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ORIGINAL ARTICLE

Bispectral index-guided intraoperative sedation with dexmedetomidine and midazolam infusion in outpatient cataract surgery

A. APAN [1], N. DOGANCI [1], A. ERGAN [2], Ü. BÜYÜKKOÇAK [1]

[1]Department of Anesthesiology, Kirikkale University Faculty of Medicine, Kirikkale, Turkey; [2]Department of Ophthalmology, Kirikkale University Faculty of Medicine, Kirikkale, Turkey

ABSTRACT

Background. This study aimed to evaluate the role of α-$_2$ agonist infusion, with dexmedetomidine or midazolam, on hemodynamic and respiratory parameters while titrating the sedation level with the bispectral index (BIS) during cataract surgery.

Methods. Ninety consenting ASA class I-III patients who were electively undergoing cataract surgery were enrolled in the double blind study. A random infusion of 0.25 $\mu g \times kg^{-1} \times hr^{-1}$ Dexmedetomidine (Group D), 25 $\mu g \times$ kg-1.hr^{-1} midazolam (Group M), or saline for controls (Group C) was administered after mounting a BIS monitor and routine anesthetic care. The target BIS level was >85. An additional bolus dose in 1 mL increments of the study drug or cessation of the infusion was adjusted according to the BIS level. Changes in respiratory and vital parameters were noted and, in case of mild pain, 25 μg fentanyl was administered as a bolus. Pain and sedation were evaluated in the early postoperative period using visual analogue and four rating sedation scales.

Results. In Group D, heart rate decreased in the later periods of surgery (35-50 min) and in the early postoperative period (5th and 15th min). Dose adjustments were required in six and ten patients in Groups D and M, respectively. Pain scores were lower with dexmedetomidine infusion.

Conclusion. Dexmedetomidine infusion mildly decreased heart rate in the later periods of surgery with better pain scores in the postoperative period. Dexmedetomidine should be an alternative for intraoperative sedation in outpatient cataract surgery.

Key words: Conscious sedation - Intraoperative period - Dexmedetomidine - Midazolam.

Dexmedetomidine, a highly selective α-$_2$ agonist drug, has been approved for use in Intensive Care Units (ICUs) for its sedative, anxiolytic and analgesic properties. There have been many reports concerning anesthetic sparing effects during the perioperative period,[1-4] reducing sedation and analgesic requirements in the ICU.[5, 6] In addition to its sedative and anxiolytic properties, dexmedetomidine has also been reported to decrease intraocular pressure.[7]

Midazolam, a water-soluble benzodiazepine derivate, is another well-known sedative and anxiolytic drug that is employed in ocular surgery.[8, 9]

Traditional methods of assessing the level of sedation have relied primarily on subjective assessment of the patient and alteration of vital signs. Subjective assessments, however, are mostly based on speech and facial expression, which are often difficult to assess in a patient undergoing ocular procedures since the drapes or surgery preclude observation and prevent the patient from responding. The bispectral index (BIS) monitor offers a distinct advantage of objective, real-time assessment of the sedated patient without the application of external stimuli.[5]

A recent publication comparing dexmedetomi-

dine infusion in cataract surgery failed to find any advantage of midazolam and revealed its hemodynamic side effects.[10] A possible explanation is that the loading dose might influence the circulatory system, and no similar previous experience has been reported for this drug in the elderly.

We decided to compare hemodynamic and respiratory parameters, in addition to postoperative pain and sedation, of lower infusion doses of dexmedetomidine or midazolam in day-case cataract surgery under the guidance of BIS.

Materials and methods

We obtained institutional Ethics Committee approval and written informed consent from 90 patients who were scheduled for elective cataract surgery under regional anesthesia. Inclusion criteria were age ≥18 years and ASA physical status I through III. Exclusion criteria were age <18 years, pregnancy, excessive obesity (i.e., body weight >50% above ideal body weight for height), uncontrolled systemic pathology, known central nervous system disorder, debility or disease affecting cooperation, history of sleep apnea, significant arrhythmia or high degree atrioventricular nodal block, and current or recent (within 30 days) treatment with as well as contraindication for α-$_2$ agonists or antagonists.

The randomization procedure was performed by choosing sealed envelopes before the operation by one of the anesthetists. The study drugs were prepared, coded and stored by the hospital pharmacy, and the codes were broken after all data had been finalized. Labeled syringes were prepared immediately before the surgery.

Standard monitoring (Datex-Ohmeda, Cardiocap 5, Helsinki, Finland) included ECG lead II, pulse oximetry, respiratory rate, end tidal O_2 and CO_2 measurements (obtained from nasal port), and non-invasive arterial blood pressure recorded every 5 min. A nasal cannula was applied to the nostril opposite the surgical site, and supplemental oxygen was given throughout the procedure at 2 L.min^{-1}.

Intravenous administration of 5 mg ephedrine was administered when the systolic arterial blood pressure was <90 mmHg or when the mean arterial blood pressure decreased by >15% of the initial value. Esmolol (Breviblock, Baxter, USA) infusion was indicated when the mean arterial blood pressure exceeded 15% of the initial value. Bradycardia was defined as a decrease in the heart rate to <60 bpm, and atropine (0.5 mg) was given intravenously at a value of <45 bpm.

Patients were instrumented with BIS (Aspect monitor XP version, Nattick, MA, USA) leads (two-channel-referential measurements, frontotemporal application) upon entry into the operation room. The electrode impedances were confirmed to be <10 kJ before initiation of the study drug. A 10-min period was allowed after positioning the instrumentation and before baseline measurements. Baseline BIS values were collected, separated by an interval of ≥2 min. After study drug initiation, BIS values were obtained every 5 min during the operation period and every 10 min in the recovery room. In order to preserve cooperation of the patient during the operation, the target BIS value was set at 85, and infusion was stopped when values were <85. The infusion dose was changed in 1 mL increments when required.

Dexmedetomidine (Precedex, Abbott, Chicago, IL, USA) was available in 2 mL ampules (100 μg/mL) and diluted in 48 mL 0.9% saline. Midazolam (20 mg) was also diluted with saline to obtain a final volume of 50 mL. The infusion rate of the study drug was calculated according to the patients' weight (body weight in kg/16=rate of infusion in mL×hr^{-1}) and began immediately before the regional block. Patients were randomly assigned to receive the study drugs 0.25 μg×kg^{-1}×hr^{-1} dexmedetomidine (Group D) or 25 μg×kg^{-1}×h^{-1} midazolam (Group M) infusion using the infusor (Arcomed AG, Switzerland). In the Control Group, the same volume of saline was infused, and a 7 μg×kg^{-1} bolus dose of midazolam was administered as required when initial adjustments of infusion had no effect on the clinical outcome. The infusion was discontinued at the end of the operation.

Peribulbar block was performed using a local anesthetic mixture consisting of 4-5 mL of 2% lignocaine with adrenaline 1:200 000 (Jetosel, Biosel, Istanbul, Turkey). Eyelid immobilization was achieved with periorbital infiltration using the same anesthetic solution at about 2-3 mL. Orbital compression was performed for 10 min using a mechan-

ical device with a maximum pressure of 30 mmHg. Surgical interventions were performed by the same surgeon (A. E.). In case of mild pain during the operation, 25 μg fentanyl was given as a bolus and repeated as needed. Patients suffering from intense pain that required more than two bolus doses, which might influence sedation scales, had their hemodynamic variables and respiratory parameters excluded from the study.

Pain and sedation scores were assessed hourly by an investigator who was blinded to the patient group assignment between the 1st to 4th h during the postoperative period. The procedure for assessment of pain was explained in detail before the operation. Pain was assessed using a standard scaled plastic measure and determined as 0=no pain to 100=worst imaginable pain; when unavailable (*e.g.*, impaired vision on the non-operated site), patients were asked to determine their pain between 0 (no pain) and 100 (worst imaginable) on a numerical scale (Verbal Rating Scale). Sedation was evaluated and graded according to a 4-point rating scale in the recovery unit (1=patient fully awake; 2=patient somnolent, but responds to verbal commands; 3=patient somnolent, but responds to tactile stimuli; 4=patient asleep, but responds to pain) during the same period.

Adverse effects during the early postoperative period were evaluated and recorded before transferring to the ward. Patients were questioned on light-headedness, dizziness, mouth dryness, nausea, vomiting, headache, changes in skin at the infusion site, and any other complaints that were described during observations in the hospital. The side effects mentioned above and satisfaction with the surgery were questioned in a telephone interview on the day after hospital discharge using a questionnaire by the nurse who was unaware of the procedure. Patients were asked to comment on their satisfaction and the effectiveness of sedative infusion as follows: "Yes": I would have the same procedure when required; "No comment, or no": I do not want to have the same procedure again. The satisfaction of the surgical team was also determined by questioning about the operation using a 4-point rating scale: 1=satisfied, calm patient; 2=cooperative, mildly anxious; 3=deeply sedated; and 4=unsatisfied, uncooperative and restless patient that precluded the surgery.

TABLE III.—*Independent predictors of postoperative outcome with multivariate analysis.*

	Group D (N.=30)	Group M (N.=30)	Group C (N.=30)
Age (y)	65.7±11.3	65.8±11.8	66.3±9.8
Weight (kg)	72.5±9.7	71.5±13.5	74.7±13.7
Height (cm)	164.8±7.5	164±8.8	167.1±8.9
Sex (F/M)	12/18	13/17	14/16
ASA physical status (I/II/III)	2/24/4	2/25/3	3/23/4
Duration of surgery (min)	54.8±23.8	51.5±17.8	53.4±26.9

No significant difference between groups. Values are mean ± standard deviation. ASA: American Society of Anesthesiologists.

Statistical analysis

Our preliminary results indicated that at least 26 patients in each group would be required to determine a 10% difference in heart rate or mean arterial pressure in any observation period with a β value of 0.2. (The initial value for heart rate determined at the end of surgery was 78.1±8.6: mean±SD). Demographic variables were analyzed using χ^2 and Fisher's exact test. ANOVA for repeated measures and Bonferroni correction were used to compare continuous variables. A Kruskal-Wallis test was used to compare non-parametric variables such as pain or sedation scales. A P value <0.05 was considered to be significant.

Results

Ninety-eight patients were screened, and eight patients were excluded due to refusal or being unavailable for participation in the study. We studied 90 patients. One patient in Group M required more than two bolus doses of fentanyl during the operation, which necessitated exclusion from further analysis. There were no differences between study groups with respect to demographic characteristics and duration of surgery (Table I).

None of the patients required rescue therapy for hypotension or bradycardia. On the other hand, esmolol infusion was indicated in one patient each in Groups D and C, each in order to decrease blood pressure. Their initial systolic/diastolic arterial blood pressures were 180/130 mmHg and 190/150 mmHg, respectively, and a loading dose of 500 $\mu g \times kg^{-1}$ esmolol, and maintenance was started at a rate of 50 $\mu g \times kg^{-1} \times min^{-1}$, then gradually increased to 150 $\mu g \times kg^{-1} \times min^{-1}$ for 25 and

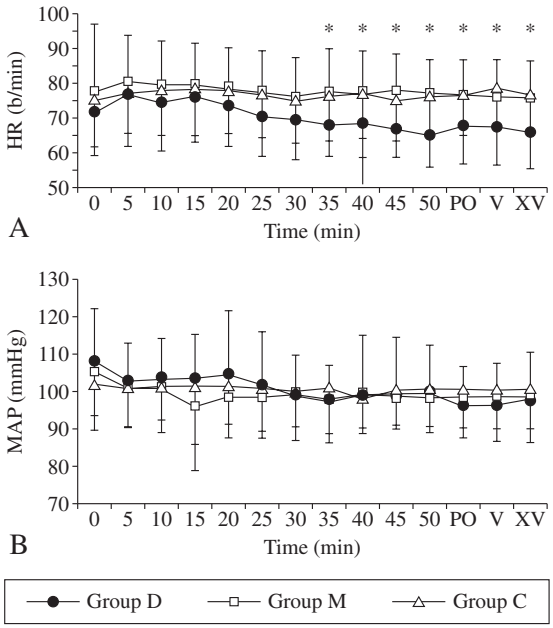

Figure 1.—Intraoperative changes in heart rate (A), and mean arterial blood pressure (B). ♦: Group D; ◊: Group M; △: Group C. HR: heart rate; MAP: mean arterial pressure; PO: postoperative; V: PO 5th min; XV: PO 15th min. *P<0.05.

35 min, respectively. The arterial blood pressure gradually decreased to 130/85 mmHg and 135/80 mmHg, respectively. No difference was found between study groups in terms of mean arterial blood pressures. In Group D, however, a mild reduction in pulse rate was found in later periods of the surgery (35-50 min) and during the early postoperative period (0, 5th and 15th min). Mean values of heart rate and arterial blood pressure are shown in Figure 1.

Changes in infusion rates were required in six patients (increased in three and decreased in three) in Group D and in ten patients in Group M (increased in six and decreased in four). Intraoperative BIS, respiratory rate and end tidal CO_2 values were also similar between study groups. BIS values were not decreased to the desired level despite dose increments in three patients in Group D, four patients in Group M, and five patients in Group C. Bolus doses of fentanyl were required for four patients in Group D (mean: 31 μg), three patients in Group M (mean: 25 μg), and four patients in Group C (mean: 25 μg) to supplement analgesia. In Group C, eight patients did not require sedation; 15 received one bolus dose; four received two bolus doses; and three required three or more bolus doses of midazolam (mean: 0.56 mg).

TABLE II.—*Pain and sedation scores in the early postoperative period.*

PO period (h)	1	2	3	4
VAS pain				
Group D	0 (0)[a]	0 (13)[b]	5 (16)[b]	0 (19)
Group M	0 (13)	8 (32)	13 (31)	16 (35)[a]
Group C	0 (12)	0 (21)	7.5 (31)	9 (31)
Sedation scores				
Group D	2 (2)	1 (1)	1 (1)	1 (1)
Group M	2 (2)	1 (1)	1 (1)	1 (1)
Group C	1 (1)[a]	1 (1)	1 (1)[c]	1 (1)

[a]P<0.05 from other two groups; [b]P<0.05 from Group M; [c]P<0.05 from Group D. Data are presented as median (range). Abbreviations: PO: postoperative VAS: Visual Analogue Scale.

The sedative consumptions were 18.8±11.6 μg and 1.8±0.6 mg for Group D and Group M, respectively. In addition, the mean delivered volumes were nearly the same: Group D with 4.6±2.9 mL and Group M with 4.5±1.6 mL. Therefore, the relative sedation ratio was calculated to be about 1:100 for midazolam to dexmedetomidine. While there were no changes in sedation scales, pain scores in the early postoperative period were decreased in patients who received dexmedetomidine (P<0.05) (Table II).

While VAS scales were decreased in the postoperative period in Group D compared to Group M (1-4 h) and Group C (1st h), 4-point sedation scores were lower in Group C compared with the other two groups (1st h) and with Group D (3rd h) (Table II).

During the post-surgery period two patients in Group D and M suffered from mild headache, and 17 patients in Group D complained of dryness of mouth. On the other hand, no side effects were noted during the telephone interview. The surgical conditions were found to be good for both groups, and no significant difference was stated by the surgical team (Group D: 23/6/1/0; Group M: 21/7/2/0; Group C: 24/5/1/0 for scores 1 to 4, respectively). Patients were commonly pleased to receive sedative infusion, and patients treated with dexmedetomidine also stated that they experienced a painless postoperative period. On the other hand, two patients in Group M, three patients

in Group D, and one patient in Group C did not have any comments on the study or whether the protocol was comfortable for them.

Discussion

The present study demonstrates that infusion of 0.25 μg×kg^{-1}×h^{-1} dexmedetomidine or 25 μg×kg^{-1}×h^{-1} midazolam under BIS control achieves the required sedation. We demonstrated a more favorable outcome than previous reports by not using the loading dose, which affects the circulatory system.[10] In addition, we did not observe any difference between arterial pressures, with only mild alterations in pulse rate observed in the later periods of surgery.

There is only one publication concerning the use of dexmedetomidine bolus and infusion in an elderly population in which decreases in both heart rate and arterial blood pressure were observed in nearly all periods.[10] In their recent report, Lee *et al.*[11] found that a moderate loading and infusion dose of dexmedetomidine decreased anesthetic requirement in vitreoretinal surgery. While there were no significant differences between mean arterial blood pressure recordings, heart rates were decreased in the dexmedetomidine treatment group in all observation periods. Despite administering a loading dose, their observations were similar to ours. Several points in the study protocol might explain this discrepancy. Their patient population was younger than ours was; prehydration was performed before induction, which might prevent an obvious decrease in mean arterial pressure; and the dexmedetomidine dose was decreased according to hemodynamic changes in patients >65 years. The last precaution shows that major hemodynamic alterations could be observed, especially during the loading period of dexmedetomidine infusion, supporting our approach of excluding the loading dose. Overall, these studies and our observations indicate that the influence of dexmedetomidine on the cardiovascular system was dose-dependent and that a decrease in heart rate was observed at lower infusion doses. Changes in arterial pressure, in addition to pulse rate, could be expected with a loading dose or higher infusion doses in a population of this age.

The pharmacokinetic parameters for dexmedetomidine, demonstrated in young male volunteers, indicate that the equilibrium phase requires 15-20 min to reach the maximum.[12] The difference between heart rate seen in our study, however, demonstrates that the clinical effect, which reflects the peak plasma concentration, might be somewhat longer in elderly patients. In addition, a limitation of our study was not investigating the plasma concentration of dexmedetomidine, which remains to be determined in this population.

In outpatient cataract surgery, the optimal dose of dexmedetomidine was found to be 1 μg.kg^{-1} since intramuscular premedication produced sedation and reduction of intraocular pressure at a rate of about 32% with minimal hemodynamic side effects.[7] Hypotension and/or bradycardia, however, have frequently been observed with concomitant anesthetic drug administration when this nonretrievable route is used.[1, 13] The desired sedation level can be reached easily, and infusion can be stopped in case of undue side effects.

Besides its sedative actions and influence on the cardiovascular system, dry mouth is one of the prominent clinical side effects.[14] Although we observed dryness of mouth in our study, other studies found that dexmedetomidine at various doses as intramuscular premedication had no influence on dryness of mouth.[7] In addition, infusion was not associated with this symptom in cataract surgery.[10] Further studies should be performed to determine the reasons behind these conflicting reports of dryness of mouth in the elderly population.

BIS is a new processed electroencephalographic variable that monitors anesthetic and sedation levels on a relative scale during the administration of different drugs. It was demonstrated that BIS may correlate with dose-dependent levels of anesthesia for various agents,[15] and for patients undergoing intravenous conscious sedation for day case dental surgery.[16] The limitations of this study included not performing psychomotor tests that require visual performance and not determining senility induced hearing and cognitive problems.

In clinically relevant doses, dexmedetomidine infusion seems not to influence ventilatory parameters.[17] Respiratory parameters were stable, and complications such as apnea, airway obstruction,

and hypoxemia did not occur in our study. Clinical features such as an infusion-dependent drug that has a shorter elimination half-life, lack of any active metabolite, and no potential influence on respiration with contribution to reducing pain make dexmedetomidine a sedative drug of choice for short-term outpatient procedures. The possible indications for dexmedetomidine treatment in patients with high sympathetic output and increased arterial pressure or heart rate are the subject of future investigations. Ocular surgery under local anesthesia is associated with low pain; therefore, the influence of dexmedetomidine on pain should be determined in procedures that are more painful.

Conclusions

Dexmedetomidine mildly reduced heart rate in the later periods of surgery and better preserved changes in arterial blood pressure using a lower infusion regimen and excluding the bolus dose. Pain scores were in favor of the patients treated with midazolam. Dexmedetomidine infusion should be considered an acceptable alternative for outpatient cataract surgery in elderly patients.

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Conflict of interest.—There is no conflict of interest.

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Corresponding author: A. Apan, MD, Urankent THK Bloklar› E-2 Blok, No: 15 Yenimahalle/Ankara, Turkey. E-mail: alpaslanapan@gmail.com