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The superiority of midazolam-pethidine combination in three different anesthetic methods applied in conscious sedation during transesophageal echocardiography procedure

Hulya Yilmaz AK[1], Yasemin Ozsahin[2], Mehmet Ali Yeşiltaş[3], Sükrü Arslan[4], Cem Bostan[5], Ismail Haberal[6], Mustafa Yildiz[7]

[1,2]Specialist, Department of Anesthesiology and Reanimation, Istanbul University-Cerrahpaşa, Cardiology Institute, [3]Specialist, Department of Cardiovascular Surgery, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, [4]Specialist, [5]Associate Professor, [7]Professor, Department of Cardiology, [6]Associate Professor, Department of Cardiovascular Surgery, Istanbul University-Cerrahpaşa, Cardiology Institute, Istanbul, Turkey

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ABSTRACT

Background: During the transesophageal echocardiography (TEE) procedure, as in many other diagnostic semi-invasive applications, moderate sedation is preferred over deep sedation. Rarely, patients who cannot tolerate moderate sedation may require deep sedation when difficulties are encountered during TEE probe insertion. Although many different methods have been tried for the TEE procedure in clinical practice, the most appropriate sedation method is still controversial. **Aims and Objectives:** We aimed to evaluate the clinical effects of three different sedoanalgesia methods consisting of midazolam, propofol, and midazolam-pethidine combination protocols applied for conscious sedation in the patients undergoing a TEE procedure, and to evaluate the patient and doctor satisfaction during the procedure. **Materials and Methods:** One-hundred twenty five patients who underwent TEE for diagnostic purposes in our hospital were included consecutively in our prospective randomized trial. The patients were divided into three groups as those who were administered midazolam (group M), propofol (group Pr), and midazolam-pethidine (group MPe) during the TEE procedure. **Results:** In the MPe group, both patient and doctor satisfaction were significantly higher than the two groups. The rate of difficulty in probe placement was lower in the Pr and MPe groups compared to the M group ($P<0.05$). **Conclusion:** In this study, it has been observed that conscious sedation with the combination of midazolam-pethidine was significantly advantageous in terms of patient and physician satisfaction compared to the use of only midazolam and only propofol.

Key words: Conscious sedation; Patient satisfaction; Transesophageal echocardiography

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INTRODUCTION

Transesophageal echocardiography (TEE) is a semi-invasive diagnostic method applied in echocardiography laboratories, operating rooms, and intensive care units.[1] During the TEE procedure, patients may experience nausea, shortness of breath, agitation, distress, and pain due to esophageal intubation.[2] Although some studies suggest that sedation is not necessary for the TEE procedure, there are also studies indicating that sedoanalgesia provides significant comfort to the physician and patient by reducing the patients' anxiety.[2-4] Although TEE is generally a safe procedure, when considering the cardiorespiratory complications that may occur and also the cardiovascular and respiratory depressant effects of the anesthetic drugs administered on patients with cardiovascular diseases, it becomes crucially important that an experienced person performs the TEE procedure and sedoanalgesia.[5]

Address for Correspondence:
Mehmet Ali Yeşiltaş, Specialist, Department of Cardiovascular Surgery, Istanbul Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey. **Mobile:** +90 212-4147171. **E-mail:** dr.maliyes@gmail.com

During the TEE procedure, as in many other diagnostic semi-invasive applications, moderate sedation is preferred over deep sedation. Rarely, the patients who cannot tolerate moderate sedation may require deep sedation when difficulties are encountered during TEE probe insertion.[2] The American Society of Anesthesiologists (ASA) defines moderate sedation (conscious sedation) as a drug-induced depression of consciousness in which patients respond voluntarily to verbal commands with mild tactile stimulation. In general, the patient's spontaneous breathing and cardiovascular functions are preserved.[6] Although many different methods have been tried for the TEE procedure in clinical practice, the most appropriate sedation method is still controversial.

Aims and objectives

In our study, we aimed to evaluate the clinical effects of 3 different sedoanalgesia methods consisting of midazolam, propofol and midazolam-pethidine combination protocols applied for conscious sedation in patients undergoing a TEE procedure, and to evaluate the patient and doctor satisfaction during the procedure.

MATERIALS AND METHODS

This prospective, randomized study was performed in the echocardiography laboratory of Istanbul University - Cerrahpaşa (IUC), Institute of Cardiology between March 2019 and December 2020 after the approval of the IUC Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (Date: 13.02.2019, Number: 38082516-900-18898), and the written informed consent of all patients were obtained.

Study population

In the study, 135 adult patients who aged between 18 and 75 years, had a cardiac disease (atrial septal defect, patent foramen ovale, mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency, etc.), and would undergo TEE for diagnostic purposes (cardiac tumors, suspected cardio embolic event, infective endocarditis). The study contained a total of 125 patients who met the inclusion criteria (Figure 1). All patients were outpatients for the TEE procedure. The patients with heart failure (ejection fraction ≤30), history of allergy to pethidine, midazolam or propofol, TEE contraindication (esophageal stenosis, tumor, diverticulum, perforation, laceration, fistula, esophageal or gastric surgery history, history of dysphagia, full stomach, neck and mediastinal radiation), with severe neurological or psychological disorders, unstable hemodynamics (symptomatic tachycardia, bradycardia, hypotension), and the patients with tracheal intubation were not included in the study.[2] Randomization was done by the closed envelope method. The drugs and drug combinations we used in our study are routinely used in endoscopic interventions such as TEE, according to the preference of the anesthesiologist. The groups were named as group M, Pr, MPe by shortening the drug names for clarity.

The patients, the cardiologist who performed the TEE procedure, and the anesthesiologist who would provide sedation were blinded to the study drugs. The drugs to be administered in our study was prepared by an anesthesia technician who was not involved in the TEE procedure, and the injector and infusion line in which the drug was prepared were covered with silver colored tape. Since the person administering the drug was blinded to the study, the amount of drug to be made was completed to 10 cc with physiological saline using the same size injector by the person who prepared the drug. Separate injectors covered with silver paper were prepared for additional doses and the doses to be given once were completed with physiological saline in a total of 5 cc. The injectors of the M, Pr and MPe groups were numbered as I, II and III respectively, in order to avoid possible confusion.

Anesthesia procedure

General physical examination, demographic characteristics, medical history, and laboratory tests of all patients were evaluated before anesthesia procedure. The patient was informed about the TEE procedure and the anesthesia procedure to be performed in the study, and written informed consents was obtained. Solid food intake and fluid intake was stopped 8 and 2 h before the procedure, respectively.

Before the procedure, the monitoring device, aspirator, and oxygen supply in the TEE laboratory were checked. The patients were monitored with electrocardiogram, noninvasive blood pressure measurement, pulse oximetry, end-tidal carbon dioxide ($EtCO_2$). Nasal oxygen was provided at a rate of 2 L/min. Before the procedure, oropharyngeal anesthesia was applied to the oropharyngeal region topically with 3–4 puffs of 10% lidocaine spray (Xylocaine pump spray, Astra Zeneca, Istanbul, Turkey). After the patients were positioned on their left side, the drugs were intravenously administered for sedation and sedoanalgesia according to randomization as follows: Group M: 3 mg of midazolam (Dormicum 5 g/5 ml, Deva Holding, Istanbul, Turkey) and 1 mg of midazolam if additional doses were required; Group Pr: 0.5 mg/kg propofol (Propofol-Lipuro 1% 10 mg/ml, Braun Melsungen AG, Melsungen, Germany) and 0.25 mg/kg propofol if additional dose were needed; Group MPe: 2.5 mg midazolam + 25 mg pethidine (Aldolan 100 mg/2 ml, Liba Laboratories, Istanbul, Turkey) and 1 mg midazolam + 25 mg pethidine if additional doses were needed. The occurrence of the patients' agitation and the recurrence of reflexes such as gagging and coughing during the procedure were considered as the events

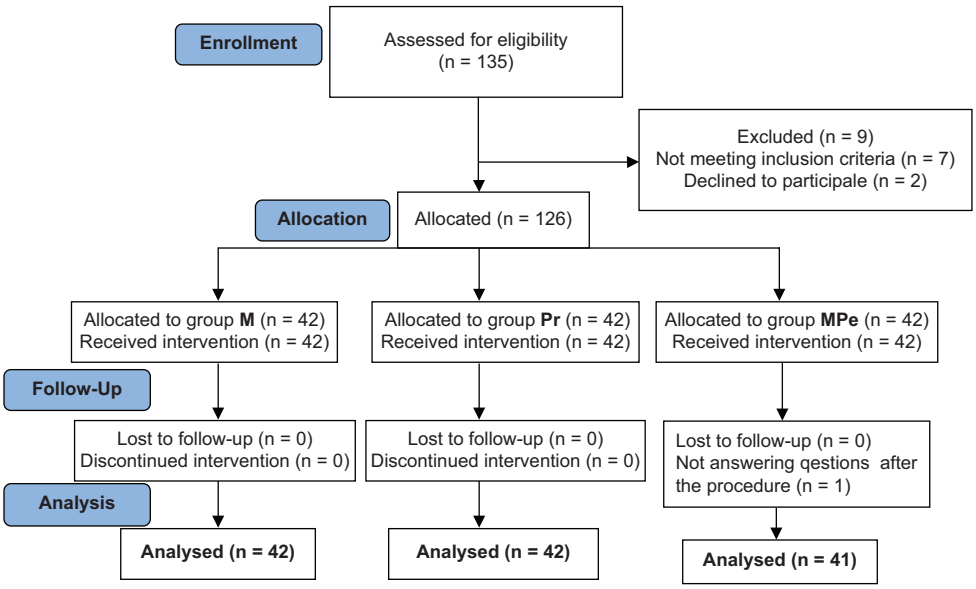

Figure 1: The study flow diagram

for additional dose requirement. Heart rate (HR), oxygen saturation (SpO_2), and mean arterial pressure (MAP) of all patients were recorded before induction. After 2 min post-induction, HR, SpO_2, MAP, and Ramsay sedation score (RSS) were recorded (Table 1).[7] After the probe placement, the ease of probe placement was questioned to the cardiologist who performed the TEE procedure. We determined the ease of probe placement with a scoring system derived from the literature (1) as follows: Very easy: one trial or <1 min, easy: two trials or 1–5 min, difficult: >2 trials or with one of the difficult probe insertion maneuvers (jaw-thrust, neck flexion, lateral pressure), very difficult: categorized as more than one of the difficult probe insertion maneuvers or placement with laryngoscopy. Heart rate, SpO_2, MAP, and RSS were recorded at every 5 min intervals after probe placement.

Additional dose was administered to the patients if required. Coughing, gag reflex, hypotension, nausea, vomiting, desaturation, apnea, pain at the injection site, the need for assisted ventilation, myoclonus, waking agitation, and psychotomimetic effects during the procedure were recorded. When the TEE evaluation was completed, the probe was removed and the procedure time was recorded. The patient was taken to the recovery unit, and the Modified Aldrete score system (MASS) was evaluated at 5 min after the procedure (Table 1).[8]

At the end of the procedure, the cardiologist and patients were asked about their level of satisfaction with the quality of sedation (in terms of patient comfort, respiratory and hemodynamic stability, and recovery rate) by a blinded investigator. Doctor and patient satisfaction was questioned as bad, moderate, good, very good.

A blood pressure below 20% of baseline levels was defined as hypotension, and if no response was obtained with a 200 cc intravenous (IV) liquid bolus administration, administration of 0.01 mg IV bolus noradrenaline was planned. Apnea was defined as no $EtCO_2$ measurement for more than 20 s or an $EtCO_2$ measurement <15. Desaturation was defined as SpO_2 <90%. The need for mask ventilation/airway devices was defined as assisted ventilation. Bradycardia was defined as HR <60 beats per min (bpm) and when HR <40 bpm, 0.5 mg IV bolus injection was planned.

The sample size was calculated based on reference studies and calculations were made by means of a power analysis program. Including at least 129 patients as a result of the assessment allowed a statistical power of 80% with conventional 2-sided type 1 error of 5%.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. ANOVA, Kruskal-Wallis, and Mann-Whitney U tests were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fischer test was used when Chi-square test conditions were not met. SPSS 27.0 (IBM, USA) program was used in the analyses.

RESULTS

The study was started with 135 patients between the ages of 18-75 and completed with 125 patients (Figure 1). The

Table 1: RSS and the MASS

RSS[7]		MASS[8]
Score	**Definition**	
1	Anxious and agitated or restless or both	Activity: Able to move voluntarily or on command • Four extremities 2 • Two extremities 1 • Zero extremities 0
2	Cooperative, oriented, tranquil	
3	Responds to commands only	
4	Brisk response to light globellar tap or loud audiotory stimulus	
5	Sluggish response to a light glabellar tap or loud audiotory stimulus	Respiration • Able to deep breathe and cough freely 2 • Dyspnea, shallow or limited breathing 1 • Apneic 0
6	No response to a light glabellar tap or loud auditort stimulus	Circulation • Blood pressure±20 mm of preanaesthetic level 2 • Blood pressure±20–50 mm preanaesthesia level 1 • Blood pressure±50 mm of preanaesthesia level 0
		Consciousness • Fully awake 2 • Arousable on calling 1 • Not responding 0
		O_2 saturation • Able to maintain O_2 saturation >92% on room air 2 • Needs O_2 inhalation to maintain O_2 saturation >90% 1 • O_2 saturation <90% even with O_2 supplementation 0
Sessler CN, Grap MJ, Ramsay MA. Evaluating and monitoring analgesia and sedation in the intensive care unit. Crit Care. 2008; 12 Suppl 3(Suppl 3):S2.		A score ≥9 was required for discharge. Aldrete JA. The post-anesthesia recovery score revisited. J Clin Anesth. 1995 Feb; 7 (1):89-91.

RSS: Ramsay sedation scale, MASS: The modified aldrete scoring system

patients were divided into three groups randomly as group M (n=42), group Pr (n=42), and group MPe (n=41). There were no significant differences between the demographic data (age, weight, and gender) of the patients in different groups (P>0.05). When the existing chronic diseases were evaluated, the rate of diabetes mellitus (DM) in the M group was significantly lower than the other two groups (P<0.05). Total time period for the procedure were similar between groups (P>0.05). When the complications during the TEE procedure were evaluated, the rate of nausea was higher in the M group compared to the Pr group, and the pain at the injection site was less than in the Pr group. There was no statistically significant difference between the groups in terms of other complication rates (P>0.05; Table 2).

Both doctor and patient satisfaction rates were found to be significantly lower in the M group compared to the other two groups (Figure 2). In the MPe group, both patient and doctor satisfaction were significantly higher than the two groups. The rate of difficulty in probe placement was lower in the Pr and MPe groups compared to the M group (P<0.05). The rate of difficulty in probe placement did not differ significantly between the Pr and MPe groups (P>0.05; Table 2 and Figure 3).

When the hemodynamic changes during the TEE procedure were compared, although SpO_2 in group M was found to be significantly lower than the other two groups at the 2nd min OD post-induction, hypoxia did not occur in any patient. Besides, MAP, HR, and SpO_2 measured before induction and at 2nd, 5th, and 10th min after induction were similar in all groups (P>0.05). The additional dose requirement at the 5th min in the M group was significantly higher than in the MPe group (P<0.05). On the other hand, no significant difference was found in the additional anesthetic requirement between the groups at the 2nd and 10th min after induction (P>0.05; Table 3).

Except that RSS was scored as 4 in one patient in group M, RSSs were between 1 and 3 in all groups and results were similar (P>0.05; Table 3). In the post-procedure MASS evaluation, the results between the groups were similar (P>0.05) and none of the patients had a MASS value below 8. All patients were followed up in the recovery unit for an equal period of time (2 h) and were discharged.

DISCUSSION

The results of this study showed that patients who were sedated with the combination of midazolam-pethidine during the TEE procedure led to better physician and patient satisfaction levels than patients who were sedated with only midazolam and only propofol.

Since the TEE procedure is usually performed on cardiac patients, the hemodynamic stability is aimed. Therefore, physicians are in favor of preferring the safest drug when sedating these patients, and midazolam, a benzodiazepine that is thought to have the least impact on hemodynamics and respiration, is generally preferred. Another reason midazolam is preferred more is that it can be antagonized

Table 2: Demographic data between groups and evaluation during the TEE procedure

	Group M (n=42)		Group Pr (n=42)		Group Mpe (n=41)		P
	Mean ± s.s/n-%		Mean±s.s/n-%		Mean±s.s/n-%		
Age	52.8 ± 13.9		53.3±12.0		50.4±12.7		0.554
Gender							
Male	14	33.3%	21	50.0%	11	26.8%	0.077
Female	28	66.7%	21	50.0%	30	73.2%	
Weight	81.8 ± 13.9		77.8±10.5		79.5±14.2		0.568
Cronic illness	27	64.3%	22	52.4%	16	39.0%	0.070
AF	3	11.1%	0	0.0%	1	6.3%	>0.05
AVR	2	7.4%	3	13.6%	1	6.3%	>0.05
DM	0	0.0%	14	63.6%	8	50.0%	**0.000**[12]
HT	19	70.4%	10	45.5%	10	62.5%	0.203
CVA	3	11.1%	1	4.5%	5	31.3%	0.054
CAD	0	0.0%	1	4.5%	2	12.5%	>0.05
Other	9	33.3%	8	36.4%	3	18.8%	0.474
Probe placement							
Very easy	6	14.3%	7	16.7%	19	46.3%	**0.000**[12]
Easy	17	40.5%	27	64.3%	19	46.3%	
Difficult	14	33.3%	6	14.3%	3	7.3%	
Very difficult	5	11.9%	2	4.8%	0	0.0%	
Physician satistaction							
Bad	2	4.7%	0	0.0%	0	0.0%	**0.000**[123]
Not bad	16	38.1%	9	21.4%	2	4.9%	
Good	13	31.0%	24	57.1%	11	26.8%	
Very good	11	26.2%	9	21.4%	28	68.3%	
Patient satisfaction							
Bad	8	19.1%	0	0.0%	0	0.0%	**0.000**[123]
Not bad	13	31.0%	8	19.0%	2	4.9%	
Good	11	26.2%	27	64.3%	10	24.4%	
Very good	10	23.8%	7	16.7%	29	70.7%	
Complication							
Cough	20	47.6%	21	50.0%	19	46.3%	0.944
Gag reflex	24	57.1%	32	76.2%	22	53.7%	0.073
Hypotension	3	7.1%	0	0.0%	2	4.9%	>0.05
Nausea	13	30.9%	4	9.5%[1]	8	19.5%	**0.049**[1]
Vomiting	2	4.8%	0	0.0%	0	0.0%	>0.05
Desaturation	0	0.0%	0	0.0%	0	0.0%	1.000
Injection Pain	0	0.0%	4	9.5%	1	2.4%	**<0.05**[1]
The need for ventilation	0	0.0%	0	0.0%	0	0.0%	1.000
Myoclonus	0	0.0%	0	0.0%	0	0.0%	1.000
Agitation	2	4.8%	0	0.0%	0	0.0%	>0.05
Psychomimetic effects	0	0.0%	0	0.0%	0	0.0%	1.000

AF: Atrial Fibrillation, AVR: Aortic valve replacement, DM: Diabetes mellitus, HT: Hypertension, CVA: Cerebrovascular Accident, CAD: Coronary artery disease, TEE: Transesophageal echocardiography. [1]Difference between Group M & Group Pr p <0.05, [2]Difference between Group M & Group MPe p <0.05, [3]Difference between Group Pr & Group MPe p <0.05

with flumazenil.[6,9] Since midazolam does not cause significant changes in hemodynamics in cardiac patients and even reduces heart rate without changing cardiac contractility, its cardiocirculatory effects have been shown to be more favorable.[10,11] Although it was observed that patients who underwent sedation with midazolam had better probe placement convenience and patient comfort compared to those who were not sedated at all, Wenzel et al., observed in their study with TEE patients that midazolam caused central side effects such as aggression, euphoria, depression, and intense hiccups.[12,13] Therefore, this brings to mind the question of "Is midazolam enough for sedation during TEE?" Although it was not statistically significant in this study, agitation was observed during awakening in two patients who were used midazolam. Although we did not observe any significant hemodynamic changes and complications in the midazolam group, it was observed that the comfort of the patient and the doctor was significantly lower, and the probe placement was more difficult compared to other two groups. In addition, the group that received only midazolam required more additional doses of medication than the midazolam-pethidine group.

Propofol is used for sedation in short-term diagnostic and interventional procedures due to the early onset and early termination of its effect. Although propofol is mostly preferred for deep sedation during TEE, there are studies where it was also used for conscious sedation.[14-16] Although, it is used at lower doses in conscious sedation, respiratory depression due to propofol may still occur.[17] In this study,

Table 3: Hemodynamic evaluation during the TEE procedure

	Group M (n=42)		Group Pr (n=42)		Group Mpe (n=41)		P
Processing time (min.)	12.1±4.7		12.3±4.9		11.2±4.5		0.510
Heart rate							
Before induction	83.0±20.8		92.2±19.3		82.4±15.9		0.052
After induction 2 min.	82.5±22.9		88.7±20.1		82.5±15.9		0.273
5 min	80.3±24.9		84.7±19.6		80.5±13.4		0.432
10 min	76.1±25.0		86.5±24.2		80.1±14.3		0.184
SpO_2							
Before induction	98.5±3.2		98.0±1.6		98.6±1.2		0.052
After induction 2 min.	99.2±1.3		98.0±1.9		98.0±1.8		**0.000**[12]
5 min	98.9±1.8		98.0±2.3		98.1±2.0		0.077
10 min	98.5±2.4		97.7±2.7		97.6±2.6		0.257
Mean arterial pressure							
Before induction	103.2±20.2		102.2±15.8		106.6±19.0		0.408
After induction 2 min.	100.9±19.4		95.0±15.4		101.7±18.3		0.230
5 min	91.4±17.6		89.8±19.8		96.5±16.8		0.074
10 min	87.8±15.5		85.1±12.9		88.4±13.5		0.621
RSS							
5 min							
1	4	9.5%	2	4.8%	1	2.4%	0.265
2	29	69.0%	36	85.7%	35	85.4%	
3	9	21.4%	4	9.5%	5	12.2%	
10 min							
1	1	4.0%	0	0.0%	0	0.0%	0.751
2	18	72.0%	25	83.3%	15	83.3%	
3	6	24.0%	5	16.7%	3	16.7%	
Additional dose							
After induction 2 min.	5	11.9%	6	14.3%	2	4.9%	0.346
5 min	5	11.9%	1	2.4%	0	0.0%[1]	**<0.05**[2]
10 min	2	8.0%	1	3.3%	1	5.6%	>0.05

SpO_2: Oxygen saturation. RSS: Ramsay sedation score, TEE: Transesophageal echocardiography. [1]Difference between Group M & Group Pr p <0.05, [2]Difference between Group M & Group MPe p <0.05

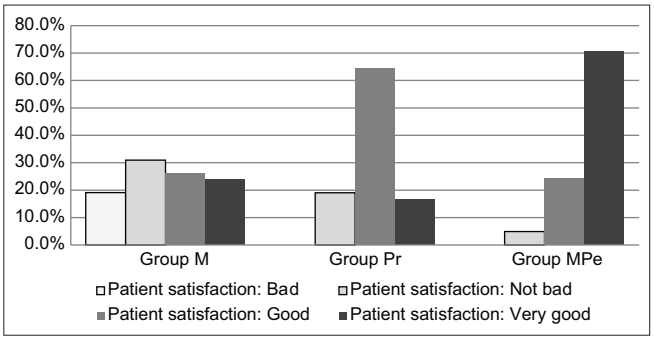

Figure 2: Comparison of patient satisfaction between groups

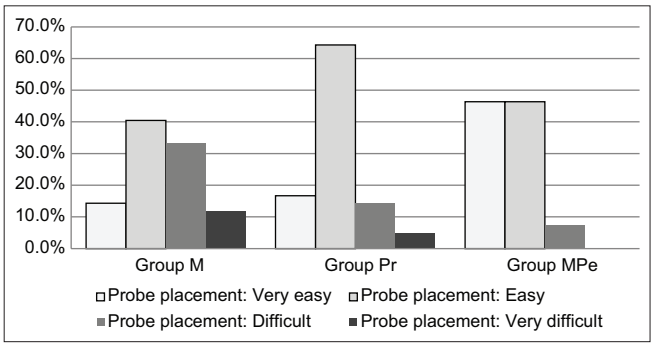

Figure 3: Comparison of probe placement between groups

severe respiratory depression was not observed in the propofol group and the SpO_2 level remained within safe limits. In the study conducted by El Mourad et al., including patients who underwent TEE under conscious sedation, it was observed that propofol had a higher satisfaction score than dexmedetomidine and caused less hemodynamic alterations.[14] In the study of Toman et al., it was observed that propofol provided faster sedation than the combination of midazolam and midazolam-alfentanil, the depth of sedation was better and the length of hospital stay was shortened.[18] In some studies conducted with different diagnostic procedures such as colonoscopy and endoscopy, it has been shown that the application of deep sedation with propofol provided similar physician and patient satisfaction when midazolam was applied in combination with opioid.[19,20] In our study, it was observed that the use of propofol provided better patient and doctor satisfaction compared to midazolam.

Despite previous studies showing the potential benefits of combining opioids and benzodiazepines for conscious sedation, many different the sedation protocols are used in clinical practice during the TEE procedure.[21] In the study of Renna et al., it was observed that the combination of remifentanil infusion and low dose midazolam showed better

tolerance and faster recovery compared higher doses of midazolam alone in patients who were sedated for the TEE procedure.[22] In a similar study using opioid-benzodiazepine combination, it was shown that alfentanil and midazolam combination was more advantageous than only midazolam.[18]

Visualization is an important technique during TEE. Pethidine has two advantages regarding pharyngeal observation. Firstly, it reduces gag and cough reflexes and secondly, it facilitates pharyngeal observation.[23,24] Although midazolam reduces discomfort during pharyngeal observation, it does not improve pharyngeal observation itself.[24] In the study of Mankia et al., where the combination of these two drugs was used, it was shown that the conscious sedation protocol for the TEE procedure was safe and effective. In this study, in terms of patient and doctor satisfaction, better results were observed in the group in which the combination of midazolam-pethidine was used compared to the group using only midazolam and only propofol.[21] In another study comparing the combination of opioid and benzodiazepine with only benzodiazepine, while the two applications showed similar satisfaction, additional oxygen support was required in the combination of benzodiazepine and opioid.[25] On the contrary, in this study, SpO_2 levels after induction were lower in the group that received only midazolam compared to the other two groups. However, SpO_2 did not fall below 90 in any patient and remained within safe limits, and increased oxygen support or airway intervention was not required.

With this study, we think that this study will contribute to the literature about the appropriate sedation method in the TEE procedure, which has not been fully clarified. However, our study had some limitations. The underlying cardiac pathologies of the patients were different. However, all patients underwent TEE under elective conditions. All patients were ASA I-II outpatients. Although $EtCO_2$ was measured during the process, its values were not recorded. In addition, using the bispectral index in the measurement of sedation depth would have been valuable in terms of providing more objective data.

Limitations of the study

Department of Cardiovascular Surgery, Istanbul University-Cerrahpaşa, Cardiology Institute, Istanbul, Turkey.

CONCLUSION

In this study, it was observed that midazolam, which is used frequently by both anesthesiologists and cardiologists, was not sufficient for the sedation during the TEE procedure when used alone. In addition, it has been observed that conscious sedation with the combination of midazolam-pethidine was significantly advantageous in terms of patient and physician satisfaction compared to the use of only midazolam and only propofol.

ETHICS COMMITTEE APPROVAL

Ethics committee approval was received.

INFORMED CONSENT

Informed consent was obtained from the participants.

ETHICS NUMBER

Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (Date: 13.02.2019, Number: 38082516-900-18898).

THE STUDY DESIGN

Prospective cohort study.

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Authors Contribution:
HYAK, YO, SA, MAY- Concept and design of the study, prepared first draft of manuscript; **HYAK, YO, MAY-** Interpreted the results; reviewed the literature and manuscript preparation; **HYAK, CB, IH, SA, MAY-** Concept, coordination, statistical analysis and interpretation, preparation of manuscript and revision of the manuscript.

Work attributed to:
Istanbul University-Cerrahpaşa, Cardiology Institute, Istanbul, Turkey

Orcid ID:
Hulya Yilmaz AK - https://orcid.org/0000-0002-8682-6254
Yasemin Ozsahin - https://orcid.org/0000-0002-8653-2272
Mehmet Ali Yeşiltaş - https://orcid.org/0000-0002-5208-0626
Sükrü Arslan - https://orcid.org/0000-0003-0962-0540
Cem Bostan - https://orcid.org/0000-0001-8179-1526
Ismail Haberal - https://orcid.org/0000-0001-6128-5212
Mustafa Yildiz - https://orcid.org/0000-0003-3502-4785

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