Effects of age and gender on intravenous midazolam premedication: a randomized double-blind study

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Background. Given the potentially important effects that age and gender may have on midazolam premedication, this study aimed at determining if these factors alter anxiety, sedation, and cardiorespiratory outcomes when administering two different doses of i.v. midazolam.

Methods. After randomization, patients were premedicated 1 h before surgery with either i.v. midazolam 0.02 or 0.06 mg kg\(^{-1}\) depending on their age and gender group. Levels of anxiety and sedation, heart rate, respiratory rate (RR), mean blood pressure (MBP), and oxygen saturation (\(S_{\text{PO}_2}\)) were measured before and 15 min after midazolam administration.

Results. A higher level of preoperative anxiety was more often observed in women than in men, and in young than in older patients. The female or younger patients showed significant anxiolytic benefits from midazolam. A deeper sedation level was found in men compared with women. Forty-two of 45 patients (93.3%) with excessive sedation received midazolam 0.06 mg kg\(^{-1}\). The elderly patients receiving midazolam 0.06 mg kg\(^{-1}\) showed significant reductions in MBP, RR, and \(S_{\text{PO}_2}\). Of the patients with an \(S_{\text{PO}_2}\) ≤90%, 72.7% had received midazolam 0.06 mg kg\(^{-1}\).

Conclusions. Age and gender differences in neuropsychological and physiological responses after midazolam premedication were evident. Midazolam is effective for producing sedation and anxiolysis at a dose of 0.02 mg kg\(^{-1}\), with minimal effects on cardiorespiration and oxygen saturation to patients. Dosage adjustments based on these covariates are, therefore, necessary.

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Midazolam is a short-acting benzodiazepine, widely used as an anxiolytic, sedative, and anaesthetic adjuvant, and has numerous advantages, such as a short elimination half-life, a significant anterograde amnesia, only minimal haemodynamic effects in a sedation dose, mild respiratory depression, and a relief of anxiety. Most patients are quite anxious while waiting for surgery in the preoperative holding area. Excessive anxiety adversely influences anaesthetic induction, and often leads to functional impairment, and also a poorer recovery after surgery. Anxiety can also decrease patient satisfaction with the perioperative experience. It is therefore not surprising that many studies have examined interventions to reduce preoperative anxiety. Pharmacological anxiolysis is the most common method used in the holding areas of surgical rooms.

Various dosage schemes of i.v. midazolam premedication are previously published. According to the Canadian Compendium of Pharmaceuticals and Specialties, the dose of midazolam recommended for premedication is 1–1.5 mg (≈0.02 mg kg\(^{-1}\)), and a total dose of midazolam should not exceed 3.5 mg or 0.07 mg kg\(^{-1}\) in the elderly. When midazolam is administered at the recommended dose, age and gender may also have clinically relevant effects on pharmacokinetics and pharmacodynamics. Only a
few studies are published, investigating the influence of either age or gender on some aspects of neuropsychological and physiological parameters when applying i.v. midazolam premedication.

Given the potentially important effects that age and gender may have on midazolam premedication, this study was primarily undertaken to determine if these covariates alter anxiety, sedation, and cardiorespiratory outcomes when administering two different doses of i.v. midazolam (0.02 and 0.06 mg kg\(^{-1}\)). We postulated that a lower dose of midazolam might be clinically effective, without the above-mentioned side-effects.

**Methods**

This was a double-blinded, randomized clinical study. Patients were recruited from those undergoing elective surgery in a large general hospital. The hospital’s Ethics Committee approval for the clinical protocol and informed patient consent have been obtained. Patients were stratified by age (young: 20–39, middle-aged: 40–59, and elderly: 60–79 yr) and gender; thus, six study groups were generated. The groups, then, were randomized to one of the two dose groups (0.02 and 0.06 mg kg\(^{-1}\)). Randomization was achieved by the computer-generated random numbers held in sealed envelopes by an individual not involved with the study. Each group had 30 subjects. The main inclusion criteria included: (i) ASA physical status class I or II and (ii) older than 19 yr. Exclusion criteria were: (i) an ASA physical status class III or higher, (ii) being pregnant, (iii) patients with psychiatric disorders, and those taking antipsychotics, (iv) chronic use of benzodiazepines, (v) use of \(\beta\)-adrenergic blockers or calcium channel blockers, and (vi) hypersensitivity or allergy to midazolam.

**Neuropsychological and physiological investigations**

Assessments were carried out before and after i.v. midazolam administration in the surgical holding areas of the operating theatre. Anxiety was evaluated by a visual analogue scale (VAS). The VAS consisted of a 100 mm horizontal line with ‘no anxiety at all’ (score 0) on one end and ‘extreme anxiety’ (score 10) on the other end. Patients were asked to indicate their levels of anxiety before and after midazolam administration. The VAS was previously validated to be a reliable and effective measure for preoperative anxiety.\(^{17}\)

Sedation depth was determined by the Observer’s Assessment of Alertness/Sedation (OAA/S) scale. The OAA/S is a five-point scale which assesses responsiveness to verbal stimuli, speech, facial expression, and eyes. The OAA/S measures sedation on a 1 (does not respond to mild prodding or shaking) to 5 (responds readily to name spoken in normal tone) scale.\(^{18}\) Patients with OAA/S scores 3, 4, and 5 could respond to verbal command and were classified as conscious. Those who did not respond (sedation scores of 1 and 2) were considered to be unresponsive or unconscious. The acceptable level of sedation depends on the psychological and physiological state of the patient and the performed surgical procedure. For the purposes of the present study, an acceptable OAA/S was defined as a score \(\geq 3\).

Vital signs, including the heart rate (HR), respiratory rate (RR), mean blood pressure (MBP), and percutaneous arterial oxygen saturation (\(\text{SpO}_2\)), were continuously monitored for safety reasons using a commercial device [HP OmniCare CMS V24 (M1205A), Germany]. \(\text{SpO}_2\) was obtained by a sensor clipped onto a finger with the patient lying quietly in the holding area.

**Intervention procedures**

When the patient was admitted to the ward, an i.v. catheter was inserted and secured. After patients had been transported to a preoperative holding area adjacent to an operating theatre, and the patients’ admission processes were completed, all patients were equipped with ECG electrodes and other measurements.

A blinded co-investigator recorded neuropsychological and physiological outcomes before midazolam administration as the baseline data. Midazolam (0.02 or 0.06 mg kg\(^{-1}\)) was diluted in normal saline to a total volume of 6 ml. The syringe containing midazolam was dispensed by an anaesthetist. The patients were premedicated with either midazolam 0.02 or 0.06 mg kg\(^{-1}\), given 1 h before surgery. Midazolam was administered i.v. in 15–20 s. All outcomes were measured again by the same co-investigator 15 min after the midazolam administration. Complications after the midazolam administration, including apnoea (intermittent respiration pause of >10 s),\(^{19}\) cardiac arrhythmia, hypotension, and subjective complaints of discomfort by the patients, were noted and recorded. A subject was judged to require supplemental oxygen at 5 litre min\(^{-1}\), if the \(\text{SpO}_2\) value decreased below 85%.\(^{20}\) After completion of the experiment, patients were ready to be transported to the operating theatre.

**Statistical analysis**

To determine sample size, Cohen’s\(^{21}\) tables were used. According to these tables, a medium-sized effect for analysis of variance (ANOVA) was 0.25. A sample size calculation of six groups (age×gender) at \(\alpha=0.05\) and a power=0.80 was conducted. The sample size per group was 35. A total sample size of 210 was needed. Therefore, the sample size of 360 in this study was appropriate. Patient characteristic data were compared using independent sample t-test. Physiological and neuropsychological data before and after premedication obtained over the 15 min measurement period were averaged and compared. ANOVA and post hoc comparisons (Scheffe’s test) was conducted to test for differences among all outcomes of each group and their interactions. Pearson’s correlation
coefficient \( r \) was used to assess the correlation of group variables (age, gender, and dose of midazolam) and all measures before and after midazolam administration. Differences in all measures (post-test score minus pre-test score) were also calculated to evaluate any pre/post-change in outcomes among the groups. The classification of gender was male, 1, and female, 2, so that a positive \( r \) value means that the corresponding parameter is higher for female than for male. Regression analysis was performed to determine the influence of age, considered as a continuous variable, on all outcome measures. Statistical significance was defined as \( P<0.05 \).

**Results**

In total, 389 patients provided consent. Twenty-nine patients were excluded because they were currently using antipsychotics, \( \beta \)-adrenergic blockers, or calcium channel blockers or were at ASA class III or higher. The remaining 360 patients (30 patients in each group) were further analysed (Table 1).

**Influence of age on midazolam sedation**

Almost all patients (98.9%, \( n=356 \)) suffered from anxiety of various levels of severity when they entered the surgical holding area. Anxiety was significantly decreased with midazolam in all age groups (\( P<0.0001 \)). In addition, younger patients showed higher anxiety scores before and after midazolam administration (Fig. 1). Particularly, patients showed an age-dependent relationship in anxiety reduction before and after midazolam administration (\( P<0.01 \)).

The majority of patients (87.5%) achieved satisfactory sedation after midazolam administration. The sedation scores differed significantly with age (\( P<0.0001 \)). Patients with an OAA/S score of <3 (12.5%, \( n=45 \)) were

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Table 1 Patient characteristics in different study groups. Data are presented as mean (range) for age and mean (SD) for weight and height.

<table>
<thead>
<tr>
<th>Dose of midazolam (mg kg(^{-1}))</th>
<th>Gender</th>
<th>Number</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>Male</td>
<td>30</td>
<td>31.0 (20–39)</td>
<td>171.5 (7.2)</td>
<td>73.7 (13.2)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30</td>
<td>31.7 (22–39)</td>
<td>158.4 (4.7)</td>
<td>57.2 (10.0)</td>
</tr>
<tr>
<td>0.06</td>
<td>Male</td>
<td>30</td>
<td>29.3 (20–39)</td>
<td>170.4 (7.6)</td>
<td>69.7 (10.8)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30</td>
<td>31.0 (22–39)</td>
<td>158.9 (5.1)</td>
<td>53.2 (8.6)</td>
</tr>
<tr>
<td>0.02</td>
<td>Male</td>
<td>30</td>
<td>48.2 (40–59)</td>
<td>161.6 (6.2)</td>
<td>72.2 (10.2)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30</td>
<td>47.6 (40–55)</td>
<td>156.0 (5.2)</td>
<td>61.5 (12.7)</td>
</tr>
<tr>
<td>0.06</td>
<td>Male</td>
<td>30</td>
<td>49.5 (41–59)</td>
<td>166.8 (5.1)</td>
<td>71.2 (8.2)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30</td>
<td>47.7 (40–55)</td>
<td>157.9 (5.1)</td>
<td>58.5 (7.5)</td>
</tr>
<tr>
<td>0.02</td>
<td>Male</td>
<td>30</td>
<td>70.9 (60–83)</td>
<td>162.2 (6.0)</td>
<td>66.4 (7.8)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30</td>
<td>66.6 (60–79)</td>
<td>152.2 (6.1)</td>
<td>61.1 (10.3)</td>
</tr>
<tr>
<td>0.06</td>
<td>Male</td>
<td>30</td>
<td>69.9 (60–78)</td>
<td>161.3 (6.2)</td>
<td>62.5 (9.6)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30</td>
<td>67.4 (61–79)</td>
<td>150.9 (4.1)</td>
<td>55.7 (9.4)</td>
</tr>
</tbody>
</table>

**Fig 1** Comparison of anxiety using a VAS and sedation by the OAA/S scale among the groups before and after midazolam administration. \(*P<0.05\) vs before; \(^{1}P<0.05\) vs \(0.02\) mg kg\(^{-1}\) of midazolam; \(^{2}P<0.05\) vs 40–59 yr; \(^{3}P<0.05\) vs 60–79 yr; \(^{4}P<0.05\) vs woman. Data are presented as mean (SEM).
Midazolam caused deeper sedation in elderly patients compared with younger ones ($P<0.01$). MBP decreased from 98.3 (12.9) to 89.8 (11.8) mm Hg with midazolam administration. A reduction in MBP by midazolam was observed in all age groups (Fig. 2). Meanwhile, HR showed significant negative correlations with age before and after midazolam administration ($P<0.01$), but no correlation was observed in HR changes. RR increased after midazolam administration (Fig. 2). $S_pO_2$ levels before and after midazolam administration and $S_pO_2$ changes were negatively correlated with age ($P<0.01$). Regression analysis of our data indicated that all parameters changed, with statistically significant correlation (anxiety: $R^2=0.18$, $P<0.001$; sedation: $R^2=0.12$, $P<0.01$; MBP: $R^2=0.13$, $P<0.01$; HR: $R^2=0.11$, $P<0.05$; RR: $R^2=0.12$, $P<0.05$; and $S_pO_2$: $R^2=0.26$, $P<0.001$), in parallel with age.

**Influence of gender on midazolam sedation**

Anxiety and sedation were significantly different in both gender ($P<0.0001$), and remarkable difference appeared in the 40–59 yr group (Fig. 1). Women showed higher levels of anxiety than men before and after midazolam

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>MBP (mm Hg)</th>
<th>HR (beats min$^{-1}$)</th>
<th>RR (bpm)</th>
<th>$S_pO_2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–39 yr</td>
<td>115±10</td>
<td>75±10</td>
<td>18±2</td>
<td>98±3</td>
</tr>
<tr>
<td>40–59 yr</td>
<td>100±10</td>
<td>65±10</td>
<td>14±2</td>
<td>95±3</td>
</tr>
<tr>
<td>60–79 yr</td>
<td>90±10</td>
<td>60±10</td>
<td>12±2</td>
<td>90±3</td>
</tr>
</tbody>
</table>

### Figure 2

Comparison of the MBP, HR, RR, and $S_pO_2$ among the groups before and after midazolam administration. *$P<0.05$ vs before; †$P<0.05$ vs 0.02 mg kg$^{-1}$ of midazolam; **$P<0.05$ vs 40–59 yr; ‡$P<0.05$ vs 60–79 yr; §$P<0.05$ vs woman. Data are presented as mean (SEM).
premedication ($P<0.01$). A deeper sedation level was found in men compared with women ($P<0.01$).

MBP was significantly lower in women than in men before and after midazolam administration ($P<0.0001$) (Fig. 2). Compared with men, women displayed significantly higher HR before and after midazolam administration ($P<0.0001$). Remarkable HR difference occurred in the 20–39 and 40–59 yr groups (Fig. 2). When we further examined both HR and MBP data, a clear gender-related separation with a compensatory pattern (i.e. a higher MBP was associated with a lower HR and vice versa) was found between HR and MBP before the midazolam intervention (Fig. 3).

RR was significantly higher in women than in men before midazolam administration ($P<0.05$). Women showed higher $S_p_{O_2}$ levels than men before and after midazolam administration ($P<0.0001$), particularly in the 20–39 yr group (Fig. 2). The age-dependent gender effect was predominant in $S_p_{O_2}$, thus leading to the occurrence of a significant difference in the age-by-gender interaction ($P<0.01$).

**Influence of dose on midazolam sedation**

No significant difference was found in the anxiety level between the two doses of midazolam ($P>0.05$). Sedation index indicated that the midazolam-induced sedative effects were more pronounced among patients receiving midazolam 0.06 mg kg$^{-1}$. Most patients (93.3%, $n=42$ of 45 patients) with excessive sedation (OAA/S score $<3$) had received midazolam 0.06 mg kg$^{-1}$.

MBP significantly decreased as the midazolam dose increased ($P<0.01$) (Fig. 2). A 25% decrease in MBP was noted in nine patients after midazolam 0.06 mg kg$^{-1}$ (one patient in the 20–39 age group; four in the 20–39 and 60–79 age groups, respectively). No patient had an MBP lower than 73 mm Hg.

The dose of midazolam produced little effect on HR ($P=0.66$). No patient required treatment for bradycardia after either dose of midazolam. Slight reductions in both MBP and HR with a clear gender-related discrepancy appeared after the administration of midazolam 0.02 mg kg$^{-1}$ (Fig. 3).

The dose of midazolam caused a significant effect on RR ($P<0.0001$). After the midazolam administration, RR increased as the midazolam dose increased ($P<0.01$). There was a significant effect of midazolam dose on $S_p_{O_2}$ ($P=0.05$). The negative correlation between RR and $S_p_{O_2}$ was evident in all groups, particularly for the group 0.06 mg kg$^{-1}$. When we further correlated response patterns of both RR and $S_p_{O_2}$, higher RR was frequently accompanied by a lower $S_p_{O_2}$ after midazolam administration (Fig. 4).

No patient showed a decrease in the $S_p_{O_2}$ to $<85\%$ 15 min after midazolam administration. Twenty-two patients exhibited an $S_p_{O_2}$ of $<90\%$, and they were in the groups of 40–59 and 60–79 yr old. Similarly, 72.7% of the patients with an $S_p_{O_2}<90\%$ ($n=16$ of 22) had received midazolam 0.06 mg kg$^{-1}$. Only four of 60 patients 60–79 yr old (6.6%) displayed an $S_p_{O_2}<90\%$ after 0.02 mg kg$^{-1}$ midazolam administration.

There was a higher incidence of apnoea 5 min after premedication in the group 0.06 mg kg$^{-1}$ (six patients: 60–79 yr—three men and one woman; 20–39 and 40–59 yr—one man, respectively) and in the group 0.02 mg kg$^{-1}$ (two patients: 40–59 and 60–79 yr—one man,
respectively). However, no treatment was required. If these patients with apnoea during premedication were excluded from the statistical analyses, patterns of significant differences in any of the parameters remained (data not shown).

Discussion
This study demonstrates that age and gender have clinically relevant effect on midazolam premedication and may provide valuable information about gender-related alterations in both neuropsychological and physiological parameters before and after midazolam administration. To our knowledge, this is the first study which systematically evaluates the effects of age and gender using two doses of midazolam premedication. The safety of midazolam 0.02 mg kg\(^{-1}\) was found to be acceptable as only rarely did patients receiving midazolam 0.02 mg kg\(^{-1}\) develop clinically important adverse events before anaesthetic induction.

In this study, midazolam produced a significant decrease in the anxiety levels. This is consistent with the previous studies.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\) Furthermore, midazolam is known to reduce arterial pressure, lower oxygen level, and increase sedation level.\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\) A high MBP in the elderly patients may be due to an age-related decrease in the baroreflex sensitivity,\(^2\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\) age-dependent changes in basal sympathetic nerve activity,\(^2\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\) and a reduction in systemic vascular responsiveness.\(^2\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\) The deeper sedation and lower \(\text{Sp}_0_2\) observed in the elderly patients after midazolam administration are consistent with several previous publications.\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\)\(^22\)\(^23\)\(^24\)\(^25\) The increased pharmacological effect of midazolam in the elderly patients may imply that ageing increases the pharmacodynamic sensitivity to midazolam.\(^2\)\(^6\)\(^2\)\(^7\) Thus, midazolam may induce a long-lasting deep sedation effect in elderly patients, hereby worsening MBP and \(\text{Sp}_0_2\).

In the present study, we observed that women received remarkable benefits from midazolam. This observation is in agreement with the results of a previous study.\(^2\)\(^8\) The gender-related differences we observed are in contradiction with some other studies.\(^10\)\(^2\)\(^5\)\(^2\)\(^9\)\(^10\) The reason for this gender discrepancy with midazolam premedication may be due to the fact that young women may experience the endogenous actions of sexual hormones, such as oestrogen and progesterone, which strongly affect mood and control of the autonomic nervous system.\(^3\)\(^0\)\(^3\)\(^1\) Female hormones can potentially influence the GABA receptors of the hippocampus and other portions of the affection-related limbic system,\(^3\)\(^2\) which are the same target of midazolam. Female hormones decline with age. This may explain why several gender-related significant differences occurred in young patients.

Midazolam has been shown to be effective when used for preoperative sedation. Midazolam sedation is known to produce few deleterious effects such as respiratory depression, hypoxaemia, and apnoea, which are associated with dose\(^3\)\(^3\)\(^1\)\(^3\) and age.\(^3\)\(^4\) Excessive sedation is often accompanied by low oxygen saturation during midazolam administration.\(^10\)\(^12\) We also observed a similar phenomenon, particularly for patients who received midazolam 0.06 mg kg\(^{-1}\). In addition, a high RR was accompanied by a low \(\text{Sp}_0_2\) with the two doses of midazolam. Possible reasons for the generation of a higher RR with midazolam administration may be associated with compensatory regulation of hypoxaemia,\(^10\)\(^12\) a reduction in the tidal volume,\(^10\) alteration of sensitivity to blood oxygen levels in the peripheral or central nervous systems, or both.\(^3\)\(^5\)

An optimal premedication dose of i.v. midazolam should provide sufficient sedation and comfortable anxiolysis and
allow a smooth anaesthetic induction without associated adverse effects. Accordingly, the present study provides evidence about the advantage of the 0.02 mg kg⁻¹ midazolam dose. Preoperative anxiety was significantly reduced by both 0.02 and 0.06 mg kg⁻¹ midazolam doses, without any difference between the two dosages. Midazolam produced a sufficient sedative effect at the dose of midazolam 0.02 mg kg⁻¹, but may increase the risk of excessive sedation at a dose of 0.06 mg kg⁻¹. Additionally, a significant reduction was shown in MBP after midazolam 0.06 mg kg⁻¹ administration in all groups, but only a minor decrease appeared with midazolam 0.02 mg kg⁻¹. HR displayed no obvious changes under either dose of midazolam. However, HR–MBP revealed similar gender-related compensatory patterns before and after midazolam 0.02 mg kg⁻¹, but it differed in response to midazolam 0.06 mg kg⁻¹, particularly in men. RR was significantly elevated by midazolam 0.06 mg kg⁻¹ administration in all groups, but only a minor decrease appeared with midazolam 0.02 mg kg⁻¹. HR displayed no obvious changes under either dose of midazolam. However, HR–MBP revealed similar gender-related compensatory patterns before and after midazolam 0.02 mg kg⁻¹, but it differed in response to midazolam 0.06 mg kg⁻¹, particularly in men. RR was significantly elevated by midazolam 0.06 mg kg⁻¹, but only a slight change took place with midazolam 0.02 mg kg⁻¹. Finally, decreases in SPO₂ were significantly greater after sedation with midazolam 0.06 mg kg⁻¹. Thus, midazolam 0.02 mg kg⁻¹ was relatively safe and effective, particularly for patients above 60 yr.

In conclusion, we found consistent trends in preoperative anxiety with age and gender, i.e. high anxiety in women and in the young group. Additionally, anxiety reduction revealed no difference with these two doses of i.v. midazolam. Results from anxiety, sedation, and physiological outcomes with regard to the effects of age and gender indicated a potential benefit of the dose of midazolam 0.02 mg kg⁻¹. We encouraged that dosage adjustments based on these covariates are, therefore, necessary for midazolam premedication. This study extends our knowledge that age and gender strongly influence sedation and cardiorespiratory functions in response to midazolam.

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