The Minimum Alveolar Concentration of Isoflurane in Patients Undergoing Bilateral Tubal Ligation in the Postpartum Period

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Background: The minimum alveolar concentration (MAC) of volatile anesthetics is decreased during pregnancy, but MAC in the early postpartum period has not been reported. The aim of this study was to determine the MAC of isoflurane and to evaluate the relation between MAC and serum progesterone and β-endorphin concentrations after delivery.

Methods: Eight patients undergoing elective bilateral tubal ligation during general anesthesia in the early postpartum period (<12 h postpartum) and eight patients undergoing this procedure in the late postpartum period (12–25 h postpartum) were studied. Eight patients undergoing bilateral tubal ligation more than 6 weeks after delivery served as control subjects. Anesthesia was induced with propofol and maintained with isoflurane in oxygen to a steady end-tidal concentration of 0.8–1.0 vol% for 10 min. Reaction to a standardized electric stimulation applied to the forearm was graded as positive (gross or delayed movement) or negative. By using the bracketing technique, the concentration of isoflurane was increased or decreased by 0.1 vol%, depending on the positive or negative response.

Results: The MAC (mean ± SD) in patients in the early postpartum period was significantly less (0.75 ± 0.17 vol%) than in control subjects (1.04 ± 0.12 vol%; P < 0.01) and in patients in the late postpartum period (0.95 ± 0.2 vol%; P < 0.05). The difference in MAC values between late and control was not significant (P > 0.05).

Conclusions: Isoflurane MAC remains 28% less than normal within the 1st 12 h postpartum and then returns to normal 12–25 h after delivery. (Key words: Anesthesia, obstetric; postpartum. Anesthetics, intravenous: propofol. Anesthetics, volatile: isoflurane. Hormones: β-endorphin; progesterone. Potency, anesthetic: minimum alveolar concentration.)

MANY women undergo tubal ligation during general anesthesia within 24–56 h after delivery. The interval between delivery and surgery may even be decreasing with new discharge policies of 24–36 h after normal delivery in healthy patients. However, the anesthetic requirements of inhalation agents for this population of patients has not yet been studied.

Minimum alveolar concentration (MAC), defined as the alveolar concentration of an anesthetic preventing purposeful movement in 50% of patients in response to a painful stimulus, is recognized as a standard for anesthetic potency and anesthetic requirement.2,3 Many physiologic and pharmacologic variables, including pregnancy, alter MAC.3,4 During pregnancy, MAC for isoflurane decreases by 40% in ewes,4 whereas MAC for halothane decreases by 16–19% in rats.5 Recently, it has been shown that isoflurane MAC is decreased by 28% in pregnant women at 8–12 weeks’ gestation.6 The mechanism underlying the decrease in MAC during pregnancy remains unknown. However, it has been suggested that this decrease in anesthetic requirement may be associated with progressive increases in progesterone and β-endorphin during gestation.7–9

This study was designed to determine the MAC of isoflurane in patients undergoing bilateral tubal ligation by the tetanic stimulation method10 after delivery and to evaluate the relation between MAC and serum concentration of isoflurane.

Materials and Methods

This study was approved by the Mississippi Medical Center Institutional Review Board. Twenty-four women undergoing bilateral tubal ligation for general anesthesia, with signed informed consent. They were assigned to control group or one of two early postpartum groups: 0–6 h postpartum; and 7–12 h postpartum. Exclusion criteria were drug abuse, coagulopathy, normal blood pressure, hypertension (measured either systolic or diastolic), serum electrolyte, liver function abnormalities, and a history of chronic procliniad antagonists, benzodiazepines, or sedatives exceeding 3 weeks.

All patients were given metoclopramide before surgery. Anesthesia was induced intravenously with propofol and maintained through the tracheal route with isoflurane in oxygen. After tracheal intubation, anesthesia was administered with 2.0 vol% for 10 min. Ventilation was continued with 8.0–10.0 ml/kg at a rate of 8 l/min. End-tidal isoflurane concentrations were maintained at 0.5–1.0 vol% and were increased in the late postpartum group by 0.2 vol% to maintain an end-tidal isoflurane concentration of 0.2–0.4 vol%, which was determined by a calibrated infrared gas analyzer interfaced to a respiratory gas monitor. A gas analyzer was used to determine the end-tidal isoflurane concentration at 0.20-ms sample intervals, and the end-tidal isoflurane concentrations were determined with the tetanic stimulation method.

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Materials and Methods

This study was approved by the University of Mississippi Medical Center Institutional Review Board. Twenty-four patients, American Society of Anesthesiologists (ASA) physical status 1 or 2, aged 21–38 yr, undergoing elective bilateral tubal ligation during general anesthesia were studied after written informed consent. The patients were divided into three groups according to the duration between delivery and surgery: control group (n = 8): at least 6 weeks postpartum; early postpartum group (n = 8): less than 12 h postpartum; and late postpartum group (n = 8): 12–25 h postpartum. Exclusion criteria were a history of alcohol or drug abuse; severe anemia (hematocrit < 10%); abnormal body temperature (<36°C or >38°C); hypotension (mean blood pressure < 50 mmHg); abnormal serum electrolyte concentrations; impaired renal or liver function; cardiopulmonary disease; or exposure to clonidine, methyl dopa, reserpine, verapamil, lithium, benzodiazepines, or progesterone within the preceding 3 weeks.

All patients received ranitidine (150 mg, oral) and metoclopramide (10 mg, oral) 60–90 min before surgery. Anesthesia was induced with lidocaine (20 mg, intravenous) and propofol (2 mg/kg, intravenous), and the trachea was intubated after administration of succinylcholine (1.5 mg/kg, intravenous).

After tracheal intubation, isoflurane in oxygen was administered to achieve an end-tidal concentration of 2.0 vol% for 10 min with a total gas flow of 10 l/min. Ventilation was controlled with tidal volume of 8–10 ml/kg at a rate of 8–12 breaths/min to keep end-tidal carbon dioxide tension between 26 and 32 mmHg. The end-tidal isoflurane concentration was decreased to 0.7 vol%10 and then was adjusted to maintain a steady concentration of 1.0 vol% in control subjects and patients in the late postpartum period and of 0.8 vol% in patients in the early postpartum period for 10 min. The difference between inspiratory and end-tidal concentration of isoflurane was maintained at about 0.1 vol%. Respiratory gases were continuously monitored by an infrared gas analyzer (Ohmeda 5250 RGM, British Oxygen Company Health Care, Louisville, CO) in all patients.

A painful electric stimulus (60 mA, 50 Hz, 5 s, in 0.20-ms square-wave pulses) was delivered by a peripher- nal nerve stimulator (750 digital, Dackmed, Buffalo, NY) though two electrocardiographic electrodes placed on the volar surface of the dominant forearm, 5 and 13 cm below the skin fold in the cubital fossa and 1 cm to the fingers side from the midline of the forearm, with the positive electrode placed proximally. A positive response was considered to be gross movement of head or extremity. A delayed movement of extremity within 1 min after stimulation also was considered a positive result. However, the movement of the arm on the stimulated side during the tetanic stimulation and the movement caused by endotracheal tube, including coughing and swallowing, were not considered as positive reactions. If a positive response was observed, the concentration of isoflurane was increased by 0.10 vol%. If no response to stimulation occurred, the concentration was decreased by 0.10 vol%. The stimulation was repeated after at least 10 min of establishing a steady end-tidal concentration.

The bracketing technique was used to achieve a pattern of positive—negative—positive or negative—positive—negative responses. The anesthetic concentration midway between that allowing and that preventing movement was the individual MAC value. In each patient the surgical procedure began after determination of isoflurane MAC. Each patient was interviewed within 24 h after surgery for awareness of intraoperative events.

In patients in the early or late postpartum period, 15 min before induction, a venous blood sample (3 ml) was collected from each patient. The plasma concentrations of progesterone were assayed with a radioimmunoassay technique with a sensitivity of 0.1 ng/ml and interassay coefficients of variation of 11.8% at 1.1 ng/ml and 15.9% at 19.9 ng/ml. The plasma concentrations of β-endorphin were assayed by a radioimmunoassay technique with a sensitivity of 14 pg/ml and interassay coefficients of variation of 9% at 190 pg/ml and 7.7% at 892 pg/ml.

Data were analyzed with a statistical program (Systat, Evanston, IL). Student’s unpaired t test and Dunnett’s test were used for analysis of variance among the groups. The effects of independent variables (progesterone or β-endorphin) on a dependent variable (MAC) and the effect of progesterone or β-endorphin versus MAC were analyzed with linear regression. P values less than 0.05 were considered significant.

Results

The demographic data were not significantly different between the three groups (table 1). The durations
Table 1. Demographic Data in Three Groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 8)</th>
<th>&lt;12 h Postpartum (n = 8)</th>
<th>12–25 h Postpartum (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>27.4 ± 6.3</td>
<td>27.1 ± 4.9</td>
<td>26.4 ± 5.0</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77.6 ± 21.9</td>
<td>76.0 ± 22.0</td>
<td>71.5 ± 15.5</td>
</tr>
<tr>
<td>Time after delivery</td>
<td>19.3 ± 20 (mo)</td>
<td>7.3 ± 1.9 (h)</td>
<td>19.6 ± 5.4 (h)</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>NA</td>
<td>35.8 ± 2.9</td>
<td>37.4 ± 3.7</td>
</tr>
<tr>
<td>Duration of 1st stage labor (h)</td>
<td>NA</td>
<td>8.3 ± 4.2</td>
<td>11.8 ± 8.8</td>
</tr>
<tr>
<td>Duration of 2nd stage labor (min)</td>
<td>NA</td>
<td>9.8 ± 10.6</td>
<td>12.4 ± 13.3</td>
</tr>
<tr>
<td>Dose of butorphanol administration during delivery (mg)</td>
<td>NA</td>
<td>1.3 ± 1.0</td>
<td>0.9 ± 1.0</td>
</tr>
<tr>
<td>Time between last dose of butorphanol and induction (h)</td>
<td>NA</td>
<td>9.4 ± 4.8</td>
<td>21.5 ± 6.6</td>
</tr>
<tr>
<td>Time between induction and MAC determination (min)</td>
<td>63.8 ± 13.0</td>
<td>64.4 ± 7.8</td>
<td>75.0 ± 17.3</td>
</tr>
<tr>
<td>Temperature at MAC determination (°C)</td>
<td>36.1 ± 0.6</td>
<td>36.1 ± 0.5</td>
<td>36.6 ± 0.4</td>
</tr>
<tr>
<td>Progesterone concentration (ng/ml)</td>
<td>NA</td>
<td>38.8 ± 21.5</td>
<td>26.0 ± 23.9</td>
</tr>
<tr>
<td>β-Endorphin concentration (pg/ml)</td>
<td>NA</td>
<td>34.9 ± 8.5</td>
<td>37.8 ± 9.7</td>
</tr>
</tbody>
</table>

(mean ± SD) between induction and MAC determination in the control, early postpartum, and late postpartum groups were 63.8 ± 13.0, 64.4 ± 7.8, and 75.0 ± 17.3 min respectively. The body temperature (mean ± SD) at MAC determination in these groups were 36.1 ± 0.6, 36.6 ± 0.5, and 35.6 ± 0.1 degrees respectively. They were not significantly different from each other (table 1).

The MAC (mean ± SD) of isoflurane in patients in the early postpartum period (0.75 ± 0.17 vol%) was significantly different from MAC values in control subjects (P < 0.01) and in patients in the late postpartum period (P < 0.05), whereas the MAC in the late postpartum period (0.95 ± 0.20 vol%) was not significantly different from that in the control group (1.04 ± 0.12 vol%) by Student’s unpaired t test and Dunnnett’s t test.

The MAC value in the early postpartum period at 7.3 h (range 4.5–11 h) after delivery was 28% less than that in the control group. Seven (88%) of eight patients in the early postpartum period and four (50%) of eight patients in the late postpartum period had MAC values lower than the mean value of the control group. The lowest MAC value was 0.45 vol%, which was 57% less than the MAC in control patients.

By linear regression, there was an inverse correlation (fig. 1A) between progesterone concentration postpartum and time after delivery (r = -0.527; P = 0.036) but no relation between β-endorphin concentration and time after delivery (fig. 1B) (r = 0.089; P = 0.744).

Linear regression analysis of plasma progesterone (r = 0.005; P = 0.985) or β-endorphin (r = 0.154; P = 0.568) against MAC showed no correlation (fig. 1C and 1D), a result confirmed by multiple regression (r = 0.166; P = 0.950).

Discussion

Previous studies have demonstrated that MAC during pregnancy is decreased by 28% (isoflurane) in humans, by 40% (isoflurane) in ewes, and by 19% (halothane) in rats. In this study the MAC of isoflurane was decreased by 28% in the 1st 12 h of the postpartum period.

Traditionally, MAC determination in humans has involved inhalation anesthetics to eliminate the synergistic effect of intravenous anesthetic agents given during induction of anesthesia. However, in the postpartum period, the risk of aspiration of gastric contents is well recognized, prompting us to use propofol, a short-acting induction agent, with application of Sellick’s maneuver to intubate the trachea rapidly. After a single bolus injection of 2 mg/kg propofol, the concentration in blood at 1 h decreases to 0.28 μg/ml in patients postpartum and 0.5 μg/ml in pregnant patients, concentrations comparable with those in non-pregnant women (0.54 μg/ml). These blood propofol concentrations are less than the concentration (0.7 μg/ml) at the time of awakening, suggesting that the residual concentration of propofol 1 h after induction may have minimal effects on the central nervous system. Furthermore, the MAC of isoflurane in our control group (64 min after propofol injection) was similar to the isoflurane induction dose of 0.5 MAC for a minimal clinical effect.

Patients’ carbon dioxide partial pressure (CPA) that would produce MAC differences after the postpartum period would be 37.2 to 141 mm Hg when arterial pH levels range from 42 to 1.4 mm Hg.

Recently, a number of studies have suggested that the MAC of isoflurane in patients is an individual value in a period of time after delivery. Isoflurane (0.5 vol%) is suitable for use in anesthetized patients (adjusted to 0.7 vol%) in the postpartum period without verifying the equilibrium of MAC at least 1 h before the procedure.

The MAC of isoflurane (0.5 vol%) appears to be about 0.15 vol% (1.15 vol%) over the MAC of isoflurane in normal patients (0.15 vol%) adjusted to 0.7 vol% for the difficult macrolideinduced arm.
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Fig. 1. Linear regression analysis. A reverse correlation was found between progesterone concentration and time after delivery (A) ($r = -0.527; P = 0.036$). However, no correlation was found between $\beta$-endorphin concentration and time (B) ($r = 0.089; P = 0.744$). There was no correlation between isoflurane minimum alveolar concentration (MAC) and progesterone concentration (C) ($r = 0.005; P = 0.985$) or between isoflurane MAC and $\beta$-endorphin concentration (D) ($r = 0.154; P = 0.568$).

The isoflurane MAC obtained by others using inhalation induction of anesthesia.\textsuperscript{6, 21} This finding suggests that an induction dose (2 mg/kg) of propofol may have minimal effect on MAC after 1 h.

Patients’ lungs were ventilated to keep end-tidal carbon dioxide tension between 26 and 32 mmHg, a level that would produce normocapnia in patients in the postpartum period and hypocapnia in the control group. However, MAC is unaffected by hyperventilation when arterial carbon dioxide tension is reduced from 42 to 14 mmHg.\textsuperscript{22}

Recently, the electric tetanic stimulation technique with cutaneous electrodes has been used to determine the MAC value in humans.\textsuperscript{6, 10, 21, 23} This noninvasive method has the advantage of determining MAC in individual subjects and observing the change of MAC over a period of time. Our study shows that the MAC of isoflurane in healthy nonpregnant women (1.04 ± 0.12 vol%) is similar to the isoflurane MAC of 1.05 vol% (adjusted to sea level)\textsuperscript{25} determined by the same method in ASA physical status 1 or 2 adult patients, verifying that this method is reliable and repeatable. The MAC for isoflurane with tetanic stimulation (1.04 vol%) appears to be less than the MAC with skin incision (1.15 vol%). This discrepancy has been attributed to the difficulty in evaluation of movements of a stimulated arm or by the different intensities of stimulation.\textsuperscript{21}

The anesthetic-sparing effect of opioids is well known.\textsuperscript{24, 25} Large doses of butorphanol ($\geq 0.1$ mg/kg, intravenous) decrease the MAC for enflurane by 11%,\textsuperscript{25} but smaller doses of butorphanol (22 mg and 44 mg/kg, intravenous) have no significant effect on MAC.\textsuperscript{26} In our study, even smaller doses of intravenous butorphanol (about 15 mg/kg) were administered for pain control 5–28 h before induction of anesthesia. Five hours after a single intravenous injection (2 mg), the plasma concentration of butorphanol decreases 29 times (from 20 to 0.7 ng/ml)\textsuperscript{27}; therefore, the MAC value in this study is unlikely to have been affected by residual serum butorphanol.

The mechanism explaining the decrease in MAC during pregnancy and early postpartum period is unclear. Selye was the first to report that steroids such as progesterone possessed anesthetic activity.\textsuperscript{28} Intravenous progesterone can induce sleep in women\textsuperscript{29} and decrease halothane MAC in nonpregnant rabbits.\textsuperscript{30} The increase in $\beta$-endorphin during pregnancy may decrease anesthetic requirements.\textsuperscript{30, 31} However, a recent study shows no correlation between serum progesterone and MAC in pregnant women at 8–12 weeks’ gestation.\textsuperscript{9} Similarly, our study shows no correlation between serum progesterone or $\beta$-endorphin and isoflurane MAC in the postpartum period. Alternatively, MAC may be affected by other factors. Putative candidates.
as 5α-dehydroprogesterone and 3α-hydroxy-allopregnan-20-one (metabolites of progesterone), potent inhibitors of the central nervous system (CNS), β-lipotropin, the precursor of β-endorphin, and serotonin. In addition, whether MAC is directly influenced by the substance in the plasma or in the cerebrospinal fluid has not been determined. It is recognized that plasma concentrations of β-endorphin do not correlate with the concentrations in the cerebrospinal fluid.

In conclusion, our study demonstrates that the MAC of isoflurane is 28% less than normal within the first 12 h postpartum and returns to normal at 12–25 h after delivery. Further studies are required to elucidate the mechanism responsible for the decrease in isoflurane MAC during early postpartum period.

References