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Comparison of the effects of intravenous midazolam alone and in combination with meperidine on hemodynamic and respiratory responses and on patient compliance during upper gastrointestinal endoscopy: a randomized, double-blind trial

Üst gastrointestinal endoskopide intravenöz midazolam kullanımı: Hemodinamik ve respiratuvar etkiler ve hasta uyumu açısından meperidin + midazolam kombinasyonu ile karşılaştırma: randomize çift kör çalışma

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Background/aims: *We examined hemodynamic responses during gastroscopy in healthy subjects and compared the changes with midazolam alone versus in combination with meperidine. The aim of this study was to evaluate if either method had any advantages or disadvantages with respect to patient compliance and the commonly seen side effects.* ***Methods:*** *Thirty patients who were otherwise healthy were included in each group. Either midazolam 0.05 mg/kg IV (Group I) or meperidine 0.3 mg/kg IV followed by midazolam 0.05 mg/kg (Group II) IV were used for sedation. Data of noninvasive hemodynamic and cardiac parameters were recorded before and at the 1st minute after medication, and at the 1st minute and 2-min intervals during the procedure. Endoscopists assessed the comfort of patients according to pre-determined criteria. Statistical analysis was performed for both inter-group and in-group comparisons of parameters.* ***Results:*** *Heart rate increased significantly in Group I ($p<0.05$). Blood pressures and oxygen saturation decreased significantly with sedation in both groups during endoscopy ($p<0.05$), without significant difference between the groups for the changes in these parameters ($p>0.05$). Patient compliance was significantly better in Group II than in Group I, for all measured criteria.* ***Conclusions:*** *We observed that heart rate increases significantly whereas SAP, DAP and SpO2 decrease significantly with both sedation methods. Groups did not differ except for the significantly higher increase in heart rate in Group I. Patient compliance was significantly better with combined sedation. We believe that combined sedation in selected patients provides a safe sedation with a mild to moderate increase in heart rate and a better patient compliance during gastroscopy.*

Key words : Upper gastrointestinal endoscopy, conscious sedation, midazolam, meperidine

Amaç: *Sağlıklı bireylerde gastroskopi sırasında hemodinamik değişiklikleri inceledik ve tek başına midazolam ve meperidinle kombinasyon kullanımındaki değişiklikleri karşılaştırdık. Bu çalışmanın amacı her iki yöntemin sık görülen yan etkiler ve hasta konforu ve uyumu açısından avantaj ya da dezavantajlarının olup olmadığını araştırmaktı.* ***Yöntem:*** *Her iki gruba diğer yönlerden sağlıklı olan otuz hasta dahil edildi. Sedasyon için ya midazolam 0.05 mg/kg IV (Grup I) veya meperidine 0.3 mg/kg IV ardından midazolam 0.05 mg/kg (Grup II) IV uygulandı. Non invazif hemodinamik ve kardiyak parametrelere ait veriler işlemden önce, işlem sırasında 1nci dakikada ve ardından her iki dakikada bir kaydedildi. Endoskopistler işlem sırasında önceden belirlenmiş kriterlere göre hastanın uyum ve konforunu değerlendirdiler. İstatistiksel analizde, incelenen parametrelerin hem grup içi hem de gruplar arası karşılaştırmaları yapıldı.* ***Bulgular:*** *Grup 1'de kalp hızı anlamlı şekilde arttı ($p<0.05$). Her iki grupta da sedasyon ile kan basınçları ve oksijen saturasyonları anlamlı olarak azalmakla birlikte ($p<0.05$) bu parametreler açısından gruplar arasında anlamlı farklılık yoktu ($p>0.05$). Hasta uyumu ve konforu Grup II'de Grup I'e göre değerlendirilen tüm kriterler açısından anlamlı olarak daha iyi idi.* ***Sonuç:*** *Her iki sedasyon yöntemi ile de kalp hızının anlamlı bir şekilde arttığını fakat sistolik ve diastolik kan basınçları ile oksijen saturasyonunun anlamlı bir şekilde azaldığını gözlemlediğimiz bu çalışmada Grup 1'de kalp hızındaki anlamlı artış dışında gruplar arasında incelenen parametreler açısından farklılık yoktu. Ancak hasta uyumu ve konforu kombine sedasyon yöntemi ile çok daha iyi idi. Seçilmiş hastalarda gastroskopi sırasında kombine sedasyon yönteminin kullanılmasının kalp hızında hafif bir artışla birlikte ancak güvenli bir sedasyon ve çok daha iyi bir hasta uyumu ve konforu sağladığını düşünmekteyiz.*

Anahtar kelimeler: Üst gastrointestinal endoskopi, bilinçli sedasyon, meperidin, midazolam

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INTRODUCTION

Upper gastrointestinal endoscopy (UGE) is a safe procedure that can be performed without sedation. However, because it can evoke anxiety and discomfort, which can decrease patient compliance especially in older patients, conscious sedation is commonly used during endoscopy. Furthermore, UGE itself, although safe and well tolerated, can cause increases in heart rate (HR) (1), particularly in older people with pre-existing cardiovascular comorbidity (2). HR changes occur predominantly at the beginning of the procedure (2). Decreases in oxygenation (1) and changes in blood pressure (BP) during UGE (3) have also been noted.

Conscious sedation with benzodiazepines and opioids is the method most widely employed. The sedation level for endoscopic procedures induced with an opioid and benzodiazepine, referred to as "conscious sedation" is generally considered to be moderate according to the definition of the American Society of Anesthesiology (ASA). Rapid induction of sedation and shorter recovery time with short-acting benzodiazepines and opioids, alone or in combination, provide optimal patient comfort and compliance during UGE, along with the additional benefits of shortening the procedure time and improving patient flow through the endoscopy unit (4). Although usually safe, such medications are not free of adverse effects (5, 6). Short-acting benzodiazepines, with their shorter recovery time, facilitate patients' earlier return to daily life. Combination with opioids like meperidine, on the other hand, provides a slightly longer and deeper sedation. Cardiac, hemodynamic and respiratory side effects are the most commonly seen side effects with conscious sedation during endoscopy.

The role of conscious sedation is not well defined, and its use varies from country to country: up to 98% in the United States, less frequently in European countries, and quite rarely in Asia and South America (7). In our endoscopy unit, a standardized information sheet about esophagogastroduodenoscopy (EGD) is given to all patients, and the examination is routinely performed with pharyngeal anesthesia, while conscious sedation is not routinely used and depends on the endoscopist's decision and patient's condition.

In this prospective, randomized, double-blind study, we examined hemodynamic responses during the passage of the endoscope through the laryngopharyngeal area and during the examination of the upper gastrointestinal tract, using noninvasive monitoring of BP, HR and partial arterial oxygen saturation (SpO_2) in healthy subjects and compared the sedative effects and side effects of midazolam alone versus in combination with meperidine. The aim of this study was to evaluate if either method had any advantages or disadvantages with respect to patient compliance and the commonly seen side effects.

MATERIALS AND METHODS

Patients

After we obtained ethics committee approval for the study, patients scheduled for routine UGE who were otherwise healthy were included in the study. Written consent was obtained from all patients at the time of scheduling for endoscopy. A power analysis ($\alpha = 0.05$, $\beta = 0.2$) before the initiation of the study suggested that groups of at least 22 patients each would be required to detect a 15% difference in the peak mean arterial pressure (MAP) values; therefore, the study was designed to enroll 30 patients in each group. Patients with hypertension, known ischemic heart diseases and malignancies were not included in the study.

Study design

Following noninvasive baseline BP measurements including systolic blood pressure (SAP), diastolic blood pressure (DAP) and MAP, as well as HR and SpO_2 values by a blinded observer after topical anesthesia of the throat while the patients were positioned for EGD, patients were given either a bolus dose of saline solution (0.5 ml) followed 1 min later by midazolam 0.05 mg/kg IV *(0.5 mg dosages at 30-sec intervals until total dose was achieved)* (Group I) or a bolus dose of meperidine 0.3 mg/kg IV followed 1 min later by midazolam 0.05 mg/kg IV *(0.5 mg dosages at 30-sec intervals until total dose was achieved)* (Group II) from previously labeled and numbered syringes according to a computer-generated random numbers table. Patents were taken into the endoscopy unit with their previously prepared syringes. Different nurses prepared the syringes and performed the injections to provide double blindness.

Heart rate, SAP, DAP, MAP and SpO_2 values were recorded again 1 min after the injection of medications was completed, and EGD was performed thereafter. HR, SAP, DAP, MAP and SpO_2 values were recorded at the 1st minute of the endoscopy and at 2-min intervals thereafter during the procedure by the same blinded observer.

Table 1. Criteria for scoring on upper gastrointestinal endoscopy

Overall score	Criteria
Excellent	No gagging during hypopharynx-esophagus transit, very good patient compliance, patient is asleep or near asleep, no physical resistance against endoscope
Good	Patient gags but not so severe, patient is partially uncomfortable, almost awake, partial resistance against endoscope
Poor	Severe gagging during hypopharynx-esophagus transit, patient is not compliant, totally awake, significant resistance against endoscope

Nasal oxygen supply was not given routinely and was reserved only for patients whose SpO_2 levels decreased to hypoxemic levels.

Endoscopic procedures were performed by the same investigators (MO, RO, AKG, LD, YY) and the endoscopists assessed ease of pharyngoesophageal intubation, patient response to intubation, level of consciousness, and physical resistance against the procedure. These criteria were used to score overall conditions at intubation as excellent, good or poor (Table 1).

Endoscopists were also blinded to the type of medications used for sedation.

Statistical analysis

SPSS for Windows 10.0 software was used in the analysis of the data obtained during the study. Along with descriptive statistical methods (mean, standard deviation), Kolmogorov-Smirnov test was used to determine if the parameters showed a normal distribution in comparing the measurable data. Student's t test was used in inter-group comparisons of parameters with normal distribution (baseline, after medication, 1st min, 3rd min and 5th min values) and paired-samples test was used in in-group comparisons. For the parameters without normal distribution (7th min values, due to small number of data), Mann-Whitney U test was used for inter-group comparisons and Wilcoxon signed-rank test was used for in-group comparisons. Comparison of qualitative data was performed using chi-square test. Results were evaluated at 95% confidence interval, at $p<0.05$ level.

Table 2. Age and sex distribution of patients

		Group I	Group II	Test value; p
Age (mean±SD)		46.60 ± 18.17	53.13 ± 21.16	t: 1.283; p: 0.205
Sex	Female	20 (66.7%)	12 (40.0%)	χ^2: 4.286; p: 0.038*
	Male	10 (33.3%)	18 (60.0%)	

t: Student's t test, χ^2: Chi-square test, *p<0.05.

RESULTS

Thirty patients in each group completed the study. Age and sex distributions of patients are shown in Table 2. Mean age of the patient group was 49.86±19.83 years (range 20-86). No statistically significant difference in age was observed between the groups ($p>0.05$); however, the number of females in Group 1 and the number of males in Group 2 were higher ($p=0.038$).

Hemodynamic parameters of the groups are shown in Table 3.

Table 3. Hemodynamic data *(mean ± SD)*

	HR	SAP	MAP	DAP	SpO_2
Group I (n=30)					
Baseline	87.63 ± 13.09	131 ± 15.72	99.3 ± 14.4	78.93 ± 14.13	97.33 ± 2.36
After medication	80.10 ± 12.41††	104.50 ± 15.87††	76.23 ± 12.83††	58.70 ± 12.02††	93.93 ± 4.52††
1st min	92.79 ± 17.6	116.65 ± 23.39††	86.20 ± 21.6††	70.44 ± 19.95†	94.72 ± 4.71††
3rd min	89.83 ± 14.17	112.40 ± 20.01††	84.83 ± 15.65††	64.73 ± 15.04††	95.13 ± 3.96††
5th min	86.93 ± 15.49	110.93 ± 17.03††	78.86 ± 12.01††	59.93 ± 10.15††	93.86 ± 4.32†
7th min	83 ± 9.08	112.80 ± 14.23†	81.00 ± 13.5†	64 ± 13.47	92.8 ± 4.43
Group II (n=30)					
Baseline	81.03 ± 13.69	141.33 ± 23.23	104.96 ± 17.23	79.56 ± 12.03	98.33 ± 0.99
After medication	74.76 ± 14.89††	114.40 ± 22.57††	82.33 ± 16.13††	61.66 ± 13.18††	93.00 ± 5.95††
1st min	78.06 ± 18.75	117.06 ± 20.78††	84.26 ± 16.66††	63.40 ± 12.2††	94.66 ± 3.21††
3rd min	77.51 ± 17.46	113.82 ± 21.82††	82.93 ± 15.6††	61.48 ± 10.98††	94.48 ± 2.13††
5th min	73.44 ± 14.65††	115.22 ± 21.96††	78.94 ± 13.07††	56.72 ± 8.2††	93.50 ± 2.52††
7th min	74.22 ± 14.92††	111.33 ± 24.41†	77.55 ± 18.12†	55.88 ± 10.87†	94.88 ± 1.45†

† in-group evaluation against baseline $p<0.05$, †† in-group evaluation against baseline $p<0.01$.

Baseline HRs were not significantly different between the groups ($p>0.05$). There was also no statistically significant difference between the 1st minute measurements after medication ($p>0.05$). HR values at the 1st, 3rd and 5th minute during endoscopy in Group I were significantly higher than those of Group II ($p<0.01$). When in-group analysis was performed, it was observed that HR values decreased significantly at the 1st minute after medication when compared to baseline values in both groups ($p<0.001$ for both groups). The HR values increased during the endoscopy at the 1st, 3rd, 5th and 7th minutes in Group I without significant difference from baseline measurements ($p>0.05$). In Group II, HR values were below baseline throughout the procedure. The changes reached significant value at the 1st minute after medication, then increased to non-significant levels at the 1st and 3rd minutes during the procedure, and decreased to significant level again at the 5th and 7th minutes (Figure 1).

Although baseline SAP measurements of Group I were lower than those of Group II ($p<0.05$), there were no significant differences between the groups for SAP values at the 1st minute after medication and during the endoscopy at the 1st, 3rd, 5th and 7th minute ($p>0.05$). In-group analysis revealed that SAP decreased significantly in the 1st minute after medication when compared to baseline values in both groups ($p<0.001$ for both groups). Similarly, SAPs during the endoscopy at 1st, 3rd, 5th and 7th minutes were also significantly lower than baseline measurements ($p<0.05$ for both groups) (Figure 2).

As for DAPs, there were no significant differences between the groups for baseline, at 1st minute after medication and during the endoscopy at 1st, 3rd, 5th and 7th minutes ($p>0.05$). When in-group analysis was performed, DAP decreased significantly at 1st minute after medication and also during the endoscopy at the 1st, 3rd, 5th and 7th minutes when compared to baseline in both groups ($p<0.001$ for both groups) (Figure 3).

There were no significant differences in MAPs between the groups at baseline, at the 1st minute after medication, and at the 1st, 3rd, 5th and 7th minutes during the endoscopy ($p>0.05$). When groups were evaluated individually, MAP decreased significantly at the 1st minute after medication and also during the endoscopy at the 1st, 3rd, 5th and 7th minutes ($p<0.001$ for both groups) when compared to baseline in both groups (Figure 4).

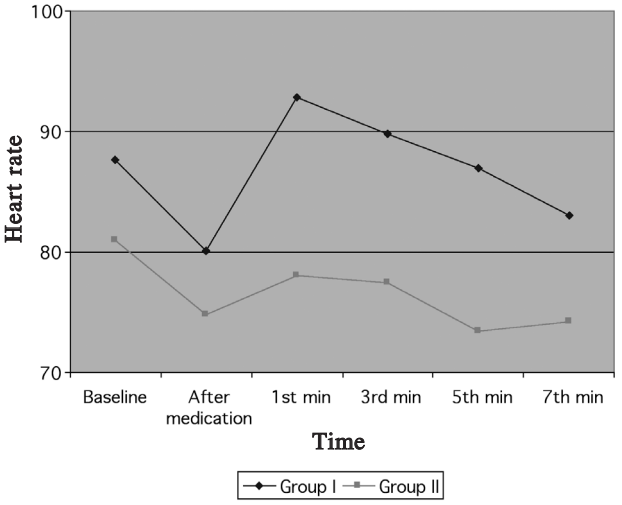

Figure 1. Changes in heart rate.

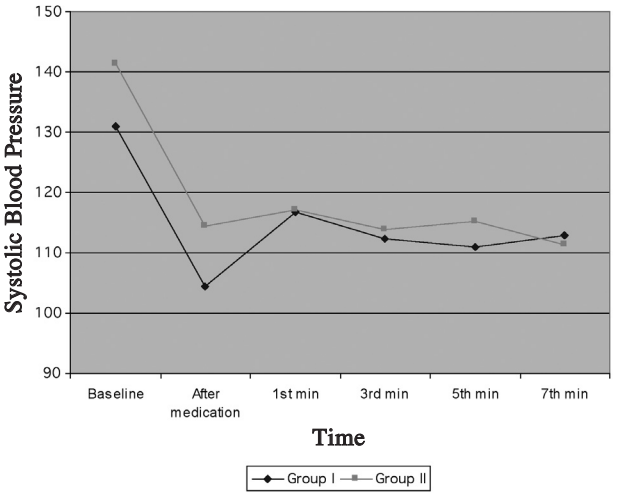

Figure 2. Changes in systolic blood pressure.

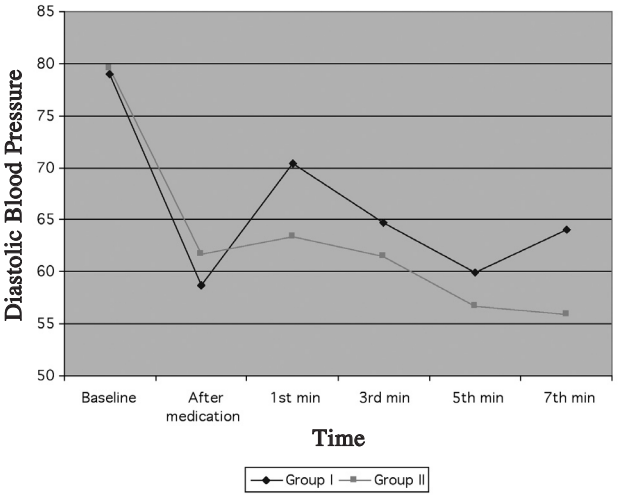

Figure 3. Changes in diastolic blood pressure.

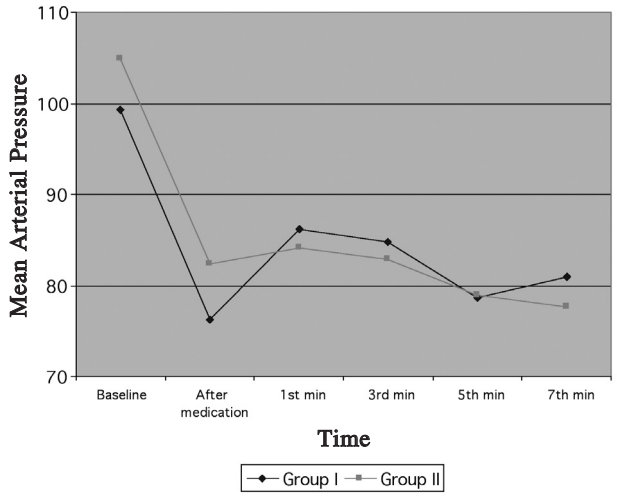

Figure 4. Changes in mean arterial pressure.

The changes in SpO_2 were also evaluated. The measurements revealed that the differences between the groups for baseline and at the 1st minute after medication and also during the endoscopy at the 1st, 3rd, 5th and 7th minutes were not significant ($p>0.05$). When Group I SpO_2 measurements were compared with baseline, the decreases were significant for the 1st minute after medication ($p<0.01$), for the 1st and 3rd minutes during the procedure ($p<0.01$), and for the 5th minute during the procedure ($p<0.05$) (p: 0.001; p: 0.003; p: 0.005; p: 0.011). The 7th minute measurements were not remarkably different (p: 0.144; $p>0.05$).

When Group II SpO_2 measurements were compared with baseline, the 1st minute decrease after medication ($p<0.01$), and the 1st, 3rd, and 5th minute decreases during the procedure ($p<0.01$) were significant (p: 0.001; p: 0.001; p: 0.001; p: 0.001). There was another significant decrease in SpO_2 measurements at the 7th minute during the procedure (p: 0.007; $p>0.05$).

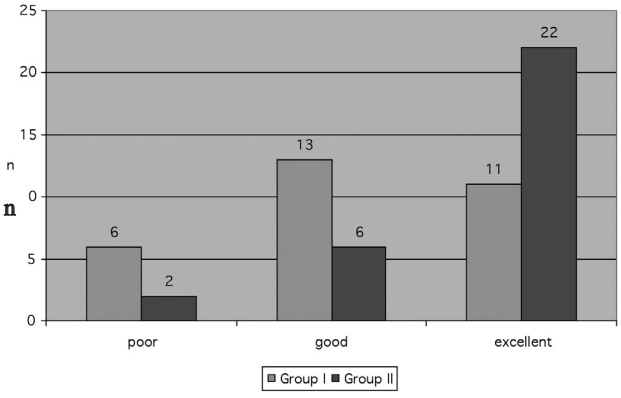

Figure 5. Patient compliance during endoscopy.

Because the decreases in SpO_2 never reached the level of hypoxemia, nasal oxygen supply was not provided to any patient.

As for the criteria for scoring on UGE, statistical analysis revealed that patient compliance was significantly better in Group II than in Group I for all measured criteria ($p<0.05$) (Figure 5).

DISCUSSION

To determine any advantages or disadvantages of midazolam alone versus in combination with meperidine with respect to the commonly seen side effects of intravenous conscious sedation and patient compliance, two groups of patients allocated to receive either midazolam alone or midazolam and meperidine together were evaluated in the present study. We observed that HR increased significantly in Group I ($p<0.01$). SAP, DAP, MAP and SpO_2 decreased significantly with sedation in both groups during endoscopy ($p<0.05$), but there was no significant difference between the groups for the changes in these parameters ($p>0.05$). As for the criteria for scoring on UGE, patient compliance was significantly better in Group II than in Group I for all measured criteria.

In accordance with the findings of other previous studies that sedation during gastroscopy increases HR markedly, especially in older patients, an effect which is not related to the type of medications used (8,9), we observed that patients sedated with midazolam alone had a significant increase in their HRs compared to patients sedated with midazolam plus meperidine. We believe this observation, when combined with the observation that Group II patients tolerated UGE better than Group I, could suggest a favorable effect of meperidine.

It has been suggested that use of sedation was associated with significant changes in SAP during the procedure (1, 9). In contrast, it has also been reported that gastroscopy without sedation can cause increases in BP (1-3,10). Our findings revealed that although BP is affected significantly by these medications at the dosages we used, the difference between the groups was not significant. Thus, we believe that the changes in BP are related not only to the type of medications used but also to other factors such as age, comorbidity, etc.

This study has important messages for gastroenterologists performing UGE. Previous findings suggested that endoscopy only with topical anesthesia of the throat without sedation can cause sig-

nificant increases in HR and BP (1-3, 8, 10). Our findings in this study have revealed that the changes that occurred in BP and SpO_2 with sedation at the dosages we used, although significant, did not have important clinical impacts (i.e. critically low BP or SpO_2). Our results have also shown that midazolam alone can increase HR significantly, but that use of meperidine in combination with midazolam does not cause significant increases in HR and does not change BP significantly. In addition, use of combination meperidine and midazolam mediates ease of pharyngoesophageal passage of the endoscope. When patient response to this passage, level of consciousness, and physical resistance against the procedure were evaluated, meperidine plus midazolam facilitated better patient adaptation in this study.

In conclusion, our findings revealed that sedation with midazolam increases HR more than sedation with meperidine plus midazolam, whereas SAP, DAP and SpO_2 decrease with both sedation methods without any significant clinical finding *(i.e. critically low BP or SpO_2)*, and that there is no difference between the groups with respect to these changes. However, patient compliance was significantly better when midazolam was used in combination with meperidine. Our results lead us to believe that use of combined sedation with midazolam and meperidine in selected patients will provide a safe sedation and a better patient compliance during UGE.

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