Comparison of midazolam, propofol and fentanyl combinations for sedation and hemodynamic parameters in cataract extraction

Varol Celiker, MD, Elif Basgul, MD, Altan Sahin, MD, Sennur Uzun, MD, Betul Bahadir, MD, Ulku Aypar, MD.

ABSTRACT

Objective: Midazolam, propofol and fentanyl were compared in terms of sedation during cataract extraction. Hemodynamic parameters, sedation level, postoperative satisfaction, and side effects were investigated.

Methods: The study was carried out in Hacettepe University Hospitals Ophthalmology Operating Theatres in 2005. The patients received only midazolam (0.02 mg kg^{-1}), or midazolam (0.02 mg kg^{-1}) + propofol (0.2 mg kg^{-1}), or midazolam (0.02 mg kg^{-1}) + fentanyl (1 microgram kg^{-1}), or midazolam (0.02 mg kg^{-1}) + propofol (0.2 mg kg^{-1}) + fentanyl (1 microgram kg^{-1}). The sedation level of patients was measured according to a 'physician questionnaire'. Postoperative nausea/vomiting, headache, and patient satisfaction were determined via a 'patient's evaluation scale'.

Results: In the groups receiving fentanyl, the hemodynamic response to peribulbar block insertion was minimal ($p<0.05$) and the sedation level was best ($p<0.05$). Respiration rate and O_2 saturation of patients receiving midazolam, propofol, and fentanyl decreased after sedation ($p<0.01$) and postoperative satisfaction was high in this group ($p<0.01$). Patients in the midazolam group showed a prominent reaction to peribulbar block insertion while movement during the operation was obvious ($p<0.05$).

Conclusion: The combination of midazolam, propofol, and fentanyl should be preferred to other study groups as the sedation level is suitable for cataract extraction with high postoperative patient satisfaction and without any side effects.

Saudi Med J 2007; Vol. 28 (8): 1198-1203

From the Department of Anesthesiology and Reanimation, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

Received 31st October 2006. Accepted 25th March 2007.

Address correspondence and reprint request to: Dr. Sennur Uzun, Department of Anesthesiology and Reanimation, Faculty of Medicine, Hacettepe University, Sihhiye 06100, Ankara, Turkey. Tel. +90 (312) 3051250/5322214325. E-mail: sennuruzun@superonline.com

Cataract extraction (CE), a common operation in the elderly, is frequently performed under regional anesthesia.[1] It is a disease of advanced age groups. Local anesthesia diminishes the morbidity and mortality of the procedure, minimizing the total stay-length of patients at the hospital, and thus diminishing total expenditure.[2] Diseases seen frequently in this age group (hypertension, diabetes mellitus, congestive heart failure and chronic obstructive pulmonary disease) obligate the anesthetists to titrate the drugs carefully. The goal of this sedation is to provide a motionless patient, thus, optimizing surgical conditions. For this reason, different drug combinations are used. The aim of this study was to compare different combinations of midazolam (M), propofol (P), and fentanyl (F) with respect to hemodynamic parameters, sedation level, patient satisfaction, and side effects.

Methods. Following hospital ethics committee approval, 100 ASA I-III patients, 40-80 years old, set to undergo CE under local anesthesia were recruited for the study. Informed consent was obtained from all patients. The study was carried out in Hacettepe University Hospitals Ophthalmology operating theatres in 2005. Patients with bradycardia (<45 beats/min^{-1}) and those with a known allergy to the study drugs and with severe pulmonary disease or heart failure were excluded from the study. The drugs were administered intravenously, and the patients were randomly divided into 4 groups: Group M (n=25): Midazolam 0.02 mg kg^{-1}. Group MP (n=25): Midazolam 0.02 mg kg^{-1} + Propofol 0.2 mg kg^{-1}. Group MF (n=25): Midazolam 0.02 mg kg^{-1} + Fentanyl 1 microgram kg^{-1}. Group MPF (n=25): Midazolam 0.02 mg kg^{-1} + Propofol 0.2 mg kg^{-1} + Fentanyl 1 microgram kg^{-1}. No premedication was given to the patients. In the operating room, standard monitoring with ECG, non-invasive blood pressure, and pulse oximetry was instituted and monitored with a Siemens SC 7000 monitor (Siemens Inc., USA). Oxygen saturation

by pulse oximetry lower than 90%, was considered as desaturation. Supplemental oxygen (4 L/min^{-1}) was administered by a nasal cannula. A 20 gauge intravenous catheter was inserted at the dorsum of the hand and attached to normal saline (9% NaCl solution). The anesthetist injected the drugs slowly over one minute and the peribulbar block insertion (PBI) was performed by the ophthalmologist 5 minutes later, with 7-10 cc 2% lidocaine. A fine 27-gauge needle was used to perform a 2-injection peribulbar block. After assessing a totally immobile eye, the patient was prepared for surgery. Hemodynamic parameters were recorded before and after sedation, after PBI and every 5 minutes during surgery. The sedation level was measured by the physician questionnaire (**Table 1**)[2] after the start of the operation and every 20 minutes thereafter. The patient satisfaction score was obtained from the sum of the scores of the first 5 questions of the patient's evaluation scale (**Table 1**)[2] during the postoperative visit by the same anesthetist. The sample size used was determined according to previous similar studies. When power analysis of the study was performed with 100 patients in total, it was 0.99 (99%), with an alpha-error of 0.05 and effect size of 0.60 (60%).

The data were analyzed by SPSS statistical software (SPSS Inc., Chicago, IL, USA) Version 10.0 for Windows. One way analysis of variance test, Chi square test, and Paired t test were used for statistics. Depending on the results of the ANOVA test, Duncan's test was added. The probability value of <0.05 was considered statistically significant.

Results. There were no significant differences in patients demographic data between the groups (**Table 2**). Results from 100 patients were analyzed. The heart rates of the groups receiving fentanyl were lower during PBI than those of the other 2 groups (p<0.05, groups M-MP and MF-MPF compared) (**Figure 1**). Oxygen saturation and the respiration rate of group MPF were lowest after sedation (p<0.01, group MPF and M-MP-MF), but later (during PBI) they increased (p<0.01) (**Figures 2 & 3**). In group M, the decline in systolic blood pressure (SBP) after sedation was minimal and the rise in the heart rate and the SBP during PBI was higher. In group MPF, there was no reaction to PBI but in group M, reaction as extremity movement to PBI was observed. Sixty percent of group MPF did not remember the PBI, but in group M, 88% of patients remembered it (p<0.01, comparison of groups M and MPF). Insufficient sedation level (measured by the answer to the second question of the physician questionnaire) was rarely observed mainly in the groups not receiving fentanyl, but this was not statistically significant (p>0.05, groups M-MP and MF-MPF comparison). Eighty-eight percent of group MF patients could be easily aroused with sound, which was the most desired state of sedation (p<0.001, group MF and groups M-MP-MPF compared). The sedation levels are shown in **Table 3**. Movement during surgery was mostly observed in group MP (p<0.01). Only one patient out of 25 in group MP slightly moved his 4 extremities twice during the operation. In groups M and MF, patient movement proportions were similar (no movements in 80% of group M and 84% of group MF during the operation). In the triple drug group, none of the patients moved during CE. Recall of pain

Table 1 - Physician Questionnaire and Patient's Evaluation Scale.

Physician Questionnaire
1. Patient response to infiltration of the local anesthetic:
0: No reaction
1: Facial grimace only and unintelligible verbalization
2: Distinct verbalization of pain perception and movement of extremities
3: Sustained and significant resistance
2. Patient sedation score:
0: Drowsy or asleep but easily arousable by verbal stimulus
1: Asleep and difficult to arouse by verbal stimulus (considered over-sedated)
2: Awake and anxious or disturbed (considered inadequately sedated)
3. Patient verbalisation score:
0: None
1: Mild (not understood)
2: Moderate (blurred speech)
3: Severe (easily understood)
4. Patient movement during surgery
0: None
1: Mild (one extremity)
2: Moderate (two extremities)
3: Severe (four extremities)
Patient's Evaluation Scale
1. How did you feel during the operation?
0: Calm
1: Can't remember
2: Anxious
2. Do you remember having pain?
0: No
1: Mild
2: Moderate
3: Severe
3. Do you remember any local anesthetic injections?
0: No
1: Yes
4. Do you remember any conversations?
0: No
1: Yes
5. If you were to have this operation again, would you agree to this anesthesia?
0: Yes
1: No
6. Have you had nausea- vomiting after operation?
0: No
1: Yes
7. Have you had headache after operation?
0: No
1: Yes

sensation during the PBI was highest in group MP (p<0.05). In group MPF, none of the patients stated any pain and in group MF, 96% of patients did not reported any pain during PBI. All the patients in the study pointed out that they felt comfortable during the operation. The patient satisfaction score was obtained from the sum of the scores of the first 5 questions of the patient evaluation scale and was highest in group MPF (p<0.01, comparison of group MPF and groups M-MP-MF) (**Figure 4**). All patients participating to the study stated that they would prefer the same sedation method in a similar operation under local anesthesia. With respect to nausea/vomiting and headache, there were no differences between the groups (p>0.05).

Discussion. The present study compared midazolam, propofol, and fentanyl in different combinations for CE in respect to sedation, hemodynamic parameters, patient satisfaction and probable side effects. The cataract surgery patients are usually elderly and have risk factors for ischemic heart disease.[3] Ophthalmic surgery is commonly performed on geriatric patients under regional anesthesia.[4] The main purposes of conscious sedation in ophthalmic surgery are to prevent the noxious stimuli and inadvertent movement during the procedure. Inadequate sedation or analgesia can provoke patient movements during regional block or during operation. However, oversedation may cause respiratory depression and lead patients to fall asleep during surgery that might complicate a sudden movement upon awakening. The efficiency of narcotic analgesics (fentanyl in this study) in sedation protocols is undeniable. The interaction appears to be specific to the combination of an opioid with a benzodiazepine. The degree of synergism could not be predicted from the behavior of the drugs alone. In the study of Short and colleagues,[5] propofol and midazolam act synergistically and the addition of fentanyl to this combination maximizes the sedative effect with no prominent increase in side effects. In many studies comparing the sedative effects of remifentanil and propofol infusion in patients undergoing CE with peribulbar blockade, it was shown that remifentanil provided equivalent and sometimes more effective sedation as compared to propofol, this shows that a single opioid without any other drug addition may be sufficient for accurate sedation.[6,7] Our results are very similar, as the sedation and hemodynamic responses to peribulbar injection were low in 2 groups receiving fentanyl. Increasing the number of drugs in combinations caused an increase in sedation and satisfaction scores accordingly. Midazolam, because of its short duration of action, is suitable for reducing anxiety in elderly ambulatory patients. It may reduce pain on injection and produce intraoperative amnesia. In healthy volunteers, intravenous midazolam was given in conscious sedation doses and it reduced

Table 2 - Demographic characteristics (mean±SD).

Demographic characteristics	Group M (midazolam) n=25	Group MF (midazolam+fentanyl) n=25	Group MPF (midazolam +propofol+fentanyl) n=25
Age (year)	65.56 ± 7.40	72.08 ± 14.86	13/12
Weight (kg)	66.32 ± 9.30	71.24 ± 12.69	11/14
Gender (male/female)	70.04 ± 6.22	67.36 ± 8.2	11/14
Gender (male/female)	66.52 ± 10.27	74.40 ± 12.71	9/16

Mean values (± SD); no significant differences between the groups.
p>0.05, there were no statistically significant differences between patients with respect to age, weight and gender

Table 3 - Sedation level of patients after the administration of drugs.

Drugs	Sedation level		
	0 (easily arousable with sound)	1 (difficult to arouse with sound/over sedation)	2 (insufficient sedation)
Group M (midazolam) n=25	14	0	11
Group MP (midazolam+propofol) n=25	10	6	9
Group MF (midazolam+fentanyl) n=25	22*	2	1
Group MPF (midazolam+propofol+fentanyl) n=25	14	11	0

Values are number of patients per group. * p<0.01, Group MF (midazolam+fentanyl) compared with group M (midazolam)-MP (midazolam+propofol) and MPF (midazolam+propofol+fentanyl)

the affective and motivational component of the pain experience.[8] Memory may be impaired at the time of discharge after sedation with intravenous midazolam.[9] There is, however, a wide variation in the sensitivity of patients to midazolam. It was shown that midazolam attenuated the hemodynamic responses to peribulbar anesthesia and reduced recall of discomfort or pain.[1] In our study, the effect of midazolam, propofol, and fentanyl on recall of pain was investigated, and we observed that memory was mostly affected in the midazolam + propofol + fentanyl group at the time of discharge. Pain and discomfort during the eye block can result from insertion of the needle or injection of the anesthetic solution. Pain from needle insertion can be virtually eliminated by topical anesthesia of the conjunctiva fornix or at the medial cantus.[10] The use of a fine gauge needle does not usually cause pain during insertion through the eyelid. In most cases, the injection of anesthetic solution causes discomfort, but this can be minimized by slow injection. Low pain

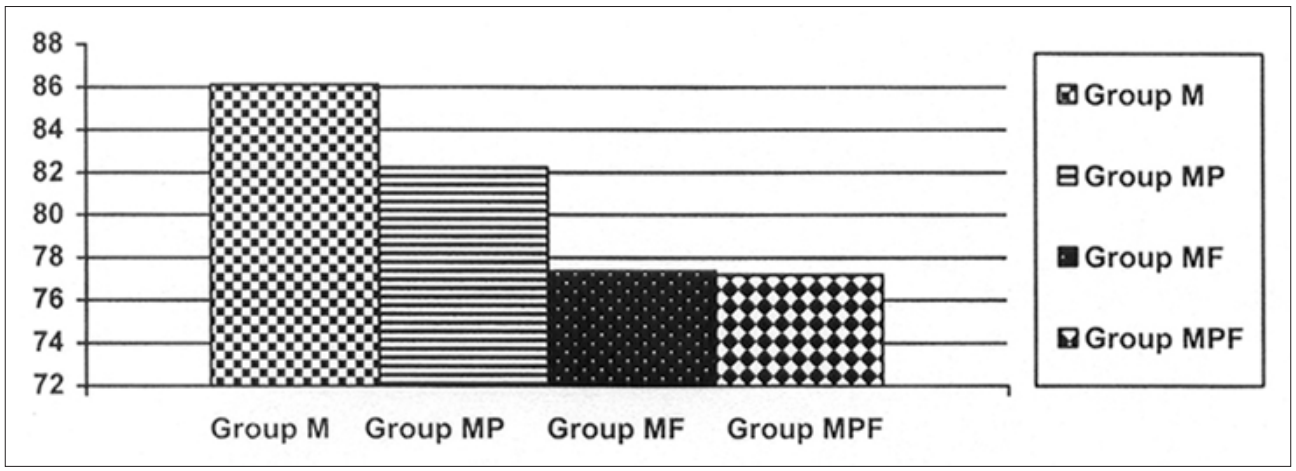

Figure 1 - Heart rates of groups during peribulbar block insertion ($p < 0.05$). Comparison within group M (midazolam) and group MP (midazolam + propofol).

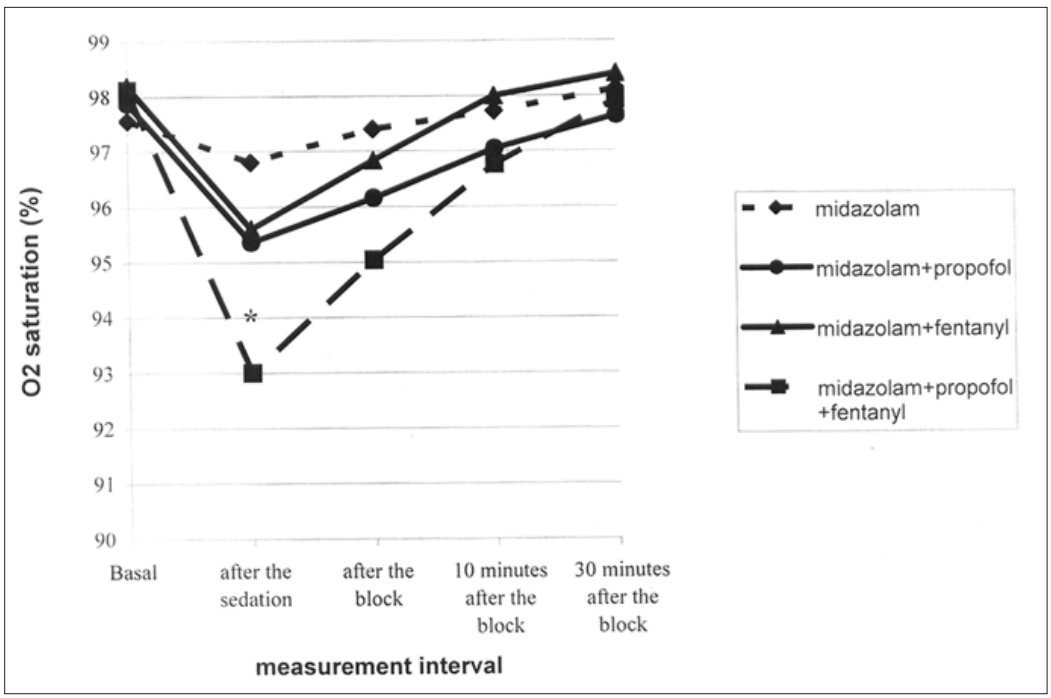

Figure 2 - Oxygen saturation of groups (* $p<0.01$), values are mean values of groups. In Group MPF (midazolam+propofol +fentanyl), decline in O_2 saturation after the administration of the sedation drug is statistically significant.

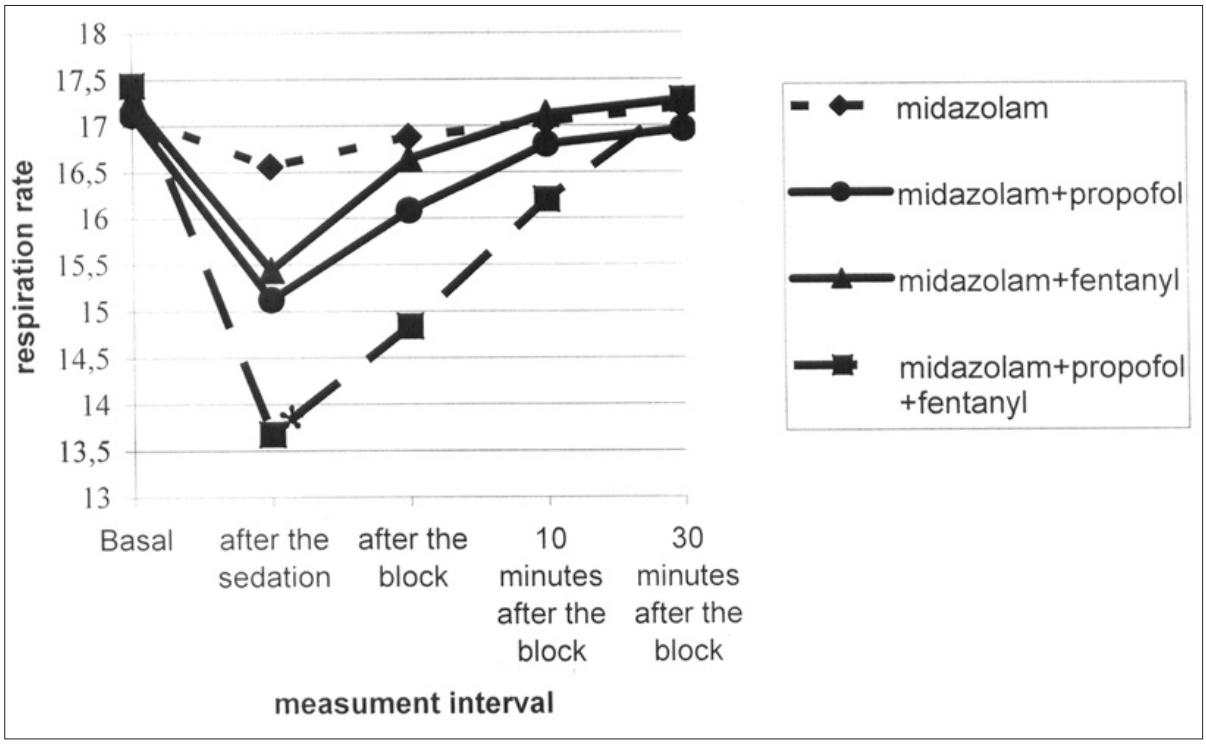

Figure 3 - Respiration rates of groups $p<0.01$, in group MPF (midazolam+propofol+fentanyl), decrease in respiration rate after the administration of the sedation drug is statistically significant.

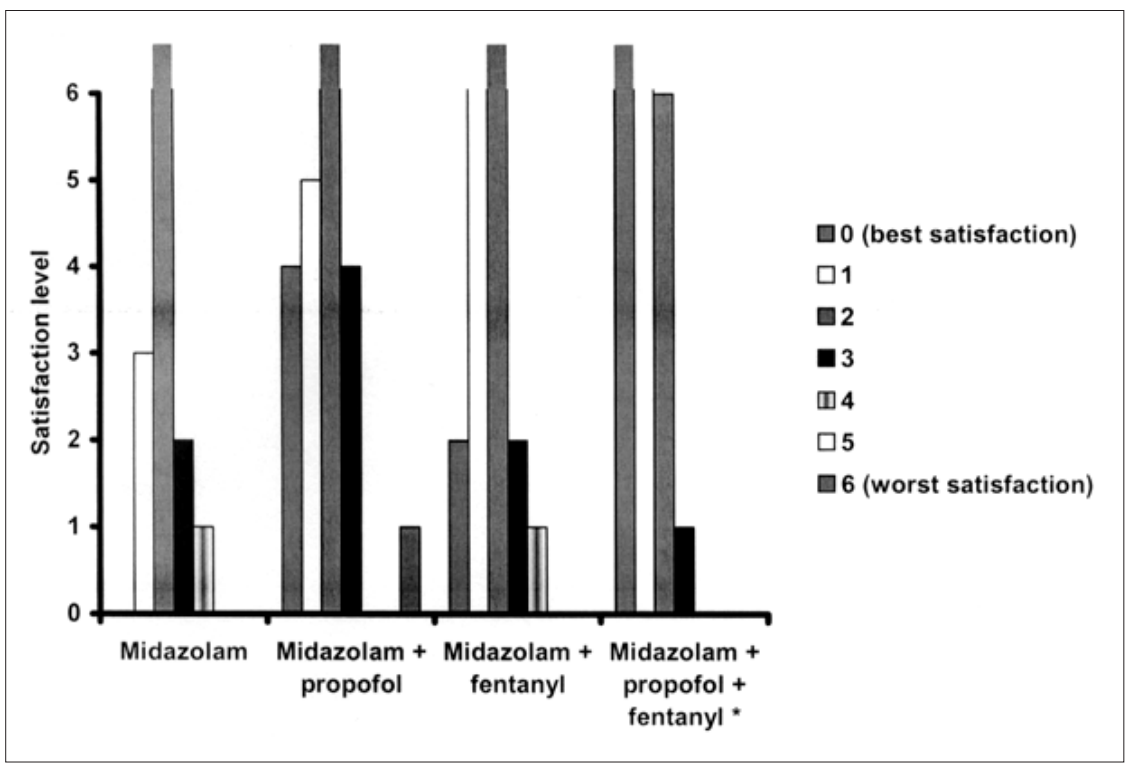

Figure 4 - Patient satisfaction scores p<0.01, patient satisfaction in group MPF (midazolam+propofol+fentanyl) is significantly higher than the other groups.

scores, lack of hemodynamic changes as hypertension and tachycardia and high patient acceptability found even in the placebo group in another study, supports the belief that ocular block may be performed with minimal pain and discomfort.[1] The care spent during eye block effects the sedation level. As in our study, fine gauge needle for blocks would increase patient satisfaction together with sedation level. When opioids are used in combination with benzodiazepines, more pronounced hypotensive effects are observed; this is shown by McHardy et al,[11] who studied midazolam-alfentanil, midazolam-propofol-alfentanil, midazolam-propofol and midazolam combinations in cataract surgery for hemodynamic variables and sedation level, and by Short and colleagues,[12] who investigated midazolam-alfentanil combination with respect to hypnotic and anesthetic interactions. In our study, no such effect on blood pressure was observed. This may be due to the comparably low drug doses.[1] Seifert et al[13] observed a decrease in systolic blood pressure below 90 mm Hg with a combination of propofol and midazolam when compared to propofol alone, which indicates synergism. Virkkila et al[14] reported that in elderly patients undergoing CE with local anesthesia, alfentanil or midazolam given intramuscularly produced sedative effects, but was associated with a reduction in oxygen saturation. Midazolam alone did not caused hypoxemia and neither midazolam nor fentanyl alone resulted in apnea; the effects of the drug combination were more pronounced than the additive effect. Thus, combining midazolam and fentanyl can result in an absence of an effective ventilatory response to hypoxemia and can lead to severe arterial oxygen desaturation within 1-2 minutes in a patient breathing room air. In light of this, all sedated patients should receive supplemental oxygen to prevent the known effects of drug combinations.[11,12,14,15] We observed a reduction in oxygen saturation in a number of patients in spite of supplemental oxygen in group receiving fentanyl and midazolam together, but this was not statistically significant.

In our study, we observed increased effectiveness of midazolam, propofol, and fentanyl combination. No reaction to PBI and no statistically significant hemodynamic side effects were observed. However, in group M there was obvious reaction to PBI. The addition of propofol to midazolam increased the effectiveness of midazolam but did not blur the pain sensation. The addition of an opioid to the sedation protocol blocks the hemodynamic responses to block insertion, decreases pain perception while increasing patient satisfaction.

References

1. Wong DH, Merrick PM. Intravenous sedation prior to peribulbar anaesthesia for cataract surgery in elderly patients. ***Can J Anaesth*** 1996; 43: 1115-1120.
2. Watts MT, Pearce JL. Day case cataract surgery. ***Br J Ophthalmol*** 1988; 72: 897-899.
3. Glantz L, Drenger B, Gozal Y. Perioperative myocardial ischemia in cataract surgery patients: general versus local anesthesia. ***Anesth Analg*** 2000; 91: 1415-1419.
4. Ahmad S, Leavell ME, Fragen RJ, Jenkins W, Roland CL. Remifentanil versus alfentanil as analgesic adjuncts during placement of ophthalmologic nerve blocks. ***Reg Anesth Pain Med*** 1999; 24: 331-336.
5. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. ***Br J Anaesth*** 1991; 67: 539-545.
6. Dal D, Demirtas M, Sahin A, Aypar U, Irkec M. Remifentanil versus propofol sedation for peribulbar anesthesia. ***M E J Anesth*** 2005; 18: 583-93.
7. Boezaart AP, Berry RA, Nell ML, van Dyk AL. A comparison of propofol and remifentanil for sedation and limitation of movement during periretrobulbar block. ***J Clin Anesth*** 2001; 13: 422-426.
8. Coulthard P, Rood JP. An investigation of the effect of midazolam on the pain experience. ***Br J Oral Maxillofac Surg*** 1992; 30: 248-251.
9. Nishiyama T. Dose-finding study of intravenous midazolam for sedation and amnesia during spinal anesthesia in patients premedicated with intramuscular midazolam. ***J Anesth*** 2004; 18: 257-261.
10. Jacobi PC, Dietlein TS, Jacobi FK. A comparative study of topical vs retrobulbar anesthesia in complicated cataract surgery. ***Arch Ophtalmol*** 2000; 118: 1037-1043.
11. McHardy FE, Fortier J, Chung F, Krishnathas A, Marshall SI. A comparison of midazolam, alfentanil and propofol for sedation in outpatient intraocular surgery. ***Can J Anaesth*** 2000; 47: 211-214.
12. Short TG, Plummer JL, Chui PT. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. ***Br J Anaesth*** 1992; 69: 162-167.
13. Seifert H, Schmitt TH, Gultekin T, Caspary WF, Wehrmann T. Sedation with propofol plus midazolam versus propofol alone for interventional endoscopic procedures: a prospective, randomized study. ***Aliment Pharmacol Ther*** 2000; 14: 1207-1214.
14. Virkkila ME, Ali-Melkkila T, Kanto JH. Premedication for outpatient cataract surgery: a comparative study of intramuscular alfentanil, midazolam and placebo. ***Acta Anaesthesiol Scand*** 1992; 36: 559-563.
15. Habib NE, Balmer HG, Hocking G. Efficacy and safety of sedation with propofol in peribulbar anaesthesia. ***Eye*** 2002; 16: 60-62.