

## WOMEN EMERGE FROM GENERAL ANESTHESIA FASTER THAN MEN

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### Abstract

Interest in the speed with which patients recover post operatively, the type of deficits that anesthesia may induce in them and the overall profile of their physiologic and psychological states, has grown rapidly over the last two decades. Recovery from general anesthesia is dependent on factors governing drug sensitivity and drug disposition.

In our study of 60 males and 60 females we have tried to find out if there is any significant difference in males and females, in their emergence from the effects of general anesthesia. This was a double blind study carried out in hundred and twenty patients, aged 18-70 years scheduled to undergo elective general surgical procedures. Patient recovery was observed continuously after the termination of anesthesia. Timings of initial wake up events were recorded by the anesthesiologist who was blinded to this study. The time from discontinuation of anesthesia to eye opening was  $6.87 \pm 2.54$  min ( $P < 0.001$ ; t test) for women versus  $8.78 \pm 2.66$  min in men; time to respond to verbal command was  $7.53 \pm 2.05$  and  $9.61 \pm 2.14$  min in women and men, respectively ( $P < 0.001$ ; t test). Considering the multitude of factors that may influence recovery, the gender effect appears to be a strong one. The

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difference could probably be explained by differences in physiology, enzyme activity etc. Investigators have noted that normal differences account for changes in function of the GABA receptor known to be important in the action of many anesthetics.

**Keywords:** Anesthesia : TIVA (Propofol + Fentanyl), Recovery : Emergence, Pharmacokinetics.

### **Introduction**

Interest in the speed with which patients recover post operatively, the type of deficits that anesthesia may induce in them and the overall profile of their physiologic and psychological states, has grown rapidly over the last two decades. This increasing concern for patients post anesthetic state has probably been fuelled by the rapid development of day care or “ambulatory” surgery.

The quest for an ideal intravenous anesthetic agent came to a halt to certain extent on introduction of propofol in clinical practice, an agent which has a metabolic clearance ten times faster than thiopentone.

Use of potent opioids in anesthesia has allowed anesthetists to deliver “balanced anesthesia” therapy reducing the risk of undesirable hemodynamic fluctuations associated with use of inhalational agent or intravenous agent alone. Fentanyl, a synthetic opioid, has been used efficiently after its extensive research over the last several years.

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).

Recovery from anesthesia is determined by the pharmacokinetic principles that determine the rate of decrease of drug from the effect compartment once administration is terminated, as well as the pharmacodynamics of the drug. Although the terminal elimination half-

life is often interpreted as a measure of how short or long lasting a drug; is the rate at which drug decreases is dependent both on elimination and on redistribution of the drug from the central compartment. The contribution of both redistribution and elimination towards the rate of decrease of drug concentration varies according to the duration for which the drug has been administered.

Gender has not previously been recognized as a factor influencing the time to emergence from general anesthesia. In our study we have tried to find out if there is any significant difference in males and females in the time they take to emerge from the effects of general anesthesia.

### **Material And Methods**

A double blind study was carried out in hundred and twenty patients (60 males, 60 females) aged 18-70 years scheduled to undergo elective general surgical procedures.

After approval from the hospital ethics committee, all patients were thoroughly examined pre-anesthetically and the assessment of the patients was based on the history, physical examination, chest x-ray and other laboratory investigations. Written informed consent was taken from all patients. Only patients belonging to ASA grade I/II physical status were included in this study. Patients with diseases, which can affect recovery times, were excluded from this study.

Upon arrival to the operation table, cardiac monitoring consisted of (lead II) ECG and pulse oximetry. After securing two peripheral i.v. lines with an 18 or 20G I.V. cannula on the non-dominant hand, all patients were preloaded with 500 ml of Ringer lactate.

All subjects were premedicated with Inj. glycopyrrolate (0.008 mg/kg), Midazolam 1-2 mg intravenously and fentanyl 1-2 µg/kg received just before induction.

Induction regimen consisted of Inj. Propofol 1-2 mg/kg given slowly over a period of 30 seconds till loss of eyelash reflex and eyeball were

fixed centrally. The occurrence of apneic episodes, coughing, twitching, hiccup or involuntary movement during induction or later, were recorded. Orotracheal intubation was facilitated with succinylcholine chloride (1.5-2.0 mg/kg). Anesthesia was maintained with an infusion of propofol (140  $\mu\text{g}/\text{kg}/\text{min}$ ) and fentanyl (0.02  $\mu\text{g}/\text{kg}/\text{min}$ ) along with 50%  $\text{N}_2\text{O}$  with oxygen, and neuromuscular blockade with inj vecuronium bromide (0.08 mg/kg).

During the intraoperative phase vital parameters such as NIBP, pulse, ECG,  $\text{SpO}_2$  etc were monitored. Patients were assessed for signs of inadequate anesthesia, hypotension or bradycardia.

About 15 minutes before the end of surgery, anesthesia was reduced to half dose to facilitate rapid recovery. This range was maintained up to 5 minutes before the end of surgery, when the propofol and fentanyl infusions along with nitrous oxide were discontinued (near to end of skin suture), and the patient were allowed to awaken. Description of all important intraoperative events including episodes of inadequate anesthesia or hypotension or bradycardia requiring intervention were recorded along with all medications administered (bolus doses, infusion rates, total amount used) and time of key intraoperative events (intubation, start of procedure, end of surgical stimulation).

The time when propofol, fentanyl and nitrous oxide were discontinued was identified as the starting point (time = 0) of patient recovery. Patient recovery was observed continuously after the termination of anesthesia.

Timings of initial wake up events (opening eyes-spontaneously and on verbal commands; times of extubation, responding to verbal commands, moving limbs and adequate muscle power) were recorded by the anesthesiologist who was blinded to the study.

Time from discontinuation of anesthesia i.e. fentanyl (propofol and  $\text{N}_2\text{O}$ ) to eye opening, response to verbal commands and extubation time was assessed for all patients. Differences in endpoint values between the male and female were analyzed and evaluated statistically.

## Results

One hundred and twenty patients (60 male and 60 female) completed the study for different surgical procedures (Table 1) and majority of the cases was upper or lower abdominal surgeries.

Table 1

Surgical Procedures	No. of Cases %	
	Male (%)	Female (%)
Upper Abdominal	10 (16.7)	8 (13.3)
Lower Abdominal	19 (31.7)	16 (26.7)
Laparoscopic surgeries	6 (10.0)	4 (6.7)
ENT surgeries	11 (18.3)	9 (15.0)
Breast surgeries	-	9 (15.0)
Miscellaneous	14 (23.3)	14 (23.3)

Table 2 shows demographic data of patients. The age, weight and duration of surgery were comparable for the two groups and there was no statistically significant gender difference in the dose of propofol and fentanyl used.

Table 2

Demographic Data

	Males (n = 60)	Females (n = 60)	P value
Age (yrs)	40.93 ± 13.84	41.05 ± 13.18	<0.05
Weight (Kg)	65.25 ± 6.25	58.47 ± 7.92	<0.001
Duration of anesthesia	73.37 ± 10.30	72.12 ± 9.82	<0.05
Total propofol dose (mg)	737.63 ± 110.20	721.45 ± 119.47	<0.001
Total fentanyl dose (µg)	144.68 ± 24.51	141.60 ± 27.05	<0.001

By comparing the time from end of anesthesia to eye opening, responding to verbal commands and extubation time in men and women in different age groups, it was observed that women woke significantly faster than men. The difference in the three variables was statistically highly significant between males and females in all the age groups (Fig. 1, 2 & 3).

Fig. 1

Comparison between males and females with respect to time from end of anesthesia to eye opening

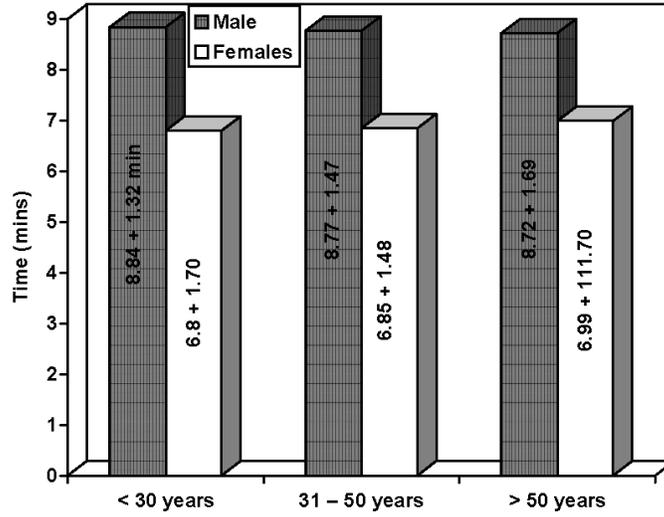


Fig. 2

Comparison between males and females with respect to time from end of anesthesia to response to verbal command

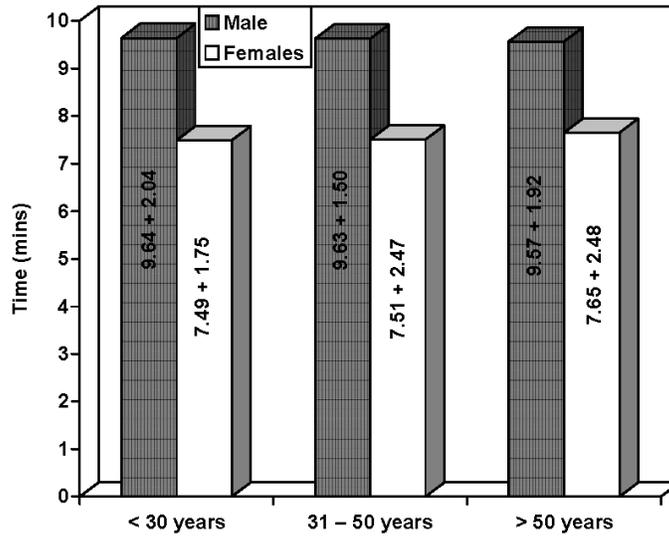


Fig. 3  
Comparison between males and females with respect to time from end of anesthesia to extubation time

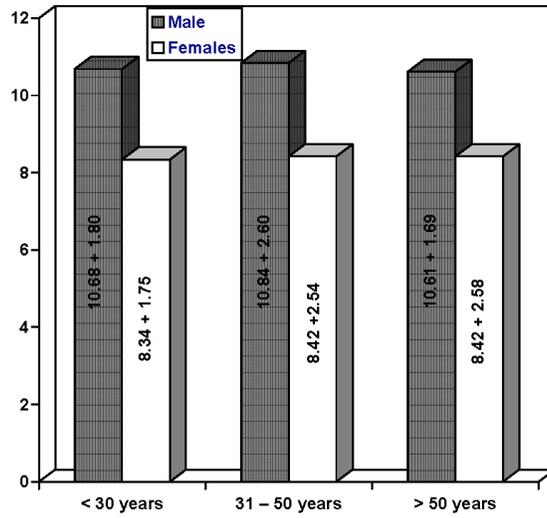
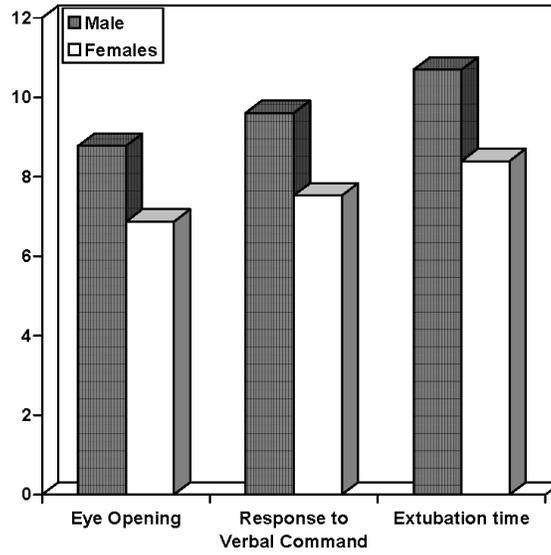


Fig. 4  
Comparison between males and females



The time from discontinuation of anesthesia to eye opening was  $6.87 \pm 2.54$  min ( $P < 0.001$ ; t test) for women versus  $8.78 \pm 2.66$  min in men; time to respond to verbal command was  $7.53 \pm 2.05$  min and  $9.61 \pm 2.14$  min in women and men, respectively ( $P < 0.001$ ; t test) and extubation time was  $8.40 \pm 1.60$  min in women and  $10.70 \pm 1.70$  min in men ( $P < 0.001$ ; t test) (Table 3 & Fig. 4).

*Table 3*  
*Comparison between males and females regarding eye opening, response to verbal command and extubation time.*

<b>Variables observed</b>	<b>Male (min. <math>\pm</math> S.D.)</b>	<b>Females (min. <math>\pm</math> S.D.)</b>
Eye Opening	$8.78 \pm 2.66$	$6.87 \pm 2.54^{**}$
Response to Verbal Command	$9.61 \pm 2.14$	$7.53 \pm 2.05^{**}$
Extubation time	$10.70 \pm 1.70$	$8.40 \pm 1.60^{**}$

\*\*  $P < 0.001$

The incidence of postoperative complications such as nausea, vomiting, headache, pain was significantly higher in women than in men (Table 4).

*Table 4*  
*Postoperative Complications*

<b>Complication</b>	<b>Male</b>		<b>Female</b>	
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>
Nausea & Vomiting	2	3.33	7	11.67
Headache	2	3.33	5	8.33
Pain	5	8.33	7	11.67
Sore throat	2	3.33	4	6.67
Hypertension	3	5.00	4	6.67
Hypotension	2	3.33	2	3.33
Tachycardia	3	5.00	5	8.33
Bradycardia	1	1.67	1	1.67

## Discussion

Recovery following propofol anesthesia is faster than with the commonly used barbiturate compounds irrespective of maintenance agent used<sup>1</sup>. The various factors, such as, drug dosage, time of administration, age, liver and renal diseases etc, have been studied which influence the time to emergence from general anesthesia. Gender, however, has not previously been recognized as a factor influencing recovery. The present study was designed to assess the role that gender plays in the emergence from anesthesia.

Our results were comparable to other similar multicenter study done by Gan T.J. et al (1999)<sup>2</sup>, a study designed to measure the effects of the bispectral index on intraoperative anesthetic management. They studied the wake-up and recovery times of 274 adults (96 men and 178 women; procedures expected to last for more than 1 hour) after propofol, alfentanil and nitrous oxide anesthesia. They noted that women woke significantly faster than men, the time from discontinuation of propofol infusion to eye opening was  $7.05 \pm 5.2$  min (mean  $\pm$  SD) in women versus  $11.2 \pm 8.66$  min in men ( $P < 0.05$ ). Time taken to respond to verbal command was  $8.12 \pm 6.23$  min versus  $11.67 \pm 8.61$  min in women and men respectively ( $P < 0.05$ ).

Paul Myles et al (2001)<sup>3</sup> in the study of 463 patients (241 men and 222 women) using inhalational anesthetic technique, observed that women tended to open their eyes close to 2 minutes sooner and obeyed commands almost 3 minutes sooner than men after surgery.

Other investigators have observed similar gender effect on human volunteers. Andrade et al<sup>4</sup> 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 cases studied, 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<sup>5</sup>.

A recent study<sup>6</sup> showed that women require higher remifentanyl blood concentrations than men during surgery. The plasma concentration for which 50% of population has no response to surgical stimulus ( $Cp_{50}$ ) of remifentanyl for men and women was, 3.81 ng/ml and 5.14 ng/ml respectively.

Previous volunteer studies<sup>7</sup> shows statistical difference in BIS values between men and women at the same propofol concentration (at the point of loss of consciousness and beyond): women consistently had higher BIS values, whereas the measured plasma concentrations were similar in both groups.

These results seem to suggest that a difference exists in the 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<sup>8</sup>. For propofol, redistribution has been shown to be the predominant factor in the dissipation of its clinical effect<sup>9</sup>. A combination of pharmacodynamics and pharmacokinetic factors are most likely involved.

Considering the multitude of factors that may influence recovery, the gender effect appears to be a strong one. It is difficult to explain why such a difference in gender should take place. The difference could probably be explained by differences in physiology, enzyme activity, etc. Investigators have noted that hormonal differences account for changes in function of the GABA receptor- a receptor known to be important in the action of many anesthetics. Differences in fat distribution and hormone levels between men and women may account for some of the differences in how they respond to anesthesia. Therefore, studies of anesthetic drug effect and recovery from anesthesia need to be designed to account for possible gender differences.

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