Women Emerge from General Anesthesia with Propofol/Alfentanil/Nitrous Oxide Faster than Men


Background: Recovery from general anesthesia is governed by pharmacodynamic and pharmacokinetic factors. Gender has not previously been recognized as a factor influencing the time to emergence from general anesthesia.

Methods: This multicenter study was originally designed to measure the effects of the bispectral index on intraoperative anesthetic management and patient recovery. We compared the wake-up and recovery times of 274 adults after propofol/alfentanil/nitrous oxide anesthesia. Patients were randomly assigned to have the titration of propofol performed with or without the use of bispectral index monitoring. Specific guidelines were given for the titration of drugs. The aim in all cases was to provide a safe anesthetic with the fastest possible recovery.

Results: There was a significant reduction in propofol dose, time to eye opening, and response to verbal command when the anesthetic was titrated using the bispectral index. Unexpectedly, gender proved to be a highly significant independent predictor for recovery time. Women woke significantly faster than men; the time from end of anesthesia to eye opening was 7.05 versus 11.22 min, \(P < 0.05\), and response to verbal command was 8.12 versus 11.67 min, \(P < 0.05\). These differences were significant at all four study sites and in each treatment group. Men consistently had prolonged recovery times compared to women, \(P < 0.001\). There was no difference in the dose of anesthetic used between gender.

Conclusions: Gender appears to be an important variable in recovery from general anesthesia. These findings may explain the increased reported incidence of awareness in women (three times more frequent) and support the need to include gender as a variable in pharmacokinetic and pharmacodynamic studies of anesthetic drugs. (Key words: Bispectral index; gender difference; recovery.)

RECOVERY from general anesthesia is dependent on factors governing drug sensitivity and drug disposition. Sleep may be prolonged in patients with increased central nervous system responses to depressant drugs (e.g., patients who are hypothermic) or factors affecting redistribution and metabolism of drugs (e.g., patients who have hepatic or renal dysfunction). Gender has not previously been reported to influence the speed of recovery after general anesthesia. As part of a multicenter study designed for a different purpose, we discovered a large and unexpected difference in the recovery times of men and women. The difference was significant in four separate institutions and occurred despite the use of a highly standardized anesthetic technique.

Materials and Methods

The study was designed to determine the role of a new processed electroencephalographic monitor in the delivery of anesthesia. The bispectral index (BIS) is a dimensionless parameter (0–100) derived from the cortical electroencephalogram, which has been shown to corre-
late with measures of drug-induced sedation and hypnosis.\textsuperscript{2,3} Awake values of BIS generally range from 90 to 100, and values less than 60 indicate a very low probability of response to verbal command. The current study was designed to test the hypothesis that use of this measurement would improve the titration of hypnotic drugs and lead to faster or better recovery. The results of the study with respect to the usefulness of the monitor have been presented elsewhere.\textsuperscript{4}

After obtaining Institutional Review Board approval and written informed patient consent, adult men and women patients, aged 18–80 yr, American Society of Anesthesiologists physical status I, II, or III, scheduled for general surgical, gynecologic, urologic, ear–nose–throat, or orthopedic procedures expected to last at least 1 h were studied from four institutions. All subjects received similar premedication: midazolam, 1 to 2 mg intravenously, fluid load (500 ml), and induction regimens consisting of propofol 1 to 2 mg/kg and alfentanil less than 30 µg/kg. After loss of consciousness, infusions of propofol at 140 µg·kg\textsuperscript{-1}·min\textsuperscript{-1} and alfentanil, 0.5 µg·kg\textsuperscript{-1}·min\textsuperscript{-1} with 50% nitrous oxide (N\textsubscript{2}O) were started and, if necessary, a neuromuscular blocking agent was administered to facilitate placement of an endotrachal tube. Additional neuromuscular blocking agents were administered as surgically indicated.

During a preliminary baseline phase, recovery data from 34 patients receiving propofol/alfentanil/N\textsubscript{2}O anesthesia were collected to study preexisting clinical practice. This group formed the historical control (control) and the data was used to test for potential learning bias or changing clinical practice during the course of the trial. After the historical controls were enrolled, subsequent patients were randomized to one of the two treatment groups (defined below).

In addition to standard monitoring, patient level of consciousness was monitored using the BIS (Aspect Medical Systems Inc., Natick, MA). The patients were randomly assigned to two groups: in one group of patients, the propofol component of the anesthetic was titrated to keep the BIS between 45–60 (BIS group), whereas in the other group, propofol was adjusted based on usual signs of inadequate anesthesia (standard practice group [SP]). The aim in both groups was to provide the fastest wake-up with or without information regarding BIS.

Approximately 15 min before the end of surgery, anesthesia was reduced in both groups to facilitate rapid recovery. In the BIS group, alfentanil infusions were discontinued, and propofol infusions were adjusted to achieve a BIS in the 60–75 range. This range was maintained until 5 min before the end of surgery, when the propofol infusion and N\textsubscript{2}O in both groups were discontinued and the patient was allowed to awaken. In the SP group, the anesthesia care provider was asked to titrate the delivery of the anesthetic drugs to achieve the most rapid emergence. Time from discontinuation of propofol and N\textsubscript{2}O to eye opening and response to verbal command was assessed for all patients. When it became apparent that average recovery times were different for men and women, an \textit{a posteriori} analysis of gender effect was performed.

Differences in endpoint values between the male and female groups were evaluated using chi-square analysis for categoric and ordinal endpoints and Student \(t\) tests for normally distributed continuous endpoints. Endpoint values were tested for normality using the Kolmogorov–Smirnov statistic. Non-normally distributed continuous endpoints were log-transformed to achieve normality. Student \(t\) tests were used to compare the log-transformed values and the results were compared with those obtained using the Mann–Whitney (nonparametric) statistic on the nontransformed values. The survival functions (distributions of time until recovery) were compared using the Kaplan–Meier procedure. A factorial analysis was used to evaluate the contribution of various factors and covariates to the observed recovery times. Statistical significance was defined as a \(P\) value of 0.05.

**Results**

Ninety-six men and 178 women completed the study. (The male to female ratio in the control group, SP group, and BIS group were 18:16, 41:84, and 37:78 respectively). The categories of surgical procedures were shown in table 1. As hypothesized, titration with BIS proved to be a strong predictor for rapid recovery and lower drug dosage.\textsuperscript{3} Gender was an independent predictor for recovery. There were no statistically significant gender differences in the doses of propofol and alfentanil used (table 1) or in the intraoperative and preoperative BIS values (table 2). Women woke significantly faster than men. The time from discontinuation of propofol infusion to eye opening was 7.0 ± 5.2 min (mean ± SD) in women \textit{versus} 11.2 ± 8.6 min in men \((P < 0.05; \ t\ test);\) time to respond to verbal command was 8.12 ± 6.23 min \textit{versus} 11.67 ± 8.61 min in women.
Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 96)</th>
<th>Female (n = 178)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41 ± 15</td>
<td>40 ± 13</td>
<td>0.69</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85 ± 15</td>
<td>76 ± 20</td>
<td>0.0001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178 ± 8</td>
<td>163 ± 6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Duration of anesthesia (hr)</td>
<td>1.8 ± 0.77</td>
<td>2.0 ± 1.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Total propofol dose (mg)</td>
<td>1,093 ± 508</td>
<td>1,119 ± 698</td>
<td>0.73</td>
</tr>
<tr>
<td>Propofol dose (mg · kg⁻¹ · min⁻¹)</td>
<td>0.13 ± 0.03</td>
<td>0.13 ± 0.03</td>
<td>0.88</td>
</tr>
<tr>
<td>Total alfentanil dose (µg)</td>
<td>5,506 ± 2,769</td>
<td>5,862 ± 3,334</td>
<td>0.37</td>
</tr>
<tr>
<td>Alfentanil dose (µg · kg⁻¹ · min⁻¹)</td>
<td>0.64 ± 0.23</td>
<td>0.68 ± 0.22</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Surgical procedure category*  
Upper abdominal | 2 (2) | 6 (3) |
Lower abdominal | 40 (42) | 79 (45) |
Laparoscopic | 14 (15) | 55 (31) |
Peripheral limb | 36 (37) | 32 (18) |
Other | 4 (4) | 6 (3) |

Data are mean ± SD. Numbers in parentheses are percentages.  
* P = 0.001 (chi-square test).

and men, respectively (P < 0.05; t test). Similar statistically significant differences were observed when wake-up time distributions were analyzed using the nonparametric Mann-Whitney test (table 2). These differences were statistically significant at all four study sites. When analysis of the individual groups (control, SP, and BIS groups) was performed, the gender difference in wake-up times remained statistically significant (fig. 1). Use of the Bonferroni correction resulted in an identical statistical outcome.

A factorial analysis found that gender (P = 4.61 × 10⁻⁶) and patient randomization (control, SP, or BIS; P = 4.61 × 10⁻⁶) were the only two independent predictors of time to eye opening, whereas gender (P = 0.000122), patient randomization (P = 1.005 × 10⁻⁷), and duration of surgery (P = 0.00868) were the only independent predictors of time to eye opening (both P < 0.01). There was no statistically significant difference in the prerecovery BIS between gender within each group.

Figure 1. The time in minutes (raw data and mean ± SD) to eye opening after discontinuation of propofol administration in bispectral index (BIS), standard practice, and control groups. Gender and randomization group are both independent predictors of time to eye opening (both P < 0.01). There was no statistically significant difference in the prerecovery BIS between gender within each group.

Table 2. Bispectral Index (BIS) Data and Recovery Parameters

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 96)</th>
<th>Female (n = 178)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative average BIS*</td>
<td>47 ± 9</td>
<td>47 ± 8</td>
<td>0.84</td>
</tr>
<tr>
<td>Prerecovery average BIS†</td>
<td>51 ± 10</td>
<td>53 ± 12</td>
<td>0.22</td>
</tr>
<tr>
<td>Time interval: propofol off to open eyes (min)</td>
<td>11.2 ± 8.6</td>
<td>7.0 ± 5.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time interval: 90th percentile</td>
<td>9.0 (20.8)†</td>
<td>6.4 (13.1)‡</td>
<td>0.0001†</td>
</tr>
<tr>
<td>Time interval: propofol off to responds to verbal command (min)</td>
<td>11.7 ± 8.6</td>
<td>8.1 ± 6.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Time interval: 90th percentile</td>
<td>9.4 (22.0)§</td>
<td>7.0 (14.6)§</td>
<td>0.001§</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
* Intraoperative average BIS = average value from start of procedure to 15 min before discontinuation of propofol.
† Prerecovery average BIS = average BIS value over 15 min before discontinuation of propofol.
‡ Median (90th percentile).
§ Statistical results from the Mann Whitney test.

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independent predictors of time to respond to commands. Other covariates, specifically, patient weight and type of surgical procedure were not predictors of recovery time. The survival analysis comparison of the cumulative probability of patients remaining unconscious after discontinuation of propofol between men and women is shown in figure 2. Only 5% of the women patients exhibited exceptionally long (>15 min) emergence times from anesthesia compared with more than 20% in the men patients (P < 0.001, Kaplan-Meier analysis).

Discussion

This is the first reported study that shows that women emerge from anesthesia faster than men. Separate analysis of the control, SP, and BIS groups again yielded similar results. Although the mean gender difference in wake-up time ranged between 3–5 min, the consistency of this difference across all study sites and treatment groups reinforces our observation. Indeed, other investigators have observed similar gender effect on human volunteers. Andrade et al.5 studied the sedative effect of propofol using auditory evoked potential. Although not a primary objective of the study, they noted an unexpected difference in sedation levels between men and women. The five men in the study became more deeply sedated than the five women, even though they received similar doses of propofol. The number of subjects involved, however, was small. Nevertheless, their observations may imply that a shorter recovery time could be related to a decreased response for the same dose of drug. These observations could also explain the higher reported incidence of awareness during surgery in women than in men.6 A recent study showed that women required higher remifentanil blood concentrations than men during surgery. The plasma concentrations for which 50% of population has no response to surgical stimulus (C_{50}) of remifentanil for men and women was 3.81 and 5.14 ng/ml, respectively.7 Reanalysis of the data in previous volunteer studies involving BIS monitoring during propofol sedation3 showed that the propofol concentrations for women were significantly higher than those of men at the point of loss of consciousness and beyond. There was also a statistically significant difference in BIS values between men and women at the same propofol concentration: women consistently had higher BIS values, whereas the measured plasma propofol concentrations were similar in both groups.3 It is important to note that BIS measures the pharmacodynamic effects rather than the propofol concentrations. These results seem to suggest a difference in sensitivity to propofol between men and women. Therefore, women may awaken at higher concentrations of propofol than men. Pharmacokinetic factors may also play a role in this gender effect. Recovery from a single dose of intravenous anesthetic agent is dependent on redistribution, whereas recovery after a prolonged infusion is progressively more dependent on metabolism and elimination of the drugs.8 For propofol, redistribution has been shown to be the predominant factor in the dissipation of its clinical effect.9 We simulated the propofol regimen used in this study using two pharmacokinetic data sets that incorporated gender as a covariate.10 This revealed a marginally more rapid clearance of propofol in women than in men. However, this difference alone would not be sufficient to account for all the gender difference in recovery times. A combination of pharmacodynamic and pharmacokinetic factors are most likely involved. We found that women emerge from propofol/remifentanil/N_{2}O anesthesia faster than men. Considering the multitude of factors that may influence recovery, the gender effect appears to be a strong one. This phenomenon is probably caused by a combination of pharmacokinetic and pharmacodynamic factors. Therefore, studies of anesthetic drug effect and recovery from anesthesia need to be designed to account for possible gender differences. In addition, more studies
need to be performed to determine whether the gender effect may be generalized to other anesthetic agents and to investigate its possible mechanism.

References

7. Drover DR, Lemmens HJM: Do women require higher remifentanil plasma concentrations than men (abstract)? Anesthesiology 1997; 87:A306