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RESEARCH ARTICLE

DREAMING DURING SEDATION WITH PROPOFOL, MIDAZOLAM OR REMIFENTANYL IN WOMEN

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ABSTRACT

Objective: The purpose of this study was to compare the effects generated ondreaming in female patientsundergoing spinal anesthesia; by three different sedative agents.
Methods: Thiswas a prospective and randomized study and it was approved by TurgutOzal University School of Medicine Ethics Committee, and the patients' informed consent was received. 120 ASA I-III female patients, 18 - 60 years of age, were planned to undergo surgery by spinal anesthesia. All the patients had bispectral index (BIS) monitorization. The patients were randomized into three groups, so that Group P received propofol infusion, Group M; midazolam infusion, and Group R;remifentanil infusion for sedation. The infusion dosages were decreased by 50% when BISwas80, and titrated thereafter to keep BIS between 60-80. The patients' post-operative sedation levels were evaluated by Assessment of Alertness and Sedation Scale (OAA/S). Following recovery, Brice interview was administered to the patients.
Results: The duration of BIS value to be 80 in Group R was significantly longer than those of the other groups. The length of stay in postanesthesia care unit (PACU) in Group P was significantly shorter while the incidence of nausea/vomiting in Group R was significantly higher.The groups did not differ with regard to objectivity/subjectivity of the dreams, vividness and dynamism of the events, relation of story to everyday life, and dream recallability.
Conclusion: These results indicate that either propofol, midazolam or remifentanil do not exert significantly dissimilar effects on dreaming, hemodynamic parameters or side effects.

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INTRODUCTION

Dreaming is one of the commonly observedside effects of anesthesia (Bagchi *et al.,* 2014; Hellwagner *et al.,* 2003; Brandner *et al.,* 1997). In various studies, the incidence of dreaming during anesthesia has been reported to vary between 5- 36% (Hogue *et al.,* 1996; Myles *et al.,* 2001). It has been considered that this wide interval of incidence is related with the variability of the drugs used in anesthesia, their dosages, and duration of administration. There are various hypotheses claiming that intraoperative dreaming is related toa low or insufficient level of anesthesia (Eer *et al.,* 2009). In addition to studies that report higher incidences of dreaming in cases with lower doses of anesthetic drug administration (Stait *et al.,* 2008),and in those existing with rapid arousal (Leslie *et al.,* 2005); there are also studies reporting that dreaming is related with deep anesthesia (Kim *et al.,* 2011; Sebel *et al.,* 2004; Lichtor *et al.,* 2009). In many studies comparing propofol and inhalational anesthetics, the incidence of dreaming has been reported to be higher in patients administered propofol (Hellwagner *et al.,* 2003; Brandner *et al.,* 1997; Leslie *et al.,* 2007). This result is considered to be due to the more rapid recovery of patients from propofol. As a result of this, the patients interact with people around early and describe their dreams if present (Hogue *et al.,* 1996). In cases of regional anesthesia, sedation has been observed to decrease the patients' stress related with surgery, and increase their orientation to the environment. Benzodiazepines, intravenous anesthetic agents, and opioids are used for intravenous sedation (Samuelsson *et al.,* 2008). In addition to general anesthesia, different agents used for sedation under regional anesthesia have also been reported to cause dreaming (Ranta *et al.,* 1998; Schredl *et al.,* 2003). In our study we investigated the effect of sedation using three different agents on dreaming, with regard to side effects and hemodynamic parameters, in the female patients planned to undergo surgery under spinal anesthesia by bispectral index (BIS) monitoring.

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MATERIALS AND METHODS

This prospective, randomized study was approved by TurgutÖzal University, School of Medicine Ethics Committee (October 18, 2013, number 99950669/1025). The study

comprised 120 ASA I-III female patients, between 18 and 60 years of age, who would undergo surgery for at least one hour under spinal anesthesia. During preparation for anesthesia in the preoperative period, all the patients were informed about the procedure that would be applied, and the possible complications, and their written consents were received. Patients with contraindications for spinal anesthesia, those with schizoaffective disorders, language and communication problems, and those who would undergo emergency operations, were not included in the study. After their admission to the operation room, the patients' heart rate (ECG), non-invasive blood pressure, peripheral oxygen saturation (SpO_2) via pulse oximeter probe, respiration frequency and end-tidal carbon dioxide pressure ($ETCO_2$, mmHg) via a nasal cannula connected to a capnograph, and level of sedation (BIS) were continuously monitored.

The patients were not premedicated. After starting the infusion of crystalloid solution via an intravenous line, spinal anesthesia with heavy marcainewas applied. Following sufficient sensory and motor blocks, we randomly started to infuse sedative agents simultaneously with the surgical incision, as follows: propofol: 1 $mg.kg^{-1}$ bolus, followed by 3 $mg.kg^{-1}.h^{-1}$ (Group P) (pofol 1% 10 $mg.cc^{-1}$, İlsan, Turkey), midazolam: 0.05 $mg.kg^{1}$, then 0.06 $mg.kg^{-1}.h^{-1}$ (Group M) (Zolamid 5 $mg.cc^{-1}$, Defarma, Turkey) or remifentanil: bolus 0.5 $\mu g.kg^{-1}$ and 0.1µg.kg-1.min^{-1}infusion (Group R) (Ultiva, 2 mg flacon, Glaxo Smith Kline, Italy) (16, 17). When the BIS value reached 80, the drug doses were decreased by 50%. We continued infusions by titrating the drug doses so that the BIS value would be held at 60 to 80. Regarding the BIS values, the drug infusion doses were varied thereafter. Hemodynamic (systolic, diastolic and the mean arterial pressures, and heart rate) and respiratory (SpO_2 (%), $ETCO_2$ (mmHg), frequency of respiration) parameters, and scores of sedation were recorded every five minutes, throughout the operation. The arterial blood pressure was permitted to vary by 30% of the basal value occurring prior to surgical incision. Hypotension was treated by 5 mg intravenous ephedrine, and hypertension by 100 µg intravenous nitroglycerin. The patients were followed-up for possible side effects of the sedative agents. Drug infusions were continued until the surgery was completed. The time interval from the termination of the drug infusions to the patients' eyes opening, was recorded. Following the recovery period the patients were evaluated using the Observer Assessment of Alertness and Sedation Scale (OAA/S). Observer Assessment of Alertness and Sedation Scale (OAA/S). The patients with OAA/S scores reaching 5 were asked the following standardised questions (Brice *et al.,* 1970)

- "What was the last thing you remember before going to sleep?"
- "What was the first thing you remember when you woke up?"
- "Can you recall anything between?"
- "Did you have any dreams during your procedure?

As a result; if dreaming was reported, the patient was further asked questions about characteristics and content of their dreams (Gyulaházi *et al.,* 2016). The patients with OAA/S scores reaching 5 were transferred to their wards, and the length of stay in postanesthesia care unit (PACU) was recorded. All patients included in the study, were subjected to a Brice interview postoperatively (Xu *et al.,* 2013).

Statistical Analysis

By reference to similar studies conducted earlier in the literature, 0,33 impact range (effect size), power analysis revealed a sample size of at least 120 individuals for One-Way Analysis of Variance (One-Way ANOVA). Thus, the test power is expected to achieve approximately 89%. Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). While, metric discrete variables were shown as mean± SD, otherwise, number of cases and (%) were used for categorical data. Categorical data were analyzed by Fisher's exact and Pearson Ki-Square Test, where applicable. The differences between groups regarding for normally distributed data were compared by Student's t-test, otherwise, Mann-Whitney U test (for two independent groups) and Kruskal Wallis Test (for three independent groups) were used for not normally distributed data. When the p-value from the Mann-Whitney U test was statistically significant to know which measurement differed from which others by using Bonferroni adjusted multiple comparison test was used. For two dependent groups, significance was tested by Wilcoxon Signed-Rank Test. A p value less than 0.05 was considered statistically significant.

RESULTS

The study group included 120 female patients who underwent surgical interventions under spinal anesthesia, during which they were administered propofol, midazolam or remifentanil for sedation. The mean age of the patients was 52.1±9.8 years. 89.1%(n=107) of the patients had orthopedic surgery.The duration of anesthesia did not vary between types of surgical proceduresv (mean, 53±26.5 min). The time of BIS value to reach 80 was found to be 23.6±12.7 min (mean) in the patients in Group R. This value was significantly longer when compared with the other groups ($p<0.001$). However Group P and Group M did not differ significantly in this regard (9.1±6.4 minvs 8.7±9.6 min, $p>0.05$). In the patients sedated with propofol, the duration of stay in PACU was significantly shorter compared with other groups ($p<0.001$). The incidence of dreaming in our study was 15.8%. Among these, six (15%) patients were in the propofol group, another six (15%) were in the midazolam group, and seven (17.5%) were in the remifentanil group. When the characteristics of the dreams were evaluated there was no difference among the groups ($p>0.05$). Except for two cases, one for each of the propofol- and midazolam-administered groups, all the dreamers expressed meaningful stories related with real life (Table 1). Except for the values measured in 5^{th} minute, all the other mean arterial pressure (MAP) values evaluated during surgery differed significantly compared with the corresponding initial values, in both dreamers and non-dreamers ($p<0.05$), the intraoperative values being lower than the initial values. The MAP values, which were measured at all times during surgery, did not differ significantly between the dreamers and non-dreamers ($p>0.05$) (Figure 1). In the non-dreamers, all the heart rate (HR) values measured during surgery, except that in 5^{th} minute, differed significantly compared with the initial value ($p<0.05$), the intraoperative values being lower than the initial value. In the dreamers, statistically significant differences were determined between the intraoperative values of heart rate (HR) measured in 20^{th}, 30^{th}, 40^{th}, 50^{th} and 60^{th} minutes, and the corresponding initial value ($p<0.05$); intraoperative values of HR measured at times other than these, did not show significant differences ($p>0.05$) (Figure 2).

Table 1. The characteristics of dreams

	Propofol (n=6)	Midazolam (n=6)	Remifentanil (n=7)	p
	number (%)	number (%)	number (%)	
Nature				
cinematic like	1 (16,7)	1 (16,7)	0	0,521
thought like	5 (83,3)	5 (83,3)	7 (100)	
Content				
other people	1 (16,7)	1 (16,7)	2 (28,6)	0,828
family	5 (83,3)	5 (83,3)	5 (71,4)	
Color				
black and white	1 (16,7)	1 (16,7)	1 (14,3)	0,991
color	5 (83,3)	5 (83,3)	6 (85,7)	
Mood				
negative	1 (16,7)	1 (16,7)	1 (14,3)	0,991
positive	5 (83,3)	5 (83,3)	6 (85,7)	

Data: number of patients(%), p<0.05: significant

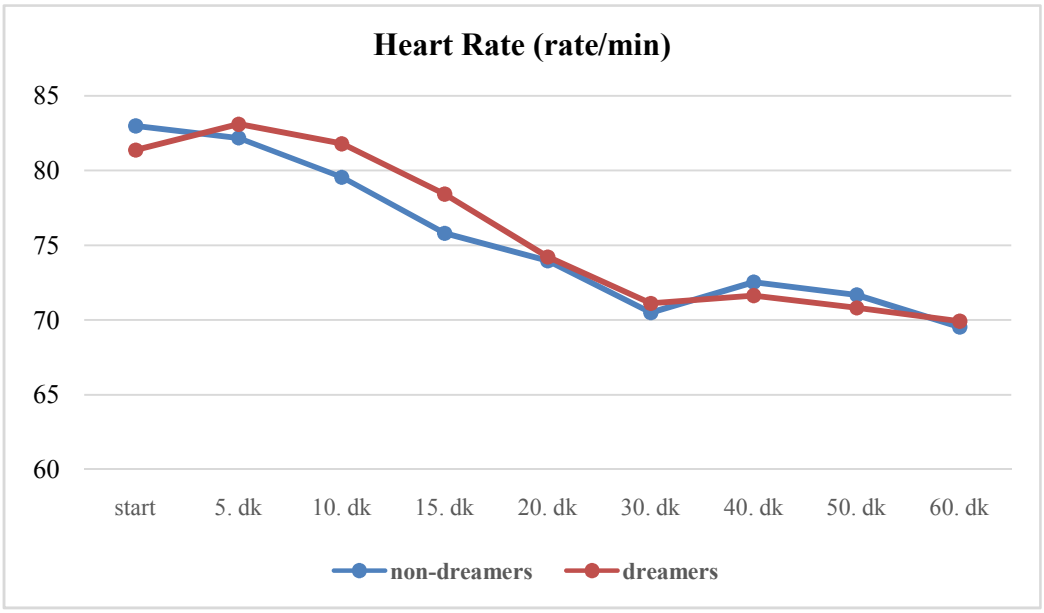

Figure 1. Intraoperative hemodynamic changes (heart rate)

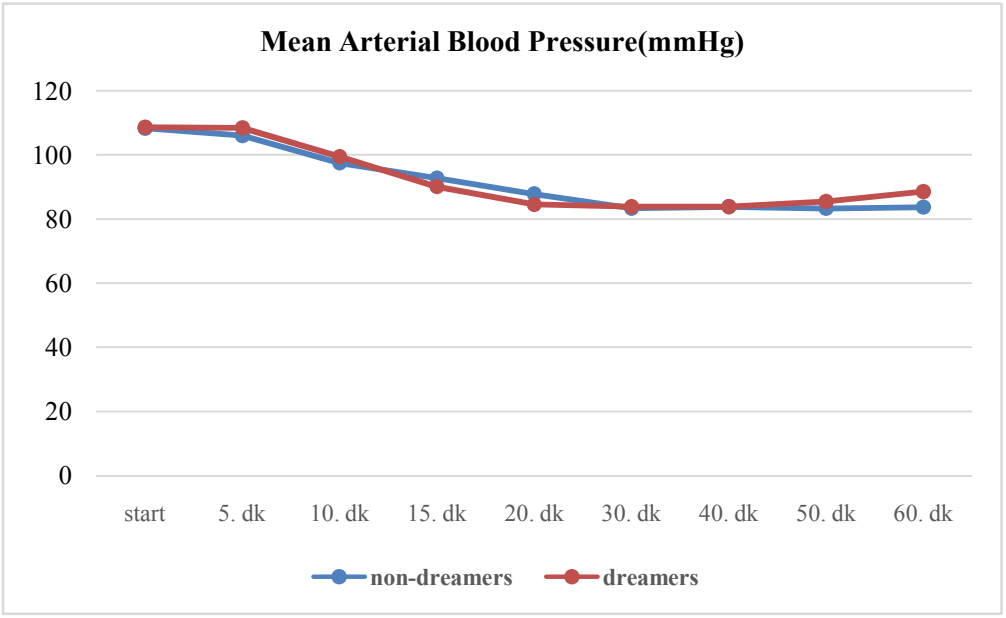

Figure 2. Intraoperative hemodynamic changes (mean arterial blood pressure)

The existence of nausea and vomiting as side effects showed statistically significant differences between the study groups ($p<0.05$). The rate of nausea and vomiting in the cases sedated with remifentanil, was found to be significantly higher than those sedated with the other drugs. Nausea and vomiting developed in none of the patients who were administered propofol.

DISCUSSION

In the present study, we compared the effects of sedation on intraoperative dreaming and hemodynamic parameters in patients sedated with three different agents (propofol, midazolam, remifentanil) during surgical processes under spinal anesthesia. Similar rates of dreaming were determined in all groups. Besides; the level of sedation and side effects did not differ among the groups. Dreaming is one of the common side effects of anesthesia (Bagchi *et al.,* 2014; Hellwagner *et al.,* 2003; Brandner *et al.,* 1997). In various studies, differences intype, dosage and duration of the agent have been found to affect dreaming. In the literature the rate of dreaming has been reported to vary between 5-36% (Hogue *et al.,* 1996; Myles *et al.,* 2001). There are various hypotheses claiming that intraoperative dreaming is related to low or insufficient anesthesia (Eer *et al.,* 2009). Dreamers have many clinical signs related to superficial anesthesia, or show more signs of consciousness, when compared with non-dreamers (Brandner *et al.,* 1997). The incidence of dreaming is higher in those administered lower doses of anesthetic drugs, and those with rapid arousal from anesthesia (Stait *et al.,* 2008; Leslie *et al.,* 2005). However in many studies, dreaming has been related to deep anesthesia (Hellwagner *et al.,* 2003; Kim *et al.,* 2011; Sebel *et al.,* 2004; Lichtor *et al.,* 2009). In the study of Galletly *et al*., conducted with 50 patients, a linear proportion was determined between low BIS values and dreaming (Galletly and Short, 1988). In a current b-aware study, the depth of anesthesia evaluated by BIS did not differ between patients dreaming and not dreaming (Leslie *et al.,* 2005). In our study, in order to evaluate the effects of different drugs, we maintained a depth of anesthesia between 60 and 80 by BIS monitorization; we thus tried to minimize the effects that might be related to the differences in depth of anesthesia. In various studies, the contents of dreams were frequently reported as being related to simple and pleasant issues, like family, friends, and work; they may also include surgical subjects and events (Hellwagner *et al.,* 2003; Leslie *et al.,* 2005; Lichtor *et al.,* 2009; Leslie *et al.,* 2007; Giro *et al.,* 2002).

Similar with the literature, in our study the subjects of most of the dreams were about the dreamers' everyday lives, their relationship with family members and lasted only for a short period of time. Ear *et al*. conducted a study evaluating the effects of different propofol doses on the incidence of dreaming, and determined it to be 19% in cases sedated with propofol (Eer *et al.,* 2009). Stait *et al*. determined the incidence of dreaming to be between 20-25% in cases sedated for colonoscopy (Stait *et al.,* 2008). In a similar study by Kim *et al*., where the effects of propofol and midazolam were compared, the overall rate of dreaming was determined to be 26%; however this rate was higher in the propofol group (39.8%), than in the midazolam group (12.1%) (Kim *et al.,* 2011). Likewise other results in the literature, in our study 15.8% of the patients experienced dreams. In related studies, incidences of dreaming have been reported to be higher in patients interviewed immediately following surgery (21%-34%) (Hellwagner *et al.,* 2003; Brandner *et al.,* 1997; Leslie *et al.,* 2007), and this rate dramatically decreased as time following recovery increased, due to difficulties in recall (6%) (Leslie *et al.,* 2005; Sebel *et al.,* 2004). Therefore, we interviewed our patients within one hour of surgery, to maintain a high rate of dream recall. Leslie *et al*. conducted a study with 300 patients undergoing general anesthesia. He separated the patients into groups for questioning either within two to four hours of surgery, or 24 hours following surgery. Contraversly, the rate of dream recall in this study was found to be 22%, and 25%, respectively (Leslie *et al.,* 2007).There are studies in the literature reporting that the incidence of dreaming is higher amongst females than males (Leslie *et al.,* 2005; Samuelsson *et al.,* 2008; Ranta *et al.,* 1998). This has been explained by the more rapid recovery of females compared with males, the more rapid interaction of females with the environment following surgery, the more articulate expression of their dreams, and females having an increased tendency to remember their dreams (Myles *et al.,* 2001; Leslie *et al.,* 2005; Schredl *et al.,* 2003). However, there are also studies reporting higher incidences of dreaming in males than in females, as well as demonstrating no difference between the genders in this regard (Leslie *et al.,* 2007). In a study by Xu *et al*., performed with 100 male and 100 female patients sedated for endoscopy using propofol, the rate of dreaming in males (31%) was found to be higher than that of females (17%) (Xu *et al.,* 2013). In order to minimize the effect of gender, we conducted our study only with female patients. In another study including 200 female patients; 100 cases were sedated with propofol, and the other 100 were sedated with sevoflurane, and the incidences of dreaming were found to be 33% and 60%, respectively (Xu *et al.,* 2012). However in our study, the rate of dreaming was found to be 15% in the propofol group; but this result may be related to the low number of patients included in our study.

There are many studies demonstrating that dreaming occurs more frequently in the young and healthy individuals, compared with elderly patients with comorbid diseases (Leslie *et al.,* 2005; Sebel *et al.,* 2004; Ranta *et al.,* 1998). Problems experienced by older patients with falling asleep and their difficulties in passing through the REM stage were concluded to be possible causes (Giron *et al.,* 2002; Foley *et al.,* 1995). In our study, the mean age of dreamers (51.8 years) was found to be lower than that of the non-dreamers (53.7 years); however this difference was not statistically significant. In the dreamers' group, the association of an endocrine disorder was determined at a significantly higher rate compared with non-dreamers; however we did not have any data to explain this result. In many studies that have compared propofol and inhalation anesthetics, the incidence of dreaming in the propofol group was found to be higher (Hellwagner *et al.,* 2003; Brandner *et al.,* 1997; Leslie *et al.,* 2007). The more rapid recovery of patients from propofol, and their more rapid interaction with the environment enabling them to recall and describe their dreams, were concluded to be the causes (Hogue *et al.,* 1996). The incidence of dreaming is considered to increase with increasing doses of propofol. In the study by Stait *et al*., the incidence of dreaming was found to be 35% in the patients given more than 140 mg of propofol, while in cases who were administered propofol 80 mg or lower, the incidence was 16% (Stait *et al.,* 2008). Contrary to this finding, Schaer *et al*. administered 50, 100, 150, and 200 $\mu g.kg^{-1}.min^{-1}$ of propofol infusions to 40 patients undergoing minor gynecologic procedures, and determined that the rate of dreaming decreased as the propofol dose increased (40%, 40%,

10%, 0) (Schaer, 1988). In the study of Ear *et al* dreaming occurred in 38 of 200 patients. Of these dreamers, nine patients were administered a total of 200 mg propofol or lower, ten cases were administered propofol between 201 mg to 300 mg, and nineteen cases received the drug doses above 300 mg (Eer *et a.,* 2009). In our study, the total propofol dose administered was (mean) 299 mg, and propofol dosage did not show any statistically significant difference between the dreamers and non-dreamers.

Conclusion

Dreaming is a frequently observed side effect of anesthesia, commonly reported following anesthesia and sedation. In our study, by monitoring BIS, we evaluated the effects of different sedative agents on dreaming, also taking into account hemodynamic effects and side effects in patients who were sedated under regional anesthesia. We believe that sedation with different agents did not cause any differences in patients in the aspect of dreaming, hemodynamic parameters, side effects.

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