After sedative agent, **Rec R:** Recovery room, **RR:** Respiration rate.

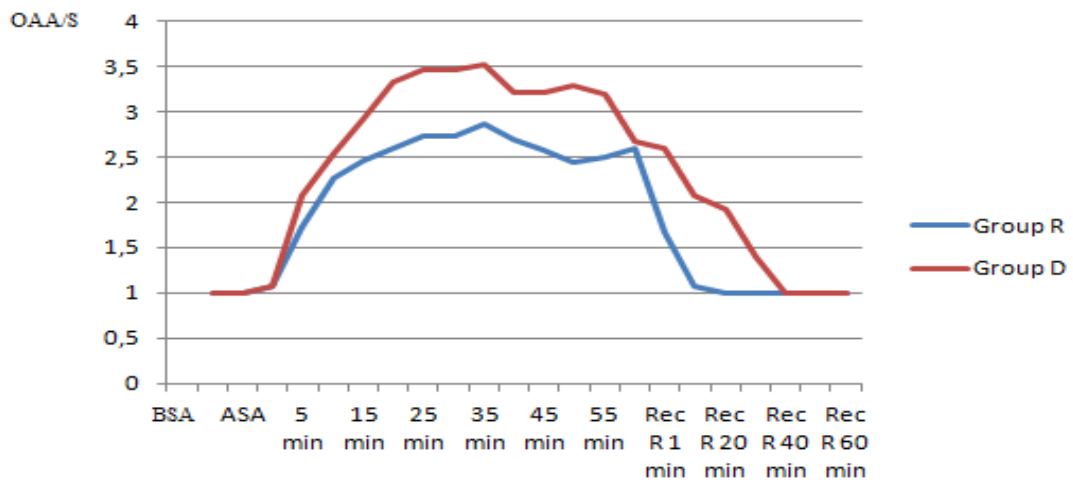


Figure 4. Comparison of OAA/S between the Groups
BAS: Before sedative agent, **ASA:** After sedative agent, **Rec R:** Recovery room, **OAA/S:** Observer's Assessment of Alertness/Sedation Scale.

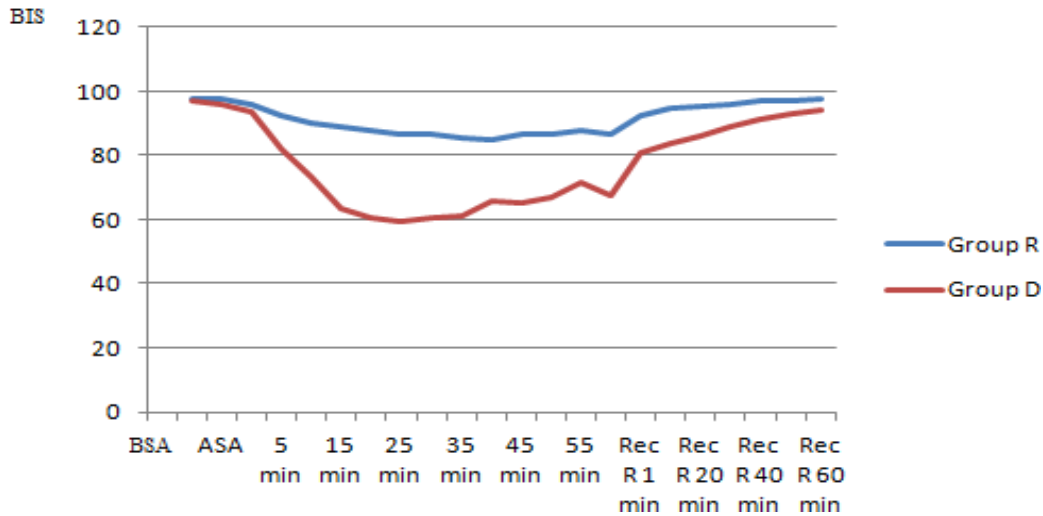


Figure 5. Comparison of BIS Values between the Groups
BAS: Before sedative agent, **ASA:** After sedative agent, **Rec R:** Recovery room, **BIS:** Bispectral index.

measured at corresponding times before spinal anesthesia ($p > 0.05$), BIS values measured at all of the other times were significantly lower in the group D than the group R ($p < 0.05$), (Figure 5).

Recovery times in group R and group D were significantly different and measured as $7,67 \pm 5,50$ and $33,33 \pm 6,17$ minutes, respectively, ($p < 0.001$).

Treatment necessitating hypotension or bradycardia was not occurred in any of the patients. No side effects during the study were observed, except nausea seen in 1 patient in group R that was treated with 10 mg iv metoclopramide.

DISCUSSION

Our study revealed that, lower BIS values and higher OAA/S scores, which mean deeper sedation, were observed with dexmedetomidine compared to remifentanyl. On the other hand, shorter recovery time was observed in remifentanyl group.

Remifentanyl is a short acting agent different from the other opioids with its infusion time independent half life of 3-6 min and terminal half life of 10-20 min. Due to short time of both onset and cessation of action it is an appropriate agent for sedation and analgesia in ambulatory anesthesia (Lauwers et al., 1999).

Dexmedetomidine is a central acting α_2 -receptor agonist having a fast distribution phase with approximately 6 min distribution half life and 2 hour elimination half life. It has many characteristics such as inhibition of sympathetic activity, diminution in hemodynamic response, anxiolysis, and sedation, and analgesia, intraoperative sparing effect on anesthetics and even in high doses not causing respiratory depression.

Sedation related risks are associated with sedation level. It should be monitored for prevention of these risks. In our study in order to monitorize the consciousness and sedation levels of patients, we used BIS and frequent assessment of OAA/S scores.

Dexmedetomidine has been used in different doses to provide intraoperative sedation in many studies so far. In general, it has been administered with a loading dose of 0.5-1 $\mu\text{g}/\text{kg}$ in 10 minutes and an infusion rate of 0.2-0.7 $\mu\text{g}/\text{kg}/\text{min}$. Remifentanyl dose for intraoperative sedation is generally 0,025-0.1 $\mu\text{g}/\text{kg}/\text{min}$, following a bolus dose of 0.5-1 $\mu\text{g}/\text{kg}$.

The basic effects of α_2 -agonists on cardiovascular system consist of decreasing heart rate and systemic vascular resistance, indirectly lessening myocardial contraction, decreasing systemic blood pressure and cardiac output (Reves et al., 2005). Remifentanyl decreases heart rate and blood pressure like the other μ opioid receptor agonists in dose dependent manner (Thompson and Rowbotham, 1996). Many studies have investigated cardiovascular effects of dexmedetomidine and remifentanyl. Apan et al. (Apan et al., 2009) have compared dexmedetomidine and midazolam administered for sedation and found reduction in heart rate in late surgical and early postoperative periods in dexmedetomidine group. Balci et al. (Balci et al., 2006) have investigated effects of propofol and dexmedetomidine administered for intraoperative sedation on hemodynamics and revealed greater effect of dexmedetomidine on decreasing MAP and HR. Richa et al. (Richa et al., 2008) have compared dexmedetomidine and remifentanyl administered for sedation and found lower MAP and HR values with remifentanyl group than that with dexmedetomidine. Chaves et al. (Chaves et al., 2003) have investigated hemodynamic and metabolic effects of dexmedetomidine and remifentanyl and found

higher SAP and DAP values with dexmedetomidine than those with remifentanil. In our study HR and MAP values have been determined to be significantly low in dexmedetomidine group compared to remifentanil group. However, this difference was clinically insignificant and has not necessitated any intervention.

During dexmedetomidine infusion and in particular during loading dose administration, hypotension and bradycardia can occur. These cardiovascular side effects can be brought to ignorable levels by reducing initial bolus dose. After the termination of infusion, rebound cardiovascular effects and effects due to withdrawal syndrome won't be observed because of the slow increase of these values (Alagöl et al., 2006). Hemodynamic effects due to dexmedetomidine administration are biphasic like the other α_2 -agonists (Paris and Toner, 2005). This biphasic effect consists of an initial blood pressure increase caused by peripheral α_2 -adrenoceptor stimulation and a latter blood pressure decrease due to stimulation of α_2 -adrenoceptors in central nervous system (CNS). Because the biphasic effect of dexmedetomidine is associated with drug administration rate, it can be attenuated by administering the drug over 5 minutes (Hall et al., 2000). No biphasic effect on blood pressure was occurred in dexmedetomidine group in our study.

One of the most important and feared conditions in sedated patients operated under local or regional anesthesia is respiratory depression. Lauwers et al. (Lauwers et al., 1999) compared iv midazolam and 3 different infusion doses of remifentanil administered for sedation and have observed that, remifentanil added to midazolam caused respiratory depression in dose dependent manner. Alhashemi et al. (Alhashemi, 2006) who compared dexmedetomidine and midazolam administered for sedation have determined that SpO₂ values were lower without any desaturation and expired-CO₂ was not markedly different in midazolam group. Mingus et al. (Mingus et al., 1998) compared propofol with the least dose of remifentanil (3 μ /kg/h) for sedation and have observed more respiratory depression in propofol group. Ramsey et al. (Ramsay et al., 2006) haven't observed desaturation in spontaneously breathing and consciously sedated patients using dexmedetomidine. Scher et al. (Scher and Gitlin, 2003) preferred dexmedetomidine due to antisialagogue effects and sparing respiratory depression in awake fiberoptically intubated patients. In our study, SpO₂ values measured at certain intervals were lower and ETCO₂ values measured at certain intervals were higher in group R than in group D. Respiratory rates were lower in group R during the entire follow up period; however we didn't experienced respiratory depression in any of the patients. We linked this to oxygenizing the patients with 3 L/min oxygen via face mask during their stay in operation room. As well as we haven't experienced respiratory depression due to dexmedetomidine administration in our study and

no reports concerning it were found in the literature, we think, dexmedetomidine should be the first choice in conscious sedation for the patients having risks of respiratory depression.

Another parameter should be evaluated in monitored patient care is sedation level. Consciousness is evaluated by many scale systems such as subjective five-point sedation scale, Ramsay sedation scale scoring and OAA/S scoring. It can also be evaluated by BIS, a practical and objective method of electroencephalogram to measure the direct effects of sedation on brain. BIS values of 40-60 necessitate immediate intervention of anesthetist (Song et al., 1997) and decreased anesthetic drug requirements (Gan et al., 1997). One of the objective advantages of BIS usage is administering real-time sedation without any need of external stimulations (Apan et al., 2009). Ease of use, being automatic and objective make BIS an effective method in overcoming interrupted and deep sedation.

Many studies in the literature have used various sedation scores at different time intervals. Bower et al. (Bower et al., 2000) and Ibrahim et al. (Ibrahim et al., 2001) have determined that, BIS level and OAA/S score are correlated. Liu et al. (Liu et al., 1996) compared OAA/S score with BIS, 95% spectral edge frequency, median frequency and delta, theta, alpha, beta power band correlation and have determined that, OAA/S scores best correlate with BIS. Therefore, in our study we evaluated the sedation levels by BIS and OAA/S. OAA/S scores from 5th minute of sedative infusion to 50th minute of recovery room were higher in dexmedetomidine group. Furthermore, BIS scores were lower in dexmedetomidine group during the entire follow up period. These results show that, dexmedetomidine provides better sedation than remifentanil. Ayoglu et al. (Ayoğlu et al., 2007) have shown that dexmedetomidine provides effective sedation. Koroglu et al. (Köroğlu et al., 2005) compared dexmedetomidine with midazolam administered for sedation during magnetic resonance imaging (MRI) in children and have obtained better and shorter sedation with dexmedetomidine. Balcı et al. (Balcı et al., 2006) compared propofol with dexmedetomidine administered for sedation and have found that, postoperative BIS values were significantly lower in dexmedetomidine group.

Muttu et al. (Muttu et al., 2005) have concluded that postoperative recovery with dexmedetomidine is faster than midazolam. Koroglu et al. (Köroğlu et al., 2005) have observed that recovery from sedation during MRI with dexmedetomidine and midazolam were in 24 and 25 minutes respectively. Yaddanapudi et al. (Yaddanapudi et al., 2007) have demonstrated that, recovery times from sedation in patients undergoing urological surgery with spinal anesthesia under propofol and midazolam sedation were average 8.9 and 12.5 minutes, respectively. Aantaa et al. (Aantaa et al., 1990) compared dexmedetomidine and midazolam administered via

intramuscular route and have demonstrated that, recovery times in midazolam and dexmedetomidine groups were 11.3 and 8.5 minutes, respectively. Remifentanyl has short onset action time and fast recovery period (Dal et al., 2005). We have compared the recovery time as the period which starts from the cessation of the sedative infusion to the BIS>85 and OAA/S score of 1, meaning the patient is fully awakened. Recovery periods were 7.67 ± 5.50 min. and 33.33 ± 6.17 minutes in remifentanyl and dexmedetomidine groups, respectively. In this respect, recovery periods with remifentanyl were markedly shorter.

CONCLUSION

In conclusion, both dexmedetomidine and remifentanyl could be used safely in the aim of sedation, provided the respiratory effects are monitored. Remifentanyl provides faster recovery, whereas dexmedetomidine provides deeper sedation.

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