Efficacy of Low Doses of Midazolam in Combination with Verbal Sedation during Transesophageal Echocardiography

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ABSTRACT **Background:** Traditionally, transesophageal echocardiography (TEE) has been performed under moderate sedation and local pharyngeal anesthesia. Respiratory complications during the TEE can occur.

Objectives: To test the effectiveness of low-dose midazolam combined with verbal sedation during TEE.

Methods: The study comprised 157 consecutive patients who underwent TEE under mild conscious sedation. All patients received local pharyngeal anesthesia and low doses of midazolam combined with verbal sedation. The course of TEE and clinical characteristics of the patients were analyzed.

Results: The mean age was 64 ± 15.3 years, 96 males (61%). In 6% of the patients, low dose midazolam in combination with verbal sedation was insufficient and propofol was administrated. In women under 65 years of age with normal renal function, there was a 40% risk of low-dose midazolam being ineffective ($P = 0.0018$).

Conclusions: In most patients, TEE can be conducted easily using low-dose midazolam combined with verbal sedation. Some patients need deeper sedation with anesthetic agents like propofol. These patients tended to be younger, in good general health, and more often female.

IMAJ 2023; 25: 332–335

KEY WORDS: verbal sedation, transesophageal echocardiography, low dose midazolam

TEE in awake patients is performed under pharyngeal anesthesia and moderate sedation usually with midazolam. Sometimes combinations of different drugs are used. Respiratory depression due to excessive sedation is the main reason for the search for additional techniques of sedation to ensure the safe insertion of the transesophageal probe. The need for close collaboration between the cardiologist and the patient during TEE makes a difference in the level of sedation necessary for gastroscopy and TEE. Gastroscopy is performed under the control of vision in a deeply sedated patient and the patient's cooperation does not matter. Insertion of the TEE probe is performed blindly and requires cooperation with an awake patient. The cardiologist performing the TEE administers midazolam in doses that are usually 2–4 mg [1]. Verbal sedation has been recommended in TEE guidelines as an additional method [1]. In cases where the patient does not cooperate, it is necessary to call the anesthesiologist for deeper sedation [1], which takes additional time for the procedure and post-procedural observation.

We sought clinical predictors of the need for deeper sedation during the TEE examination. To identify those patients in whom deeper sedation will be necessary, we analyzed the course of TEE in awake consecutive patients.

PATIENTS AND METHODS

A retrospective observational study was conducted in the echocardiography unit in the department of cardiology at Shamir Medical Center. The study was approved by the local Helsinki Committee. Consecutive patients who underwent TEE while awake were included in this study. Patients who underwent TEE under general anesthesia in the critical care unit and other medical departments were excluded.

The patients were prepared for TEE following standard recommended procedures [1]. Patients fasted for at least 6 hours before the procedure. Initially, all patients were examined and interviewed by a nurse and received an initial explanation about the TEE procedure. Next, the cardiologist scheduled to conduct the TEE talked with the patient about the procedure and explained the need for cooperation. All patients signed informed consent. Patients were asked to lie on their left side in a lateral decubital position. After local anesthesia of the oropharynx using a 10% lidocaine spray, a bite block was inserted. Small divided doses of midazolam, up to 2 mg, were administered intravenously to achieve the required level of sedation. In fragile and elderly patients, a dose of 0.5 mg of midazolam or less was often sufficient. The patients simulated swallowing a probe before the examination. The patient's head is tilted anteriorly, and the probe is inserted. During probe placement, we used a bite block with side holes to allow insertion of the index finger of the left hand into the mouth for better manipulations with the probe. Initially, during placement of the probe through the mouth, the patient was asked to take a breath, just for distraction, while the probe was advanced. At that point, the patient swallows. During swallowing, the probe is placed gently in the esophagus. In cases where this technique does not work, and the patient does not cooperate, propofol is added intravenously by the anesthesiologist. After TEE, all patients are followed for at least half an hour. During and after the TEE procedure, the patient is connected to a pulse oximeter and a blood pressure monitor. Measurements are taken every 3 minutes during the procedure and every 5 minutes after that.

Demographic, clinical, epidemiological data were collected for each patient. Details regarding the TEE course were obtained from the hospital's digital files. Hemodynamic data were analyzed before, during, and after the procedure. Doses of midazolam were recorded.

Results were presented as mean ± standard deviation. Statistical significance was assessed by Student's *t*-test. The chi-square test was used when indicated. $P < 0.05$ was considered significant. We evaluated patients in whom low dose midazolam in combination with verbal sedation was not sufficient and deeper sedation was needed. Multivariate MATLAB analysis of variance (ANOVA) was applied to calculate the probability of failure of low-dose midazolam according to the demographic and clinical data and according to education level. High education level was defined as tertiary education. These data were presented as a color-coded model [Figure 1].

RESULTS

Of 157 patients included in the study, 96 were male (61%) and 43 were ambulatory (27%).

The most frequent reason for performing a TEE was determining for an embolic source 64 (41%), followed by searching for vegetations 45 (29%), assessment before cardioversion 33 (20%), and evaluating structural heart disease 15 (10%). Of these patients, 66 were post-cerebral vascular accident (42%) and 27 (17%) had chronic obstructive pulmonary disease. The mean age was 64 ± 15.3 years.

In 10 patients (6%), low dose midazolam combined with verbal sedation was insufficient and they needed additional sedation with propofol. The average propofol dose was 53.5 ± 39 mg. These patients tended to be younger, more often were women, did not have physical disability, had better renal function tests, and less ischemic heart disease [Table 1].

Among 147 patients in which low dose midazolam was sufficient [Table 2], there were small changes in blood pressure and heart rate. During the procedure, heart rate was slightly higher, 87 ± 20 vs. 81 ± 20, $P < 0.000001$. Post-procedural heart rate was lower than during the procedure or at base 79 ± 19, $P < 0.002$ and $P < 0.000001$ respectively. Post-procedure blood pressure was slightly lower than during the procedure and at the base, systolic 128.7 ± 17.8 mmHg vs. 136.8 ± 22.1 mmHg and 136.4 ± 23.6, respectively, $P < 0.000001$. Diastolic blood pressure post-procedure was slightly lower than during the procedure 70.1 ± 13.5 mmHg vs. 71.3 ± 14.9 mmHg, $P < 0.002$. There were no significant changes in blood oxygenation, before and during the procedure 98 ± 1.9%, vs. 97 ± 3.5%, $P = 0.7$. There were no procedure-related respiratory complications.

Multivariate analysis [Figure 1] showed that females with high education levels (tertiary education) had a 33% risk of resistance to low dose midazolam combined with verbal sedation, $P = 0.00056$; in association with younger age < 65, or with normal GFR, this risk was increased to 40%, $P = 0.00056$ and $P = 0.0018$, respectively.

Figure 1. The multivariate analysis predicts the risk of resistance to low-dose midazolam combined with verbal sedation before transesophageal echocardiography according to the demographic and clinical data

Red color: the risk of resistance to low dose midazolam combined with verbal sedation ≥ 30%

Orange color: the risk of resistance to low dose midazolam combined with verbal sedation ≥ 20 but < 30%

Yellow color: the risk of resistance to low dose midazolam combined with verbal sedation ≥ 10 but < 20%

[1]Normal GFF = GFR > 60, ml/min

[2]High education level = tertiary education

*Female, high education level, age <65 years, 40% needed propofol, $P < 0.0016$

**Female, high education level, GFR > 60 ml/min, 40% needed propofol, $P = 0.0018$

***Post-CVA/TIA, high education level, GFR > 60 ml/min, 29% needed propofol, $P = 0.015$

****Female, post-CVA/TIA, GFR > 60 ml/min, 27% needed propofol, $P = 0.0007$

CVA = cerebral vascular accident, GFR = glomerular filtration rate, TIA = transient ischemic attack

	Age <65 years	Female	CVA/TIA	Normal GFR[1]	High education level[2]
Age <65 years		16%, $P = 0.03$			22%*, $P = 0.045$
Female	16%, $P = 0.03$		17%****, $P = 0.02$	15%****, $P = 0.02$	33%**, $P = 0.00056$
CVA/TIA		17%****, $P = 0.02$		16%****, $P = 0.006$	25%***, $P = 0.03$
Normal GFR[1]		15%****, $P = 0.02$	16%****, $P = 0.006$	10%, $P = 0.02$	25%***, $P = 0.029$
High education level[2]	22%*, $P = 0.045$	33%**, $P = 0.00056$	25%***, $P = 0.03$	25%***, $P = 0.029$	15%, $P = 0.015$

Table 1. Two groups of patients

	Group 1*	Group 2**	*P*-value
N	147 (94%)	10 (6%)	
Age in years	64.6 ± 15.1	55.8 ± 16.1	0.06
Sex			
Male, n (%)	92 (63%)	4 (40%)	0.08
Female, n (%)	55 (37%)	6 (60%)	
Body mass index	27.2 ± 5.3	28.9 ± 3.8	0.29
Systolic blood pressure	136.8 ± 22.1	138 ± 28	0.44
Diastolic blood pressure	73.2 ± 15.1	75 ± 8	0.28
Heart rate	81 ± 20	85 ± 17	0.28
Respiratory rate	18 ± 6	16 ± 2	0.01
Beta blockers	67 (46%)	3 (30%)	0.17
Sedatives	34 (23%)	3 (30%)	0.33
Hemoglobin g/dl	12.2 ± 2.2	12.1 ± 1.9	0.41
GFR ml/min	50.7 ± 15.9	> 60	< 0.00001
Creatinine g/dl	1.31 ± 1.2	0.76 ± 0.19	< 0.00001
Ischemic heart disease	42 (29%)	1 (10%)	0.05
Disability	35 (24%)	0 (0%)	< 0.00001
Midazolam dose	1.3 ± 0.69	1.65 ± 0.67	0.06
Propofol dose	0	53.5 ± 39	< 0.000001

*Received only midazolam

**Received midazolam and propofol

GFR = glomerular filtration rate

Table 2. Patients with low dose midazolam only

	Base	Procedure	Post-procedure	*P*-value*
SBP, mmHg	136.8 ± 22.1	136.4 ± 23.6	128.7 ± 17.8	< 0.0000001
DBP, mmHg	73.2 ± 15.1	71.3 ± 14.9	70.1 ± 13.5	0.002
Heart rate, beats/min	81.0 ± 2.0	87.0 ± 2.0**	79.0 ± 19.0	< 0.0000001
Percent Sat O	98 ± 1.9	97.0 ± 3.5	97.2 ± 7.7	0.7

DBP = diastolic blood pressure, Sat O_2 = oxygen saturation

SBP = systolic blood pressure

**P*-value of the post-procedure measurement to the baseline

**Increase of intra-procedure heart rate vs. base

P-value = 0.000001

DISCUSSION

We found that the combination of low doses of midazolam, local pharyngeal anesthesia, and verbal sedation was effective for most TEE patients.

The preferable medication used for sedation during TEE was midazolam, a short-acting benzodiazepine agent that acts quickly, within 1 to 2 minutes, to relax the patient, and creates retrograde amnesia. An insufficient dose of midazolam is not effective enough for an adequate sedative effect, which is the reason for poor cooperation of the patient and can lead to damage to the mucous membrane of the pharynx and esophagus [2]. Exceeding the midazolam dose leads to respiratory depression, desaturation, and hypotension [2-4]. Dexmedetomidine, ketofol, and nitrous oxide inhalation were administrated during TEE examination, sometimes together [4]. A combination of midazolam with alfentanil [4] or meperidine was also suggested. The role of verbal sedation should not be underestimated [1]. The use of cognitive-behavioral sedation was reported recently [5]. The stress experienced prior to the TEE procedure can be attributed to various factors, including the inherent nature of the medical procedure itself, the requirement for active participation in swallowing the probe, and the results from an excess of catecholamines.

Cardiologists prefer to conduct a TEE accompanied by anesthesiologists, but in most of the hospitals, that is not the current practice. Respiratory depression occurred in 45% of the patients who underwent TEE [6]. In our study, blood pressure and heart rate changed minimally, oxygen saturation did not change significantly. Thus, for older patients, who are the majority of those who undergo TEE, the procedure can be performed with a minimum amount of midazolam combined with verbal sedation. Verbal sedation takes extra time at the premedication stage but it provides better patient interaction during the procedure and helps to avoid potential respiratory and hemodynamic complications related to excessive sedation. Recognition of the patient's resistance to low-dose midazolam and verbal sedation is possible in some cases during the initial interview with the nurse. Failure of low-dose midazolam is more common in young and middle-aged women. Having a higher level of education, which was defined in our study as tertiary education, could be a contributive factor to anxiety, lack of cooperation, and need for deeper sedation.

CONCLUSIONS

In most patients, TEE can be performed using a low dose of midazolam combined with verbal sedation. Some patients need deeper sedation. Typically, they are women who are younger in age.

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Everyday language is a part of the human organism and is no less complicated than it.

Ludwig Wittgenstein (1889–1951), Ludwig Josef Johann Wittgenstein was an Austrian-British philosopher who worked primarily in logic, the philosophy of mathematics, the philosophy of mind, and the philosophy of language

Capsule

Interrupting endocrine therapy to attempt pregnancy after breast cancer

Prospective data on the risk of recurrence among women with hormone receptor–positive early breast cancer who temporarily discontinue endocrine therapy to attempt pregnancy are lacking. **Partridge** and associates conducted a single-group trial and evaluated the temporary interruption of adjuvant endocrine therapy to attempt pregnancy in young women with previous breast cancer. Among 516 women, the median age was 37 years, the median time from breast cancer diagnosis to enrollment was 29 months, and 93.4% had stage I or II disease. Among 497 women who were followed for pregnancy status, 368 (74.0%) had at least one pregnancy and 317 (63.8%) had at least one live birth. In total, 365 babies were born. At 1638 patient-years of follow-up (median follow-up 41 months), 44 patients had a breast cancer event, a result that did not exceed the safety threshold. The 3-year incidence of breast cancer events was 8.9% (95% confidence interval [95%CI] 6.3–11.6) in the treatment-interruption group and 9.2% (95%CI 7.6–10.8) in the control cohort. Among select women with previous hormone receptor–positive early breast cancer, temporary interruption of endocrine therapy to attempt pregnancy did not confer a greater short-term risk of breast cancer events, including distant recurrence, than that in the external control cohort. Further follow-up is critical to inform longer-term safety.

N Engl J Med 2023; 388: 1645

Eitan Israeli

Capsule

Tumors evade immune cytotoxicity by altering the surface topology of NK cells

The highly variable response rates to immunotherapies underscore our limited knowledge about how tumors can manipulate immune cells. **Zheng** et al. showed that in the membrane topology of natural killer (NK) cells from patients with liver cancer, intratumoral NK cells have fewer membrane protrusions compared with liver NK cells outside tumors and with peripheral NK cells. Dysregulation of these protrusions prevented intratumoral NK cells from recognizing tumor cells, from forming lytic immunological synapses and from killing tumor cells. The membranes of intratumoral NK cells have altered sphingomyelin (SM) content and dysregulated serine metabolism in tumors contributed to the decrease in SM levels of intratumoral NK cells. Inhibition of SM biosynthesis in peripheral NK cells phenocopied the disrupted membrane topology and cytotoxicity of the intratumoral NK cells. Targeting sphingomyelinase confers powerful antitumor efficacy, both as a monotherapy and as a combination therapy with checkpoint blockade

Nature Immunol 2023; 24: 802

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