

# Impact of Fentanyl Associated with Midazolam in Sedation for Transesophageal Echocardiography

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## Summary

**Introduction:** Transesophageal echocardiography is currently one of the main tools in the diagnosis of various cardiac abnormalities. For greater safety and comfort, the test has been performed under moderate conscious sedation and benzodiazepines were the agents of choice. In this class of drugs, midazolam is the most commonly used, however it is not free of potential complications related to its use, such as hypoxia, hypotension, among others. We know that sedation level is dose-dependent. Therefore, the lower the dose, the lower the risk of complications from the procedure.

**Objective:** To check the impact of fentanyl in the intravenous administration of midazolam in order to assess the sedation protocol efficiency on patients undergoing transesophageal echocardiography using both drugs.

**Methodology:** We have studied 201 patients (mean age 51.5 years, 115 men) who underwent transesophageal echocardiography with intravenous sedation divided into two groups: Group A (n = 89), following the protocol with fentanyl associated with midazolam; and Group B (n = 112) without the use of fentanyl. The dose of midazolam administered in both groups was then compared. Proper monitoring of vital signs was performed throughout the procedure.

**Results:** The mean dose of midazolam used was  $2.6 \pm 1.4$  mg in Group A and  $4.0 \pm 2.7$  mg in Group B ( $p < 0.01$ ). The dose of fentanyl used was  $66.2 \pm 24.8$  mcg. There was no significant difference between age ( $p = 0.08$ ) and gender ( $p > 0.1$ ) in the groups studied.

**Conclusion:** The use of fentanyl in sedation for transesophageal echocardiography associated with administration of midazolam allows the administration of a lower dose of this benzodiazepine.

**Keywords:** Transesophageal echocardiography; GABA-A receptors/drug effects; Fentanyl/adverse effects; Midazolam/adverse effects.

## Introduction

Transesophageal echocardiography is one of the methods most frequently used to help diagnosing the cardiac area. It is indicated in several situations, such as structural and functional assessment of the heart and aorta, especially in cases where there is a technical limitation of transthoracic analysis, which may be indicated in intraoperative follow-up and as a guide in some invasive catheter procedures (e.g.: atrial septal defect occlusion and left atrial appendage, aortic stenting)<sup>1</sup>.

Transesophageal echocardiography is a very safe method, when performed according to appropriate rules<sup>2</sup>. However, complications are reported, particularly in the introduction and handling of the probe, which may cause gastric, oropharynx and esophagus trauma<sup>3</sup>.

For a safer execution of the method, including patient comfort, moderate conscious sedation for the test has been used routinely<sup>4,5</sup>. Benzodiazepines are the agents of choice and midazolam is the most used one. Since it is a hypnotic agent, it produces drowsiness and facilitates the beginning and maintenance of a state of sleep that resembles natural sleep in terms of its electroencephalographic characteristics, in which case the patient can be easily waken up. Another agent widely used as a sedative and as an analgesic drug is fentanyl, an opioid of quick and efficient action, one hundred times more powerful

than morphine. Besides being safe, it enhances the sedative effect of benzodiazepines, reducing the need for higher doses of these agents. Furthermore, the combination of fentanyl and midazolam in the conscious sedation of endoscopic procedures has been described as safe, efficient and even better than midazolam administered alone<sup>6</sup>. Due to the dose-dependence of these agents, the occurrence of complications, therefore, may be more often related to dose an effective sedation. Based on that, we executed a sedation protocol for transesophageal echocardiography using fentanyl associated with midazolam intravenously, compared to its isolated use, in order to assess the impact of fentanyl in the dose of midazolam administered.

## Methods

### Patients

The study included 201 patients with mean age 51.5 years, including 115 men who underwent transesophageal echocardiography with moderate sedation, divided into two groups: Group 1 (n = 89), following the protocol with intravenous fentanyl associated with midazolam; and Group 2 (n = 112), without the use of fentanyl. Then, we compared the dose of midazolam administered in both groups.

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### Transesophageal Echocardiography

The tests were performed on a Toshiba Aplio®, Japan, esophageal 3-6.5 MHz probe with adequate monitoring of blood pressure, electrocardiography and pulse oximetry throughout the procedure. Sedation, reaching moderate level (American Society of Anesthesiologists) 5, was done after oropharyngeal anesthesia with lidocaine spray and before the introduction of the probe. When midazolam was used alone, the initial dose of midazolam was 1 to 2 mg, with 1 mg increments every three minutes. In combination with fentanyl, the initial dose was 1 mg with increments of 1 mg every three minutes. If reversal of sedation was required, administration of flumazenil or naloxone was indicated. The protocols used are shown in Figure 1.

### Statistical Analysis

Results were expressed as mean  $\pm$  standard deviation. The Student t test was performed to calculate the difference between the groups; a significance level (p) was considered when smaller than 0.05. To assess the gender proportion between groups, the Chi-Square method was used.

### Results

The mean dose of midazolam used was  $2.6 \pm 1.4$  mg in Group A and  $4.0 \pm 2.7$  mg in Group B ( $p < 0.01$ ), while

fentanyl was  $66.2 \pm 24.8$  mcg (Group A only). There was no significant difference between age ( $p = 0.08$ ), gender ( $p > 0.1$ ) and body mass index ( $p > 0.1$ ) in the groups studied. The results of each group are shown in Table 1. In nine patients of Group B, reversal was performed with flumazenil. No patient required reversal in Group A.

### Discussion

Transesophageal echocardiography is a diagnostic method of low risk, especially when performed according to safety standards<sup>2</sup>. However, it is not free of complications, particularly while passing and handling the esophageal probe<sup>3</sup>. Moderate conscious sedation has been widely used for a smoother testing, for both the physician and the patient, hence mitigating these complications. According to the American Society of Anesthesiology, moderate conscious sedation is defined as one in which the patient presents adequate spontaneous breathing, cardiac contractile function maintained with normal response to verbal and tactile stimulation<sup>5</sup>. Because of this, sedative agents have been indicated and frequently used in endoscopic procedures, including transesophageal echocardiography. Bell et al.<sup>7</sup> studied 800 consecutive patients who underwent upper digestive endoscopy and observed a marked decrease in the dose in relation to age; and in younger patients, the dose was higher than in the elderly. Although this is not the objective of our study, the population

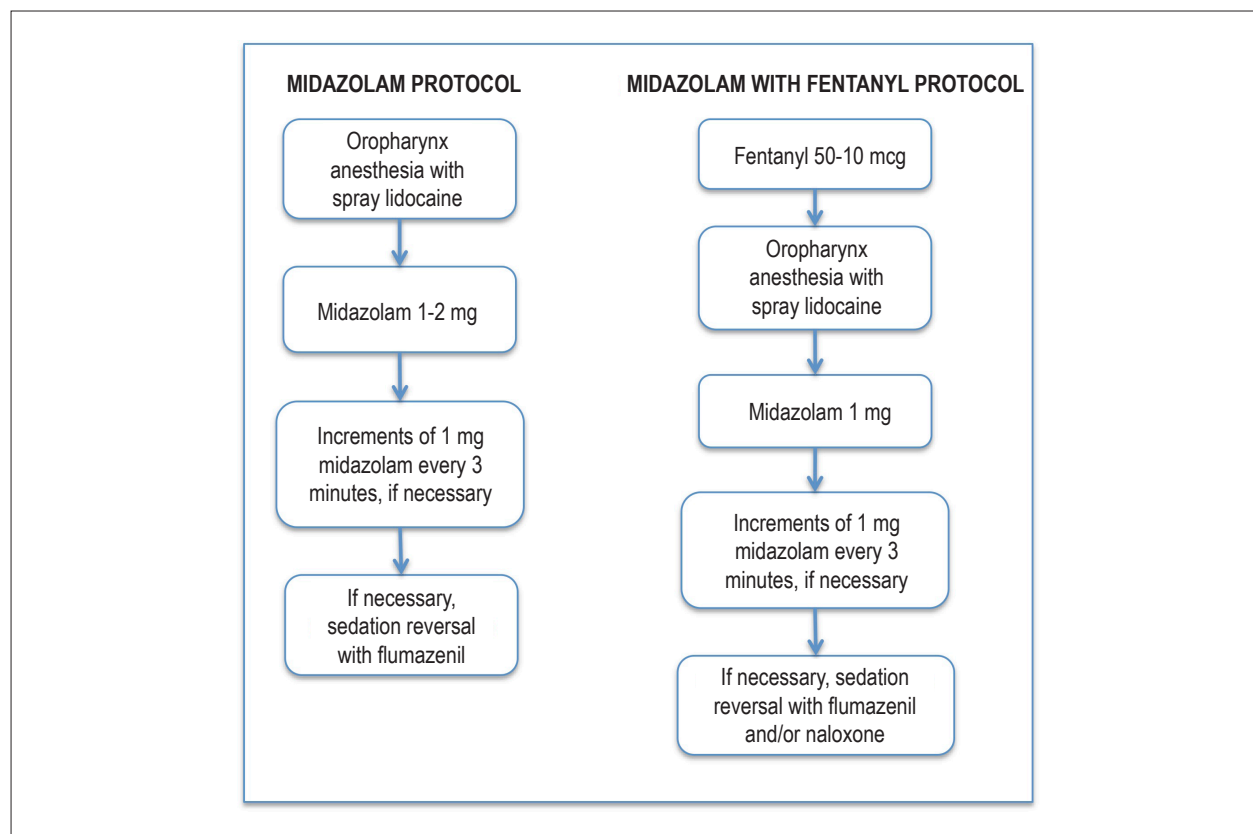


Figure 1 - Protocols used in moderate conscious sedation for transesophageal echocardiography.

**Table 1 - Results of the variables analyzed in each group**

	Group A	Group B	p
Number of patients	89	112	> 0.1
Gender (male)	54	61	> 0.1
Age (years)	47.8 ± 18.2	50.7 ± 16.1	0.08
Body mass index	22.3 ± 4.2	23.1 ± 3.7	> 0.1
Midazolam dose (mg)	2.65 ± 1.42	4.01 ± 2.71	<0.01
Fentanyl dose (mcg)	66.2 ± 24.8	-	Not evaluated

included relatively young patients and there was no difference between age and gender. As sedation complications are dose-dependent, it is possible to think that the smaller the dose, the lower the risk of complications. Cury et al.<sup>8</sup> did not describe severe complications of sedation in the transesophageal echocardiography, despite having used a higher mean dose ( $4.3 \pm 1.9$  mg) than that used in this study. Midazolam is the most widely used agent for moderate conscious sedation for endoscopic procedures because of a high level of safety<sup>9</sup> and the possibility of being administered by the physician performing the test<sup>5</sup>. McQuaid et al.<sup>4</sup> observed an increase in patient satisfaction and a low complication rate. Jose et al.<sup>10</sup> studied the association of meperidine with midazolam in 1841 patients, correlating dose with age and body surface area; however, the authors reported the limitation of being a retrospective study. Barriga et al.<sup>6</sup> described the effectiveness of the association of fentanyl with midazolam in moderate conscious sedation, suggesting that this combination would be better than the isolated use of midazolam. Using this association, we observed a significant reduction in the dose of midazolam administered for an effective action, according to the criteria of moderate conscious sedation. Furthermore, benzodiazepines have an easily accessible, effective and fast acting antidote: flumazenil<sup>11</sup>. Although in our service we use

flumazenil at a low frequency, it was used in 9 patients in the midazolam protocol group. In the fentanyl-midazolam protocol group, flumazenil was administered in none of the patients. A major advantage of this would be the financial impact of the test, since flumazenil has a relatively high cost.

### Limitations

In the midazolam protocol, only one initial variable dose according to the medical criteria of 1 to 2 mg was used. This could mean a lower total dose of midazolam if the initial dose for all patients was 1 mg. However, the total dose was related to the patient's level of sedation regardless of the dose initially used. Although the objective of this study was to evaluate the impact of fentanyl in the dose of midazolam to achieve moderate sedation, oxygen saturation and heart rate during the test could have been evaluated according to the dose of midazolam. This opens up a possibility of being done in future studies.

### Conclusion

The use of fentanyl in moderate conscious sedation for transesophageal echocardiography associated with midazolam allows the administration of a lower dose of this benzodiazepine.

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