Original Research

Evaluation of Flumazenil's Impact on Anaesthesia Recovery and Bispectral Index Post Sevoflurane/Fentanyl Anesthesia Without Premedication at a Tertiary Hospital

Komal Goel[1], G. Prasanna Kumar[2]

[1]Assistant Professor, Department of Anaesthesia, Rajshree Medical Research Institute, Bareilly, Uttar Pradesh, India.
[2]Assistant Professor, Department of Anaesthesia, Rohilkhand Medical College & Hospital Bareilly, Uttar Pradesh, India.

Corresponding Author:
Dr. G. Prasanna Kumar
Assistant Professor,Department of Anaesthesia,Rohilkhand Medical College & Hospital Bareilly, Uttar Pradesh, India. Email: dr.prasannkumar.uk@gmail.com

Received: 03March 2024 Accepted: 15April 2024

ABSTRACT

Background: Flumazenil, classified as an imidazobenzodiazepine, serves as a rapid antagonist to the sedative and hypnotic effects induced by benzodiazepines through competitive inhibition at gamma-aminobutyric acid (GABA) receptors. Hence; the present study was conducted for evaluating flumazenil's impact on anaesthesia recovery and bispectral index post sevoflurane/fentanyl anesthesia without premedication at a tertiary hospital.

Materials &Methods: A total of 40 patients who were undergoing a surgical procedure were enrolled.Complete demographic and clinical details of all the patients was obtained. The subjects were not premedicated. All the patients were randomized into two study groups with 20 patients in each group; single dose of 0.3 mg of flumazenil (n = 20) or placebo (n = 20). After arrival in the operating room, the subjects' blood pressure, heart rate, electrocardiograph, peripheral oxygen saturation and BIS were continuously measured using a patient monitoring instrument. BIS values were also recorded in two-minute intervals. Statistical analysis was performed using SPSS software.

Results: Mean age of the patients of the Flumazenil group and control group was 48.3 years and 46.2 years. Majority proportion of patients were males and were of rural residence. Eye opening on verbal command among patients of the Flumazenil group and Control group was 6.2 minutes and 8.9 minutes respectively. Recovery parameters were significantly better among patients of the flumazenil group.The BIS value was significantly higher in flumazenil group than in the control group beginning 6 min after flumazenil administration.

Conclusion: The administration of flumazenil to patients without premedication undergoing anesthesia with sevoflurane and fentanyl may facilitate recovery from anesthesia. This phenomenon could be attributed to flumazenil's ability to counteract the effects of sevoflurane or endogenous benzodiazepines. Nevertheless, a comprehensive study involving a larger sample size may be necessary to more precisely assess the impact and safety of flumazenil in the context of recovery from general anesthesia.

Key words: Flumazenil, Bispectral Index.

INTRODUCTION

Flumazenil, classified as an imidazobenzodiazepine, serves as a rapid antagonist to the sedative and hypnotic effects induced by benzodiazepines through competitive inhibition at gamma-aminobutyric acid (GABA) receptors. It has received approval for use in reversing sedation resulting from benzodiazepines administered during various therapeutic interventions.[1] Flumazenil exhibits a dose-independent antagonistic action against all effects of benzodiazepine overdose, which encompasses amnesia, sedation, and respiratory depression. Anesthesiologists frequently administer flumazenil to counteract the effects of midazolam, a specific type of benzodiazepine. A pertinent inquiry arises regarding the extent to which flumazenil influences volatile anesthetics. Isoflurane is an

inhalational agent with a blood-gas partition coefficient about 1.46, two times greater than sevoflurane approximately. An anesthetic agent with a high blood-gas partition coefficient will diffuse readily into the blood, thus lowering the alveolar partial pressure and causing a slow induction, with a slow recovery too. To appropriately titrate isoflurane during general anesthesia requires a gas analyzer to know exactly the expiratory concentration of isoflurane. Unfortunately, the use of gas analyzer is not common in many hospitals at many countries, and sevoflurane remains an inhalational agent very expensive and not routinely used. These two factors contribute to isoflurane be the most commonly used inhalational agent in general anesthesia with a slowly recovery in many times.[2- 4] Existing literature presents conflicting evidence, with some studies reporting negligible effects of flumazenil on volatile anesthetics, while others suggest a notable impact. This disparity in research findings highlights the ongoing debate regarding the role of GABA receptors in mediating the hypnotic effects of volatile anesthetics. The electroencephalogram-derived bispectral index (BIS) is a promising new method to assess anesthetic adequacy.[5, 6] Hence; the present study was conducted for evaluating flumazenil's impact on anaesthesia recovery and bispectral index post sevoflurane/fentanyl anesthesia without premedication at a tertiary hospital.

MATERIALS & METHODS

A total of 40 patients who were undergoing surgical procedure were enrolled.Complete demographic and clinical details of all the patients were obtained. The subjects were not premedicated. All the patients were randomized into two study groups with 20 patients in each group; single dose of 0.3 mg of flumazenil (n = 20) or placebo (n = 20).

After arrival in the operating room, the subjects' blood pressure, heart rate, electrocardiograph, peripheral oxygen saturation and BIS were continuously measured using a patient monitoring instrument. Oxygen and nitrous oxide were administered each at the rate of 1.5 L/min, and the expiratory sevoflurane concentration was kept at 1.5 vol/%.

The BIS was maintained at around 40 throughout the operation. End of the operation was the last skin suture, and an intravenous injection of fentanyl (0.5 µg/kg) was given five minutes before the expected end of the operation while sevoflurane was continuously administered without reducing the concentration for pain alleviation. After termination of the anesthesia, the time taken to spontaneous respiration while attempting to awaken the patient with the same words in 20-second intervals as well as hand squeezing and eye opening on verbal command, extubation of the endotracheal tube and recollection of their date of birth were measured; BIS values were also recorded in two-minute intervals. Statistical analysis was performed using SPSS software.

Table 1: Demographic data

Variable	Flumazenil group	Control group
Mean age	48.3	46.2
Males (n)	15	14
Females(n)	5	6
Rural residence(n)	12	11
Urban residence(n)	8	9
Mean BMI (Kg/m^2)	23.9	24.1

Table 2: Comparison of recovery parameters

Time from administration (mins)	Flumazenil group	Control group	p-value
Spontaneous breathing	5.1	7.2	0.001*
Eye opening on verbal command	6.2	8.9	0.000*
Hand squeezing on verbal command	6.8	9.1	0.000*
Extubation	7.5	9.5	0.000*

*: Significant

Table 3: Comparison of BIS values

Time interval	Flumazenil group	Control group	p-value
0 mins	42.3	44.1	0.25
2 mins	46.2	48.5	0.11
6 mins	68.6	52.5	0.000*
12 mins	76.9	55.8	0.000*

*: Significant

RESULTS

The mean age of the patients of the Flumazenil group and control group was 48.3 years and 46.2 years. Majority proportion of patients were males and were of rural residence. Mean BMI among patients of the Flumazenil group and control group was 23.9 Kg/m^2 and 24.1 Kg/m^2 respectively. Mean time to spontaneous breathing among patients of the Flumazenil group and Control group was 5.1 minutes and 7.2 minutes respectively. Eye opening on verbal command among patients of the Flumazenil group and Control group was 5.1 minutes and 7.2 minutes respectively. Eye opening on verbal command among patients of the Flumazenil group and Control group was 6.2 minutes and 8.9 minutes respectively. Recovery parameters were significantly better among patients of the flumazenil group. The BIS value was significantly higher in flumazenil group than in the control group beginning 6 min after flumazenil administration.

DISCUSSION

Flumazenil is a drug that acts as an antagonist of benzodiazepines, through interaction with GABA-A receptor. Thus, it could be used to more quickly reverse the hypnotic effect of isoflurane. The literature shows that the use of flumazenil may be beneficial in reversing anesthesia with sevoflurane but lacks studies with isoflurane in our knowledge.[6- 9]Hence; the present study was conducted for evaluating flumazenil's impact on anaesthesia recovery and bispectral index post sevoflurane/fentanyl anesthesia without premedication at a tertiary hospital.

The mean age of the patients of the Flumazenil group and control group was 48.3 years and 46.2 years. Majority proportion of patients were males and were of rural residence. Mean BMI among patients of the Flumazenil group and control group was 23.9 Kg/m^2 and 24.1 Kg/m^2 respectively. Mean time to spontaneous breathing among patients of the Flumazenil group and Control group was 5.1 minutes and 7.2 minutes respectively. Eye opening on verbal command among patients of the Flumazenil group and Control group was 5.1 minutes and 7.2 minutes respectively. Eye opening on verbal command among patients of the Flumazenil group and Control group was 6.2 minutes and 8.9 minutes respectively. Recovery parameters were significantly better among patients of the flumazenil group. The BIS value was significantly higher in flumazenil group than in the control group beginning 6 min after flumazenil administration.Kim YJ et al assessed the Effect of flumazenil on recovery from anesthesia and the bispectral index after sevoflurane/fentanyl general anesthesia in patientswithout premedication. Forty-five healthy patients without premedication were randomly allocated to either flumazenil or control groups. Each patient received either a single dose of 0.3 mg of flumazenil (n = 24) or placebo (n = 21). After drug administration, various recovery parameters and bispectral index (BIS) values in the flumazenil and control groups were compared. Mean time to spontaneous respiration, eye opening on verbal command, hand squeezing on verbal command, extubation and time to date of birth recollection were significantly shorter in the flumazenil group than in the control group (P = 0.004, 0.007, 0.005, 0.042, and 0.016, respectively). The BIS value was significantly higher in flumazenil group than in the control group beginning 6 min after flumazenil administration.[10]Liang P et al evaluated the effect of intravenous flumazenil on sevoflurane minimum alveolar anesthetic concentration–awake (MAC-Awake) and emergence mental status. The study included two steps. Firstly, 49 healthy patients, aged 20-40 years scheduled for elective surgeries, were randomly assigned to two groups, a flumazenil group (n=24) and a saline group (n=25). The flumazenil group received 0.006 mg/Kg IV, and the control group received the same volume of saline 20 min before induction. The flumazenil group and the control group were compared with regard to MAC-Awake (anesthetic concentration achieving 50% probability of eye opening in response to a verbal command). We used mask inhalation to measure the MAC-Awake by up-and-down method. The second steps, 60 patients undergoing lower abdomen surgeries were randomly divided into two groups, a experimental group (n=30) and a saline group (n=30). All patients were anesthetized with sevoflurane/sulfentanil. The MAC-Awake was 0.65% in the control group and 0.82% in the flumazenil group (p=0.34). After extubation, the recovery time and time to extubation showed no difference between the flumazenil group and the saline group ($p>0.05$). But the 10 min and 15 min MMSE scores after extubation were better in the flumazenil group than those in the saline group ($p<0.05$). There was no difference for MMSE scores after 30 min between two groups.[11]

CONCLUSION

The administration of flumazenil to patients without premedication undergoing anesthesia with sevoflurane and fentanyl may facilitate recovery from anesthesia. This phenomenon could be attributed to flumazenil's ability to counteract the effects of sevoflurane or endogenous benzodiazepines. Nevertheless, a comprehensive study involving a larger sample size may be necessary to more precisely assess the impact and safety of flumazenil in the context of recovery from general anesthesia.

REFERENCES

1. Schwieger IM, Szlam F and 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.
2. Kim YJ, Lee H, Kim CH, Lee GY, Baik HJ and 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; 62: 19-23.
3. Karakosta A, Andreotti B, Chapsa C, Pouliou A and Anastasiou E. Flumazenil expedites recovery from sevoflurane/remifentanil anaesthesia when administered to healthy unpremedicated patients. Eur J Anaesthesiol 2010; 27: 955- 959.
4. Sebel LE, Richardson JE, Singh SP, Bell SV and Jenkins A. Additive effects of sevoflurane and propofol on gamma-aminobutyric acid receptor function. Anesthesiology 2006; 104: 1176- 1183.
5. Karakosta A, Andreotti B, Chapsa C, Pouliou A, Anastasiou E. Flumazenil expedites recovery from sevoflurane/remifentanil anaesthesia when administered to healthy unpremedicated patients. Eur J Anaesthesiol. 2010;27:955–959.
6. Stucke AG, Zuperku EJ, Krolo M, Brandes IF, Hopp FA, Kampine JP, et al. Sevoflurane enhances gamma-aminobutyric acid type A receptor function and overall inhibition of inspiratory premotor neurons in a decerebrate dog model. Anesthesiology. 2005;103:57–64.
7. Salmi E, Kaisti KK, Metsähonkala L, Oikonen V, Aalto S, Någren K, et al. Sevoflurane and propofol increase 11C-flumazenil binding to gamma-aminobutyric acid A receptors in humans. AnesthAnalg. 2004;99:1420–1426.
8. Nishikawa K, Harrison NL. The actions of sevoflurane and desflurane on the γ-aminobutyric acid receptor type A: effects of TM2 mutations in the alpha and beta subunits. Anesthesiology. 2003;99:678–684.
9. 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
10. 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.
11. Liang P, Zhou C, Li KY, Guo LJ, Liu B, Liu J. Effect of flumazenil on sevoflurane requirements for minimum alveolar anesthetic concentration-awake and recovery status. Int J Clin Exp Med. 2014 Mar 15;7(3):673-9.