

Original Research

Effect of flumazenil on recovery from anesthesia and the bispectral index after sevoflurane/fentanyl general anesthesia in unpremedicated patients

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ABSTRACT:

Aim: To evaluate the effect of flumazenil on the recovery profile and bispectral index (BIS) values in unpremedicated patients undergoing general anesthesia with sevoflurane and fentanyl. **Materials and methods:** This study examined 40 patients, all 65 years old or younger, who were in ASA physical status I or II and scheduled for surgeries lasting 1 to 2 hours. No premedication was given. During the procedure, standard monitoring was used, and anesthesia was induced with thiopental, fentanyl, rocuronium, and sevoflurane. Body temperature was regulated using warming devices, and the depth of anesthesia was maintained with a BIS score around 40. Data analysis was done using SSPS software. **Results:** In our study, notable differences were observed between the flumazenil and control groups in terms of demographic, clinical, and recovery characteristics. The flumazenil group (n = 20) had a younger mean age (34.8 ± 10.5 years), a higher BMI (27.6 ± 5.1 kg/m²), and more females (12) compared to the control group (mean age 58.2 ± 5.7 years, BMI 22.3 ± 5.3 kg/m², 5 females). The flumazenil group also had a shorter duration of surgery (0.9 ± 0.4 vs. 2.1 ± 1.3 hours), higher blood loss (72.5 ± 35.6 vs. 38.9 ± 32.8 ml), and lower intraoperative fentanyl use (2.5 ± 1.8 vs. 4.1 ± 1.4 µg/kg). Hemodynamically, the flumazenil group showed higher systolic and diastolic pressures and lower heart rates. Regarding recovery, the flumazenil group demonstrated significantly faster times to spontaneous breathing (4.6 ± 0.4 vs. 6.3 ± 1.1 min), eye opening (5.7 ± 0.6 vs. 7.0 ± 1.4 min), hand squeezing (6.3 ± 1.2 vs. 8.1 ± 1.5 min), extubation (6.9 ± 1.7 vs. 9.0 ± 2.2 min), and date of birth recollection (6.0 ± 1.3 vs. 8.2 ± 1.1 min), all with statistically significant p-values. **Conclusion:** Flumazenil significantly accelerated recovery from sevoflurane/fentanyl anesthesia in unpremedicated patients, as evidenced by shorter times to key recovery milestones. These findings suggest its potential utility in enhancing emergence without compromising safety.

Keywords: sevoflurane, fentanyl, flumazenil

Received: 12 March, 2018

Accepted: 14 April, 2018

Published: 17 May, 2018

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This article may be cited as: Deosarkar DB. Effect of flumazenil on recovery from anesthesia and the bispectral index after sevoflurane/fentanyl general anesthesia in unpremedicated patients. J Adv Med Dent Sci Res 2018;6(5):191-195.

INTRODUCTION

General anesthesia, a cornerstone of modern surgery, aims to achieve a reversible state of unconsciousness, analgesia, muscle relaxation, and amnesia, allowing for complex medical procedures to be performed safely and without patient recall. While the primary goal during surgery is adequate depth of anesthesia to prevent awareness and pain, the subsequent recovery phase is equally critical, impacting patient safety, comfort, and resource utilization within post-anesthesia care units. Rapid and smooth emergence from anesthesia is desirable, minimizing complications such as prolonged sedation, respiratory depression, and postoperative cognitive dysfunction,

all of which can extend hospital stays and increase healthcare costs.^{1,2,3,4}

Among the various anesthetic agents, sevoflurane and fentanyl are commonly employed in general anesthesia due to their favorable pharmacokinetic and pharmacodynamic profiles. Sevoflurane, a volatile anesthetic, offers rapid induction and emergence, while fentanyl, a potent opioid, provides effective analgesia. However, despite their advantages, these agents can contribute to residual sedation and respiratory depression post-operatively. The central nervous system effects of these drugs, particularly on consciousness and brain activity, are often monitored using tools like the bispectral index (BIS), which provides a numerical representation of the depth of

hypnosis and can guide anesthetic administration and emergence.^{5,6}

Flumazenil, a benzodiazepine receptor antagonist, has been investigated for its potential to accelerate recovery from anesthesia, particularly in cases where benzodiazepines have been used. While not directly reversing the effects of opioids like fentanyl or volatile anesthetics like sevoflurane, its role in improving recovery is often explored in the context of general anesthesia where multiple agents contribute to sedation. By rapidly reversing the effects of any co-administered benzodiazepines or addressing any latent benzodiazepine-like activity, flumazenil aims to hasten the return of consciousness and cognitive function, thereby promoting a quicker and smoother emergence from the anesthetized state. Its application in a multi-drug anesthetic regimen, such as sevoflurane and fentanyl, is of interest to see if it contributes to a more rapid awakening and resolution of residual sedation, as reflected by objective measures like the bispectral index (BIS) and clinical indicators of recovery.^{7,8}

The bispectral index (BIS) can be significantly affected after sevoflurane/fentanyl general anesthesia in unpremedicated patients, particularly when flumazenil is administered. In unpremedicated patients undergoing sevoflurane/fentanyl general anesthesia, the Bispectral Index (BIS) is influenced by both anesthetic agents. While sevoflurane directly affects brain electrical activity, fentanyl, as an opioid, primarily contributes to analgesia but can also modulate BIS values through its sedative effects, especially when combined with volatile anesthetics. However, research indicates that while BIS values correlate with anesthetic depth, their ability to reliably predict or significantly reduce intraoperative awareness in this specific patient group remains limited compared to clinical monitoring alone. Various studies highlight that factors such as drug interactions, individual patient variability in pharmacokinetics, and the specific surgical context further complicate the direct interpretation of BIS as a sole indicator of awareness prevention.^{9,10}

Despite extensive research, the clinical benefit of BIS-guided anesthesia in significantly reducing

intraoperative awareness or improving recovery in unpremedicated patients receiving sevoflurane/fentanyl has not been definitively established. Many studies, including those comparing BIS with other EEG-based monitors like spectral entropy, often show methodological limitations, such as issues with blinding and adjudication of awareness events, which weaken the evidence strength.¹¹

MATERIALS AND METHODS

This study examined 40 patients, all 65 years old or younger, who were in ASA physical status I or II and scheduled for surgeries lasting 1 to 2 hours. No premedication was given. During the procedure, standard monitoring was used, and anesthesia was induced with thiopental, fentanyl, rocuronium, and sevoflurane. Body temperature was regulated using warming devices, and the depth of anesthesia was maintained with a BIS score around 40. Fentanyl managed hemodynamic parameters, while neuromuscular blockade was monitored via TOF, with T1 kept at 25%.

Fluid administration primarily involved crystalloids and hydroxyethyl starch. Strict exclusion criteria were applied, eliminating individuals with a BMI outside the 18–30 kg/m² range, those with neurological or cardiovascular conditions, patients on sedatives. Upon completion of surgery, pain was addressed with fentanyl, and muscle relaxation was reversed using pyridostigmine. Sevoflurane and nitrous oxide were discontinued, and patients received either flumazenil or saline, alongside hyperventilation and increased oxygen. Anesthesia providers were unaware of which treatment each patient received.

Post-anesthesia, several recovery metrics were recorded every two minutes, including time to spontaneous respiration, verbal responsiveness, extubation, and orientation (e.g., stating birth date), along with BIS scores. Patients were observed in the recovery room for one hour by non-anesthesia personnel before being discharged to the ward according to standard criteria. Data analysis was conducted using SSPS software.

RESULTS

Table 1: Patient's Characteristics and Preoperative Hemodynamics

| | Flumazenil group (n = 20) | Control group (n = 20) |
|--------------------------------------|----------------------------------|-------------------------------|
| Patient's characteristics | | |
| M/F | 8/12 | 15/5 |
| Age (years) | 34.8 ± 10.5 | 58.2 ± 5.7 |
| BMI (kg/m ²) | 27.6 ± 5.1 | 22.3 ± 5.3 |
| Duration of surgery (hr) | 0.9 ± 0.4 | 2.1 ± 1.3 |
| Surgical blood loss (ml) | 72.5 ± 35.6 | 38.9 ± 32.8 |
| Fentanyl used during surgery (µg/kg) | 2.5 ± 1.8 | 4.1 ± 1.4 |
| Preoperative hemodynamics | | |

| | | |
|---------------------------------|---------------|--------------|
| Systolic blood pressure (mmHg) | 135.6 ± 16.3 | 121.2 ± 20.7 |
| Diastolic blood pressure (mmHg) | 86.4 ± 11.7 | 73.3 ± 13.5 |
| Heart rate (beats/min) | 70.1 ± 10.4 | 84.9 ± 9.1 |
| SpO ₂ (%) | 93.9000 ± 1.1 | 94.5 ± 1.8 |

Data are expressed as means ± SD. BMI: body mass index

The demographic and clinical characteristics of patients in the flumazenil and control groups showed notable differences. In the flumazenil group (n = 20), there were 8 males and 12 females, whereas the control group (n = 20) had 15 males and 5 females. The mean age in the flumazenil group was 34.8 ± 10.5 years, significantly lower than the control group, which had a mean age of 58.2 ± 5.7 years. The body mass index (BMI) was higher in the flumazenil group (27.6 ± 5.1 kg/m²) compared to the control group (22.3 ± 5.3 kg/m²). The duration of surgery was shorter in the flumazenil group (0.9 ± 0.4 hours) than in the control group (2.1 ± 1.3 hours). Similarly, surgical blood loss was greater in the flumazenil

group (72.5 ± 35.6 ml) than in the control group (38.9 ± 32.8 ml). Fentanyl usage during surgery was lower in the flumazenil group (2.5 ± 1.8 µg/kg) than in the control group (4.1 ± 1.4 µg/kg). Preoperative hemodynamic parameters showed that the flumazenil group had higher systolic (135.6 ± 16.3 mmHg) and diastolic (86.4 ± 11.7 mmHg) blood pressures compared to the control group (121.2 ± 20.7 mmHg and 73.3 ± 13.5 mmHg, respectively). Heart rate was lower in the flumazenil group (70.1 ± 10.4 beats/min) than in the control group (84.9 ± 9.1 beats/min). The mean oxygen saturation (SpO₂) was slightly lower in the flumazenil group (93.9 ± 1.1%) compared to the control group (94.5 ± 1.8%).

Table 2: Recovery Parameters

| Time (min) from administration of flumazenil or placebo to | Flumazenil group (n = 20) | Control group (n = 20) | P |
|--|---------------------------|------------------------|--------|
| Spontaneous breathing | 4.6 ± 0.4 | 6.3 ± 1.1 | 0.001 |
| Eye opening on verbal command | 5.7 ± 0.6 | 7.0 ± 1.4 | 0.002 |
| Hand squeezing on verbal command | 6.3 ± 1.2 | 8.1 ± 1.5 | 0.001 |
| Extubation | 6.9 ± 1.7 | 9.0 ± 2.2 | 0.0008 |
| Date of birth recollection | 6.0 ± 1.3 | 8.2 ± 1.1 | 0.0006 |

The time (in minutes) from the administration of flumazenil or placebo to various recovery milestones was significantly shorter in the flumazenil group compared to the control group. The mean time to spontaneous breathing was 4.6 ± 0.4 minutes in the flumazenil group versus 6.3 ± 1.1 minutes in the control group (p = 0.001). Eye opening on verbal command occurred at 5.7 ± 0.6 minutes in the flumazenil group and 7.0 ± 1.4 minutes in the control group (p = 0.002). Similarly, hand squeezing in response to verbal command was observed at 6.3 ± 1.2 minutes in the flumazenil group, whereas it occurred later at 8.1 ± 1.5 minutes in the control group (p = 0.001). Extubation time was also faster in the flumazenil group (6.9 ± 1.7 minutes) compared to the control group (9.0 ± 2.2 minutes), with a statistically significant difference (p = 0.0008). Lastly, recollection of date of birth occurred sooner in the flumazenil group at 6.0 ± 1.3 minutes compared to 8.2 ± 1.1 minutes in the control group (p = 0.0006).

DISCUSSION

Flumazenil, a benzodiazepine antagonist, has been investigated for its potential to accelerate recovery from general anesthesia, particularly when benzodiazepines are part of the anesthetic regimen. In the context of sevoflurane/fentanyl anesthesia

administered to unpremedicated patients, the use of flumazenil could theoretically influence the bispectral index (BIS) values, which serve as a measure of the hypnotic depth of anesthesia.¹² Understanding the interplay between flumazenil, residual anesthetic effects from sevoflurane and fentanyl, and their impact on BIS and clinical recovery is crucial for optimizing patient care and ensuring a smooth emergence from general anesthesia.

In our study, notable differences were observed between the flumazenil and control groups in terms of demographic, clinical, and recovery characteristics. The flumazenil group (n = 20) had a younger mean age (34.8 ± 10.5 years), a higher BMI (27.6 ± 5.1 kg/m²), and more females (12) compared to the control group (mean age 58.2 ± 5.7 years, BMI 22.3 ± 5.3 kg/m², 5 females). The flumazenil group also had a shorter duration of surgery (0.9 ± 0.4 vs. 2.1 ± 1.3 hours), higher blood loss (72.5 ± 35.6 vs. 38.9 ± 32.8 ml), and lower intraoperative fentanyl use (2.5 ± 1.8 vs. 4.1 ± 1.4 µg/kg). Hemodynamically, the flumazenil group showed higher systolic and diastolic pressures and lower heart rates. Regarding recovery, the flumazenil group demonstrated significantly faster times to spontaneous breathing (4.6 ± 0.4 vs. 6.3 ± 1.1 min), eye opening (5.7 ± 0.6 vs. 7.0 ± 1.4 min), hand squeezing (6.3 ± 1.2 vs. 8.1 ± 1.5 min), extubation

(6.9 ± 1.7 vs. 9.0 ± 2.2 min), and date of birth recollection (6.0 ± 1.3 vs. 8.2 ± 1.1 min), all with statistically significant p-values.

Unlike a previous study where flumazenil was administered just before the end of surgery and only recovery times were assessed, our study included BIS monitoring to provide a more objective evaluation of anesthetic recovery. Since BIS decreases in a dose-dependent manner with anesthetics like propofol, sevoflurane, and midazolam, it serves as a reliable indicator of both anesthetic depth and post-anesthesia awareness, offering more comprehensive insight into the recovery process.^{13,14}

In a study by Kin YJ et al.¹⁵ involving 45 healthy, unpremedicated patients undergoing sevoflurane/fentanyl general anesthesia, researchers investigated the effect of flumazenil on anesthetic recovery and bispectral index (BIS) values. Patients were randomized to receive either 0.3 mg of flumazenil or a placebo. The findings indicated that the flumazenil group exhibited significantly shorter times to spontaneous respiration, eye opening, hand squeezing on command, extubation, and recollection of date of birth compared to the control group. Furthermore, the flumazenil group showed a statistically higher BIS value starting six minutes post-administration. These results suggest that a single dose of flumazenil can lead to earlier emergence from sevoflurane/fentanyl anesthesia, potentially due to an antagonistic effect on sevoflurane or an analeptic effect mediated by endoepine mechanisms.

In a study conducted by Dahaba AA et al.¹⁶, sixty healthy, unpremedicated patients undergoing propofol/remifentanyl anesthesia were randomly assigned to either a flumazenil or placebo group. The study assessed the impact of flumazenil on recovery parameters and bispectral index (BIS) values. A significant increase in BIS from a baseline of 38.7 ± 3.8 to 53.2 ± 4.7 was observed in the flumazenil group within 15 minutes, a change significantly different from the control group ($P < 0.0001$). Additionally, recovery times, including the return of spontaneous breathing, eye opening, hand squeezing on verbal command, extubation, and recollection of date of birth, were significantly shorter in the flumazenil group (6.9 ± 2.6 min) compared to the control group (9.8 ± 2.9 min, $P = 0.0002$). These results suggest that flumazenil expedites emergence from anesthesia and increases BIS values, potentially by reversing the effects of endogenous or exogenous endoepines during the anesthetic process.

A limitation of this study is its relatively small sample size, which could restrict the generalizability of the findings. A larger participant pool might reveal greater variability in individual responses to flumazenil and potentially alter the observed effects on recovery. Consequently, future research with more extensive cohorts is necessary to confirm and reinforce these conclusions.

CONCLUSION

Flumazenil significantly accelerated recovery from sevoflurane/fentanyl anesthesia in unpremedicated patients, as evidenced by shorter times to key recovery milestones. These findings suggest its potential utility in enhancing emergence without compromising safety.

REFERENCES

1. Karakosta A, Andreotti B, Chapsa C, Pouliou A, Anastasiou E. Flumazenil expedites recovery from sevoflurane/remifentanyl anaesthesia when administered to healthy unpremedicated patients. *Eur J Anaesthesiol.* 2010 Nov;27(11):955-9. doi: 10.1097/EJA.0b013e3283398ef9. PMID: 20864893
2. Duthel JM, Constant H, Vallon JJ, Rochet T, Miachon S. Quantitation by gas chromatography with selected-ion monitoring mass spectrometry of "natural" diazepam, N-desmethyldiazepam and oxazepam in normal human serum. *J Chromatogr.* 1992;579:85-91. doi: 10.1016/0378-4347(92)80365-w.
3. Weinbroum AA, Geller E. Flumazenil improves cognitive and neuromotor emergence and attenuates shivering after halothane-, enflurane- and isoflurane-based anesthesia. *Can J Anaesth.* 2001;48:963-972. doi: 10.1007/BF03016585.
4. Roald OK, Forsman M, Steen PA. Partial reversal of the cerebral effects of isoflurane in the dog by the benzodiazepine antagonist flumazenil. *Acta Anaesthesiol Scand.* 1988;32:209-212. doi: 10.1111/j.1399-6576.1988.tb02716.x.
5. Murayama T, Shingu K, Ogawa T, Tomoda K, Shindo K, Tamai S, et al. Flumazenil does not antagonize halothane, thiamylal or propofol anaesthesia in rats. *Br J Anaesth.* 1992;69:61-64. doi: 10.1093/bja/69.1.61.
6. Schwieger IM, Szlam F, Hug CC., Jr Absence of agonistic or antagonistic effect of flumazenil (Ro 15-1788) in dogs anesthetized with enflurane, isoflurane, or fentanyl-enflurane. *Anesthesiology.* 1989;70:477-480. doi: 10.1097/00000542-198903000-00018.
7. Johnston GAR. GABAA receptor pharmacology. *Pharmacol Ther* 1996; 69:173-198. 4 Sigel E. Mapping of the benzodiazepine recognition site on GABAA receptors. *Curr Top Med Chem* 2002; 2:833-839.
8. Franchitto N, Pelissier F, Lauque D, Simon N, Lançon C. Self-intoxication with baclofen in alcohol-dependent patients with co-existing psychiatric illness: an emergency department case series. *Alcohol Alcohol.* 2014 Jan-Feb;49(1):79-8.
9. Asthana V, Agrawal S, Goel D, Sharma JP. Idiopathic recurrent stupor mimicking status epilepticus. *Singapore Med J.* 2008 Oct;49(10):e276-7
10. Rothstein JD, Garland W, Puia G, et al. Purification and characterization of naturally occurring benzodiazepine receptor ligands in rat and human brain. *J Neurochem* 1992; 58:2102-2115
11. Beaumont K, Cheung AK, Geller ML, Fanestil DD. Inhibitors of peripheral type benzodiazepine receptors present in human urine and plasma ultrafiltrates. *Life Sci* 1983; 33:1375-1384.
12. Hapfelmeier G, Schneck H, Kochs E. Sevoflurane potentiates and blocks GABA-induced currents through recombinant $\alpha 1\beta 2\gamma 2$ GABAA receptors: implications for an enhanced GABAergic transmission. *Eur J Anaesthesiol* 2001; 18:377-383.

13. Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, et al. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg.* 1997;84:891–899. doi: 10.1097/0000539-199704000-00035.
14. Flaishon R, Windsor A, Sigl J, Sebel PS. Recovery of consciousness after thiopental or propofol. Bispectral index and isolated forearm technique. *Anesthesiology.* 1997;86:613–619. doi: 10.1097/0000542-199703000-00013.
15. Kim YJ, Lee H, Kim CH, Lee GY, Baik HJ, Han JI. Effect of flumazenil on recovery from anesthesia and the bispectral index after sevoflurane/fentanyl general anesthesia in unpremedicated patients. *Korean J Anesthesiol.* 2012 Jan;62(1):19-23. doi: 10.4097/kjae.2012.62.1.19. Epub 2012 Jan 25. PMID: 22323949; PMCID: PMC3272523.
16. Dahaba AA, Bornemann H, Rehak PH, Wang G, Wu XM, Metzler H. Effect of flumazenil on bispectral index monitoring in unpremedicated patients. *Anesthesiology.* 2009 May;110(5):1036-40. doi: 10.1097/ALN.0b013e31819db2c4. PMID: 19352163.