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Comparison of Isoflurane and Midazolam as Hypnotic Supplementation to Moderately High-Dose Fentanyl During Coronary Artery Bypass Grafting: Effects on Systemic Hemodynamics and Early Postoperative Recovery Profile

Jacques J. Driessen, MD, and Marianne Giart, MD

Objective: The aim of this study was to compare isoflurane and midazolam as hypnotic adjuncts to moderately high-dose fentanyl during coronary artery bypass grafting (CABG) with regard to perioperative hemodynamics and early postoperative recovery profile.

Design: Prospective open randomized clinical trial.

Setting: Single university-affiliated medical center.

Participants: Thirty patients scheduled for elective primary CABG were randomly divided into two groups receiving either isoflurane or midazolam as adjuncts to 50 μg/kg of fentanyl.

Intervention: Anesthesia was induced with intravenous fentanyl, 10 μg/kg, and midazolam, 0.1 mg/kg, and maintained with either isoflurane, 0.6%, or midazolam, 0.1 mg/kg/hour, in intravenous infusion. Before the sternotomy, all patients received 30 μg/kg of fentanyl. Midazolam and isoflurane were stopped at the start of cardiopulmonary bypass (CPB). At rewarming, all patients received fentanyl, 5 to 10 μg/kg, and either isoflurane, 0.6%, or midazolam, at a reduced rate of 0.05 μg/kg/h. Changes in systolic blood pressure of more than 20% from baseline were first treated with vasoactive drugs. Hypertension was corrected with ketanserin, 10 to 20 mg; hypotension with ephedrine, 5 mg. For a mean blood pressure of less than 50 mmHg during CPB phenylephrine, 0.25 to 0.5 mg, was administered. When hypotension persisted despite a vasopressor, the administration of midazolam or isoflurane was stopped. Postoperatively, the patients were mechanically ventilated overnight and sedated with intermittent doses of fentanyl, 0.15 mg, and midazolam, 5 mg.

Measurements and Main Results: Routine five-lead electrocardiogram (ECG) and invasive hemodynamic monitoring using a pulmonary artery catheter were performed. The mean dose of fentanyl was 3.9 mg in the midazolam group versus 3.6 mg in the isoflurane group. There were no significant perioperative differences between groups in cardiac output, filling, or pulmonary artery pressures. Systolic blood pressure from the initial incision to CPB was lower in the isoflurane group compared with the midazolam group. During this interval, ketanserin was required in nine patients from the midazolam group at a mean dose of 26 mg, compared with only one patient in the isoflurane group. During and after CPB, there was no difference in ketanserin and in vasopressor/inotropic agent requirements. Temporary cessation of midazolam was required in four patients, for a mean of 34 minutes; whereas isoflurane was stopped in 10 patients for 36 minutes, mostly in the post-CPB period. Time to awakening and to extubation in the midazolam group (217 minutes and 19.5 hours) and the isoflurane group (193 minutes and 18.2 hours) were comparable. Between intensive care unit (ICU) admission and extubation, the patients in the midazolam group received 0.89 mg of fentanyl and 36.5 mg of midazolam compared with 0.98 mg of fentanyl and 36.2 mg of midazolam in the isoflurane group. There was a tendency for a higher postoperative pulmonary shunt and more severely impaired oxygenation in the isoflurane group.

Conclusion: Midazolam supplementation to fentanyl required more frequent antihypertensive escape during the pre-CPB period than isoflurane. However, more frequent cessation of isoflurane caused by hypotension was needed in the post-CPB period. No difference in awakening and ICU discharge was found.

KEY WORDS: midazolam, isoflurane, coronary bypass surgery, maintenance of anesthesia

PURE HIGH-DOSE OPIOID (sufentanil or fentanyl) anesthesia is widely used for adult heart surgery because of its excellent hemodynamic stability in patients with limited cardiac reserve, but is often unable to sufficiently suppress the hyperdynamic hemodynamic responses to strong surgical stimuli. Furthermore, the duration of postoperative recovery and respiratory support is frequently prolonged, and awareness is not always prevented.

The most commonly used drugs to supplement opioids for anesthesia during cardiac surgery are the volatile anesthetics and intravenous hypnotic-anesthetics. From the latter, the benzodiazepines, particularly midazolam, are popular because of their mild hemodynamic effects. Few, if any, studies have compared the effects on systemic hemodynamics and the recovery characteristics associated with inhalation versus benzodiazepine supplementation to an opioid-based anesthesia technique.

The aim of the current study in 30 patients was a prospective and randomized comparison between isoflurane (ISO) and midazolam (MID) as hypnotic adjuncts to moderately high-dose fentanyl/oxygen in air anesthesia during coronary artery bypass grafting (CABG) with regard to perioperative hemodynamics and early postoperative recovery profile.

METHODS

Thirty patients scheduled for elective primary CABG were included. Patients were excluded if they were older than 70 years, had diabetes type I, uncontrolled arterial hypertension, preoperative ventricular dysfunction (radionuclide ejection fraction <35% or left ventricular end-diastolic pressure >20 mmHg), myocardial infarction within 1 month before surgery, morbid obesity (Quetelet index >30), obstructive lung disease (forced expiratory volume in 1 second [FEV1] or forced vital capacity [FVC] <70% of predicted), and with more than five anticipated bypasses. After the preoperative visit, the investigators controlled the eligibility and assigned the patients to one of the two treatment groups according to a randomization list. The study was approved by the local Ethical Committee, and informed consent from the patients was obtained.

The patients continued their preoperative cardiac medication up to

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the night before surgery. They were premedicated with diazepam, 10 mg, orally on the evening before surgery, and with diazepam, 10 mg, orally and fentanyl, 0.05 mg, and droperidol, 2.5 mg, intramuscularly, 1 hour before surgery.

Anesthesia was induced in all patients with slow intravenous (IV) injection of fentanyl, 10 μg/kg, followed by midazolam, 0.1 mg/kg, and pancuronium, 0.1 mg/kg. After oral endotracheal intubation, ventilation was controlled using the AVL anesthesia respirator (Drägerwerk AG, Lübeck, Germany) with a fresh gas flow of 4 liters, consisting of 50% oxygen in air. Minute volume ventilation was adjusted to achieve an end-tidal CO$_2$ of 30 to 34 mmHg. After endotracheal intubation, anesthesia was maintained with either ISO, 0.6%, using a Vapor 19.3 vaporizer (Drägerwerk AG, Lübeck, Germany) or MID, 0.1 mg/kg/h, by continuous IV infusion using a syringe pump. End-tidal ISO was analyzed with a Marquette analyzer. Five minutes before sternotomy, fentanyl, 30 μg/kg, was given intravenously (IV) over 5 minutes in divided bolus doses in both groups. Pancuronium, 4 mg IV, was given before the onset of cardiopulmonary bypass (CPB). Administration of MID or ISO was stopped at the onset of CPB. At rewarming, either an MID infusion, at a reduced rate of 0.05 mg/kg/h, or isoflurane, 0.6%, delivered to the oxygenator during CPB, was restarted. Fentanyl, 5 to 10 μg/kg IV, was given to all patients at the start of rewarming. Both MID and ISO were continued until closure of the skin. During the pre-CPB period, lactated Ringer’s solution and modified gelatin solution (Geloplasma, Institut Mérieux, Benelux) were infused at 100 to 200 mL/h to obtain optimal central venous pressures.

CPB was performed using a nonpulsatile roller pump and a membrane oxygenator. At 10 minutes before CPB, mephylprednisolone (2 g), heparin (3 mg/kg), and furosemide (20 mg) were administered intravenously. A balanced prime (1,500 mL of modified gelatin substitute, Geloplasma, 100 mL of mannitol 20%, 50 mEq of sodium bicarbonate, 250 mL of human albumin 20%, and 50 mg of heparin) was used. Venous reservoir, cardiotomy reservoir, hollow-fiber membrane oxygenator, arterial line filter, and tubings were similar in both groups. On-line monitoring of pH, carbon dioxide partial pressure (PCO$_2$), partial pressure of oxygen, and oxygen saturation (SO$_2$) for both arterial and venous blood was done using CDI 300 (CDI Inc/3M, Tustin, CA). Myocardial protection during aortic cross-clamping was achieved with cold Bleece cardioplegic solution and with topical ice on the myocardium. During aortic cross-clamping, the lungs were not ventilated. The pump flow was reduced to 1.7 L/min/m$^2$ during hypothermia (nasopharyngeal temperature 25 to 28°C), and raised to 2.5 L/min/m$^2$ during rewarming. During hypothermic CPB, α-stat management of acid-base balance was used by varying the fresh gas flow to the membrane oxygenator to obtain a temperature-uncorrected arterial PCO$_2$ of about 40 mmHg.

After weaning from CPB and establishment of an adequate circulation, protamine sulfate, 3 mg/kg, was given to neutralize the heparin. Blood transfusion and infusions of crystalloids or colloids were given for optimal filling and a post-CPB hematocrit of 25% to 30%.

Postoperatively, in the intensive care unit (ICU), the patients were mechanically ventilated (Servo ventilator 900 C, Siemens-Elema, Stockholm, Sweden) with a fractional inspired oxygen (FiO$_2$) of 0.4 to 0.6 and with 5 cmH$_2$O positive end-expiratory pressure for patients with internal mammary bypasses. The ICU nurses evaluated the patients’ level of sedation every 30 minutes and recorded the time at which the patients first opened their eyes and responded to a verbal command. For subsequent analgesia and sedation, fentanyl, 0.15 mg, and MID, 5 mg, were given IV when necessary, but not before awakening. Weaning from artificial ventilation was performed on the first postoperative day, and patients were extubated when pH remained 7.35 or above and arterial oxygen pressure (PaO$_2$) greater than 100 mmHg with an FiO$_2$ of less than 0.6 during 1 hour on continuous positive airway pressure. All patients remained in the ICU for at least 2 nights regardless of their clinical status.

Routine clinical monitoring using a 5-lead electrocardiogram and a radial artery invasive blood pressure was started before induction of anesthesia. Standard leads II and modified V$_5$ were continuously monitored and used for ST segment analysis to detect myocardial ischemia (Marquette Electronics Inc series 7010 recorder, Milwaukee, WI). Myocardial ischemia was defined as new downsloping or horizontal ST-segment depression of more than 1 mm or ST elevation of more than 2 mm, measured 60 ms from the J-point and lasting at least 2 minutes. A thermocoupled pulmonary artery catheter, placed through the right internal jugular vein after induction of anesthesia, was used for measurement of cardiac output (CO), central venous pressure (CVP), mean pulmonary artery pressure, and pulmonary artery capillary wedge pressure. CO was determined using the thermodilution method, and triplicate values (of measurements with intermeasurement variability of <10%) were averaged. During CPB, the pump flow rate was used for CO and CVP was determined as 0. Hemodynamic and pulmonary calculations (systemic vascular resistance, pulmonary vascular resistance, and pulmonary shunt [Qs/Qt]) were derived from standard formulas in the Marquette 7010 monitor. Measurements were made before the skin incision (T$_1$), during CPB 10 minutes after aortic cross-clamping (T$_2$), during CPB 10 minutes after release of the aortic cross-clamp (T$_3$), 10 minutes after the end of CPB (T$_4$), and 1 hour after admission to the ICU (T$_5$). Arterial and mixed venous (or venous during CPB) blood gas analysis was performed using an automatic blood gas analyzer (ABL 4 Acid-base Laboratory, Radiometer, Copenhagen, Denmark).

The primary objective for all patients was an arterial pressure within 20% of baseline values. Hemodynamic deviations were primarily adjusted by specific escape vasoactive drugs. Hypertension was treated with ketanserin in divided 10-mg doses. Ketanserin is a 5-HT$_2$ receptor blocker with central α$_1$-adrenoceptor blocking properties. It is suitable to prevent and treat hypertension during and after CABG. Hypotension before or after CPB was treated with ephedrine, 5 mg in bolus doses. Hypotension during CPB (MAP <50 mmHg with normal flow) was treated with phenylephrine, 0.25 to 0.5 mg bolus doses. When hypotension persisted despite vasopressor therapy, the administration of MID or ISO was stopped. Tachycardia was treated with metoprolol, 2.5 to 5 mg IV. Bradycardia associated with hypotension was treated with ephedrine or with external atrial or ventricular pacing at the end of CPB. Persistent low cardiac output was treated with filling adjustment and dopamine infusion.

The main data are presented as mean and SD. Statistical comparisons within and between the two groups were done using paired and unpaired Student’s t-test for continuous data with normal distribution. Comparisons of blood pressure at different times between groups were performed using the area under the curve method. When distribution was not normal, the Wilcoxon rank-sum test or the Mann-Whitney U-test was performed. The chi-square test was used for ordinal patient data. A $p$ value of <0.05 was considered significant.

**RESULTS**

There were no significant differences in the general characteristics of the patients and the surgical data (Table 1). The total perioperatively administered dose of fentanyl was 3.9 mg (SD = 0.7) in the MID group versus 3.6 mg (SD = 0.8) in the ISO group. The maintenance dose of MID was 23.9 mg (SD = 5.3) during 218 minutes (SD = 42) of administration. The calculated dose of liquid isoflurane consumed during a mean of 187 minutes (SD = 48) of administration was 22.7 mL (SD = 6.2).

During surgery, there were few statistically significant differences in systemic hemodynamics between both groups (Table 2). Mean arterial pressure before incision (T$_1$), which occurred
Table 1. Demographics and Other Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group MID</th>
<th>Group ISO</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61 (4)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 (14)</td>
<td>77 (14)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (10)</td>
<td>170 (8)</td>
</tr>
<tr>
<td>Cardiac medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>11/15</td>
<td>11/15</td>
</tr>
<tr>
<td>Nitrates</td>
<td>8/15</td>
<td>10/15</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>3/15</td>
<td>6/15</td>
</tr>
<tr>
<td>Molsidomin</td>
<td>5/15</td>
<td>5/15</td>
</tr>
<tr>
<td>Previous MI</td>
<td>10/15</td>
<td>9/15</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>10/15</td>
<td>9/15</td>
</tr>
<tr>
<td>III</td>
<td>5/15</td>
<td>6/15</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>131 (39)</td>
<td>132 (48)</td>
</tr>
<tr>
<td>Ischemic time (min)</td>
<td>70 (29)</td>
<td>69 (30)</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>388 (55)</td>
<td>366 (59)</td>
</tr>
<tr>
<td>Cardioplegia (mL)</td>
<td>984 (316)</td>
<td>1,039 (426)</td>
</tr>
<tr>
<td>No. of grafts</td>
<td>3.3 (1.1)</td>
<td>3.4 (1.2)</td>
</tr>
</tbody>
</table>

NOTE. Values represent mean (SD of mean between brackets) or number of patients.
Abbreviations: MI, myocardial infarction; CPB, cardiopulmonary bypass, NYHA, New York Heart Association.

about 15 to 30 minutes after the start of the maintenance anesthetic, was lower in the ISO group, and heart rate after weaning from CPB (T4) was significantly higher in the MID group.

Figure 1 shows the course of systolic arterial pressure (SAP) during surgery and early ICU admission. SAP in the pre-CPB period was comparable before the start of either ISO or MID, but thereafter was lower in the ISO group during the whole pre-CPB period. In the post-CPB period, there were no significant differences in SAP between the groups, although SAP

Table 2. Hemodynamics Before, During, and After CPB

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q (L/min/m²)</td>
<td>MID</td>
<td>2.4 (0.8)</td>
<td>2.0 (0.2)</td>
<td>2.3 (0.2)</td>
<td>3.9 (1.0)</td>
<td>3.0 (0.8)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>2.2 (0.3)</td>
<td>1.9 (0.2)</td>
<td>2.4 (0.1)</td>
<td>3.6 (0.5)</td>
<td>3.1 (0.5)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>MID</td>
<td>61 (11)</td>
<td>—</td>
<td>—</td>
<td>68 (8)*</td>
<td>77 (10)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>64 (18)</td>
<td>—</td>
<td>—</td>
<td>78 (12)*</td>
<td>74 (15)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>MID</td>
<td>76 (11)*</td>
<td>71 (11)</td>
<td>66 (14)</td>
<td>60 (9)</td>
<td>78 (16)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>64 (9)*</td>
<td>64 (11)</td>
<td>71 (13)</td>
<td>60 (8)</td>
<td>79 (12)</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>MID</td>
<td>14 (4)</td>
<td>—</td>
<td>—</td>
<td>20 (5)</td>
<td>19 (4)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>15 (5)</td>
<td>—</td>
<td>—</td>
<td>19 (4)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>MID</td>
<td>7 (3)</td>
<td>—</td>
<td>—</td>
<td>8 (2)</td>
<td>8 (4)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>7 (3)</td>
<td>—</td>
<td>—</td>
<td>7 (3)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>MID</td>
<td>6 (2)</td>
<td>—</td>
<td>—</td>
<td>8 (3)</td>
<td>8 (4)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>6 (2)</td>
<td>—</td>
<td>—</td>
<td>8 (3)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>SVR (dyne × s × cm⁻⁵)</td>
<td>MID</td>
<td>1,306 (340)</td>
<td>1,411 (237)</td>
<td>1,186 (283)</td>
<td>618 (185)</td>
<td>1,123 (390)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>1,168 (362)</td>
<td>1,202 (200)</td>
<td>1,234 (200)</td>
<td>630 (148)</td>
<td>1,207 (247)</td>
</tr>
<tr>
<td>PVR (dyne × s × cm⁻⁵)</td>
<td>MID</td>
<td>140 (59)</td>
<td>—</td>
<td>—</td>
<td>160 (97)</td>
<td>168 (79)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>172 (74)</td>
<td>—</td>
<td>—</td>
<td>138 (48)</td>
<td>153 (53)</td>
</tr>
</tbody>
</table>

NOTE. Data represent mean and SD (between parentheses).
Abbreviations: Q, cardiac index or pump flow per m²; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; T1, before skin incision; T2, 10 minutes after aortic cross-clamping; T3, 10 minutes after release of the aortic cross-clamp; T4, 10 min after the end of CPB; T5, 1 hour after ICU admission; HR, heart rate; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

* p < 0.05.
Table 3. Pharmacologic Intervention With Vasoactive Drugs and Frequency of the Need for Temporary Cessation of Hypnotic Supplementation

<table>
<thead>
<tr>
<th></th>
<th>Group MID</th>
<th>Group ISO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-CPB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketanserin</td>
<td>9 (24 mg, SD = 12)</td>
<td>1 (10 mg)*</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>During CPB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketanserin</td>
<td>9 (26 mg, SD = 12)</td>
<td>8 (19 mg, SD = 11)</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Post-CPB in OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketanserin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>7 (9 mg, SD = 6)</td>
<td>11 (8 mg, SD = 3)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Cessation of hypnotic supplementation 4 (34 min, SD = 13) 10 (38 min, SD = 24)*

NOTE. Values represent number of patients. Values between brackets represent mean and SD.
*p < 0.05 for differences between ISO and MID groups.

Table 4. Blood Gas and Oxygenation Data

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH4</td>
<td>MID</td>
<td>7.38 (0.04)</td>
<td>7.36 (0.03)</td>
<td>7.36 (0.06)</td>
<td>7.42 (0.05)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>7.42 (0.04)</td>
<td>7.39 (0.04)</td>
<td>7.36 (0.07)</td>
<td>7.41 (0.05)</td>
</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>MID</td>
<td>36 (4)</td>
<td>38 (4)</td>
<td>39 (4)</td>
<td>34 (4)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>33 (4)</td>
<td>36 (4)</td>
<td>38 (7)</td>
<td>36 (5)</td>
</tr>
<tr>
<td>PaO2 (mmHg)</td>
<td>MID</td>
<td>216 (47)</td>
<td>218 (47)</td>
<td>153 (52)</td>
<td>178 (51)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>212 (41)</td>
<td>236 (50)</td>
<td>123 (58)</td>
<td>144 (47)</td>
</tr>
<tr>
<td>SvO2 (%)</td>
<td>MID</td>
<td>79 (6)</td>
<td>77 (8)</td>
<td>78 (7)*</td>
<td>71 (4)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>77 (6)</td>
<td>80 (6)</td>
<td>70 (5)*</td>
<td>70 (10)</td>
</tr>
<tr>
<td>HCO3 (mEq/L)</td>
<td>MID</td>
<td>21.3 (1.4)</td>
<td>21.4 (1.6)</td>
<td>21.2 (1.8)</td>
<td>22.0 (2.0)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>21.5 (1.3)</td>
<td>21.7 (1.5)</td>
<td>21.2 (2.1)</td>
<td>21.9 (1.8)</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td>MID</td>
<td>12.4 (1.5)</td>
<td>7.7 (0.8)</td>
<td>8.6 (0.8)</td>
<td>10.7 (0.8)</td>
</tr>
<tr>
<td></td>
<td>ISO</td>
<td>12.3 (1.7)</td>
<td>7.9 (0.8)</td>
<td>8.3 (0.9)</td>
<td>10.4 (1.1)</td>
</tr>
</tbody>
</table>

NOTE. Data represent mean and SD.
Abbreviations: SvO2, mixed venous or venous (during CPB) oxygen saturation; T1, before skin incision; T2, 10 minutes after release of the aortic cross-clamp; T3, 10 minutes after the end of CPB; T4, 1 hour after ICU admission.
*p < 0.05 for differences between ISO and MID groups.

This study shows that both MID and ISO, as adjuncts to moderate-dose fentanyl (up to 50 μg/kg), generally produced satisfactory perioperative hemodynamic conditions during elective CABG. They did not, however, prevent all hypertensive tendencies to be lower in the ISO group at sternal closure and end of surgery.

The need for vasoconstrictor/inotropic or hypotensive support in each of the two groups is given in Table 3. During the incision-CPB interval, ketanserin was required more frequently and in higher dosage in patients from the MID group than in the ISO group (p < 0.05). During CPB, there was no statistically significant difference in ketanserin or phenylephrine requirements. No patient in either group received ketanserin in the post-CPB period. All patients were successfully weaned from CPB at the first attempt, and temporary inotropic support with dopamine was required in two MID patients compared with one patient in the ISO group. In the post-CPB period, there was no significant difference in the incidence and dose of ephedrine requirements. Inotropic support in the ICU was necessary in one patient from the MID group and two ISO patients. There were no statistically significant differences in the postoperative requirements for hypotensive agents in the ICU. There was a statistically higher incidence in the need to discontinue the hypnotic supplement because of persistent hypotension (Table 3). Temporary cessation of MID was required in four patients for a mean of 34 minutes (SD = 13), whereas ISO had to be discontinued in 10 patients for 36 minutes (SD = 24), mostly in the post-CPB period.

Evidence of transient myocardial ischemia from ST-segment analysis in the pre-CPB period occurred in one patient in the MID group compared with two in the ISO group. Postoperative creatine kinase MB isoenzyme activity on the first postoperative day was 21.1 U/L (SD = 14.4) in the ISO group and 22.1 U/L (SD = 21.6) in the MID group.

Table 4 shows the oxygenation and blood gas values at time points T1, T2, T4, and T5. There were no significant differences, except for a lower mixed venous oxygen saturation (SvO2) after weaning from CPB in the ISO group. Although there was no difference in mean SvO2 at 1 hour after ICU admission, two patients, both from the ISO group, had a critically low SvO2 of <50%. The PaO2/FiO2 ratio, which was comparable in both groups after induction of anesthesia, showed a strong decrease after CPB and postoperatively in either group, although the decrease tended to be greater in the ISO group (Table 5). Although the individual differences were not statistically significant, they were consistent at the three postoperative time points. Also, Qs/Qt, determined at 1 hour after ICU admission, tended to be lower in the ISO group (p = 0.055).

Time to awakening and to tracheal extubation, and the amount of fentanyl and midazolam administered in the time between ICU admission and extubation, were not significantly different between the two groups (Table 5). Discharge from ICU was also comparable in both groups. Only one patient, from the MID group, had an ICU stay of more than 4 nights because of a gram-negative sepsis.

DISCUSSION

This study shows that both MID and ISO, as adjuncts to moderate-dose fentanyl (up to 50 μg/kg), generally produced satisfactory perioperative hemodynamic conditions during elective CABG. They did not, however, prevent all hypertensive tendencies to be lower in the ISO group at sternal closure and end of surgery.

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ISO, as an adjunct to opioids, has been shown to produce stable hemodynamics overall difference between them was that, in the doses investigated, a significantly higher frequency and dose of antihypertensive escape medication during the pre-CPB period were required in the MID-supplemented group than in the ISO group. In contrast, ISO had to be stopped more frequently in the post-CPB period because of hypotension.

ISO was selected as the volatile agent of choice. Despite controversy about possible "coronary steal," ISO, as an adjunct to opioids, has been shown to produce stable hemodynamics during cardiac surgery with no greater risk of myocardial ischemia compared with pure high-dose opioid anesthesia.7,8 These authors used even higher concentrations of isoflurane episodes, and both can lead to episodes of hypotension. The overall difference between them was that, in the doses investigated, a significantly higher frequency and dose of antihypertensive escape medication during the pre-CPB period were required in the MID-supplemented group than in the ISO group. In contrast, ISO had to be stopped more frequently in the post-CPB period because of hypotension.

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The favorable hemodynamic effects of MID reported in patients with coronary artery disease5,10-12 have been confirmed in a recent study of Messina et al,13 in which a bolus of 0.1 mg/kg of MID was given between induction and incision. MID did not affect cardiac index in the entire study population despite a decrease in systolic function. The apparent myocardial depression was offset by a similar decrease in afterload. Even in high-risk patients with reduced preoperative ejection fraction, the mild adverse effects of MID were not greater. The MID dosing in this study (0.05 to 0.1 mg/kg/h) was higher than reported by Theil et al,14 who found that MID infusion rates between 0.025 and 0.04 mg/kg/hour as adjunct to fentanyl (30 to 35 µg/kg total dose) provided excellent hemodynamic stability in CABG patients with opioid drug concentrations lower than techniques based on fentanyl alone. However, they used much higher intraoperative doses of vasodilators and allowed the use of β-blockers and inhalation agents to treat hypertension.

This study could not show a difference in postoperative awakening, sedative and analgesic requirements, extubation, and ICU discharge between the MID and ISO groups. The figures for extubation and ICU discharge agree with those summarized from the literature by Mora et al4 for several different anesthetic techniques for myocardial revascularization. This shows that nonanesthetic factors largely determine the timing of extubation and that only high-dose opioid anesthesia techniques require prolonged ventilatory support compared with balanced techniques. This study, although not primarily intended to favor early extubation, showed no difference in postoperative duration of sedative-hypnotic effects between ISO or MID, and equal amounts of sedative-analgesic maintenance medication were required. The use of MID supplementation in the setting of early extubation needs to be further investigated to determine its optimal dosing regimen.

Greater impairment in oxygenation after CPB was found in the ISO group than in the MID group. Cardiac surgery is frequently followed by impaired oxygen exchange, which is due not only to increased extravascular lung water, but also to atelectasis in dependent lung areas.15 The difference between MID and ISO might be explained by the inhibition of hypoxic pulmonary vasoconstriction induced by ISO and a subsequently greater pulmonary shunt.16 The PaO2/FIO2 ratio used in this study is a simple and reliable measure of the extent of pulmonary shunt and impairment of oxygenation when the range of FIO2 is small (between 0.4 and 0.6).17 It remains, however, difficult to explain why this difference in shunt between the ISO and MID groups persisted for several hours after the end of anesthesia.

This study confirms previous observations that the choice of prebypass anesthetic does not affect cardiac outcome, but that agents used to supplement opioids such as the volatile agents and the benzodiazepines can prevent hypertension. They can, however, also lead to hypotensive episodes.18-21 The route of administration and the careful titration of the drug dose with the effect may be more important in "balanced anesthesia" for heart surgery than the drugs themselves.3

In conclusion, this study shows that both MID, 0.05 to 0.1 mg/kg/h, and ISO, 0.5 MAC, are adequate adjuncts to moderate doses of fentanyl to control perioperative hemodynamics during CABG. Further study of the optimal dose regimen of MID with respect to early extubation techniques, and of the possible effects of ISO on the postoperative impairment of oxygenation in CABG, is warranted.
REFERENCES


