



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br



SCIENTIFIC ARTICLE

The use of flumazenil for benzodiazepine associated respiratory depression in postanesthesia recovery: risks and outcomes



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Received 12 May 2017; accepted 27 December 2017

Available online 4 February 2018

KEYWORDS

Flumazenil;
Benzodiazepine;
Postanesthesia care
unit;
Postoperative
complications

Abstract

Background and objectives: The primary aim was to determine risk factors for flumazenil administration during postanesthesia recovery. A secondary aim was to describe outcomes among patients who received flumazenil.

Methods: Patients admitted to the postanesthesia recovery room at a large, academic, tertiary care facility after surgery under general anesthesia from January 1, 2010, to April 30, 2015, were identified and matched to 2 controls each, by age, sex, and surgical procedure. Flumazenil was administered in the recovery phase immediately after general anesthesia, according to the clinical judgment of the anesthesiologist. Demographic, procedural, and outcome data were extracted from the electronic health record. Conditional logistic regression, accounting for the 1:2 matched-set case-control study designs, was used to assess characteristics associated with flumazenil use.

Results: The incidence of flumazenil administration in the postanesthesia care unit was 9.9 per 10,000 (95% CI, 8.4–11.6) general anesthetics. History of obstructive sleep apnea (Odds Ratio [OR] = 2.27; 95% CI 1.02–5.09), longer anesthesia (OR = 1.13; 95% CI 1.03–1.24 per 30 minutes), use of total intravenous anesthesia (OR = 6.09; 95% CI 2.60–14.25), and use of benzodiazepines (OR = 8.17; 95% CI 3.71–17.99) were associated with risk for flumazenil administration. Among patients who received midazolam, cases treated with flumazenil received a higher median (interquartile range) dose than controls: 3.5 mg (2.0–4.0 mg) vs. 2.0 mg (2.0–2.0 mg), respectively ($p < 0.001$). Flumazenil use was correlated with a higher rate of unanticipated noninvasive positive pressure ventilation, longer postanesthesia care unit stay, and increased rate of intensive care unit admissions.

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PALAVRAS-CHAVE

Flumazenil;
Benzodiazepínico;
Sala de recuperação
pós-anestésica;
Complicações
pós-operatórias

Conclusions: Patients who required flumazenil postoperatively had received a higher dosage of benzodiazepines and utilized more postoperative health care resources. More conservative perioperative use of benzodiazepines may improve postoperative recovery and use of health care resources.

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O uso de flumazenil para depressão respiratória associada ao benzodiazepínico na recuperação pós-anestésica: riscos e resultados

Resumo

Justificativa e objetivos: Determinar os fatores de risco da administração de flumazenil durante a recuperação pós-anestésica e descrever os desfechos entre os pacientes que receberam flumazenil.

Métodos: Os pacientes admitidos em sala de recuperação pós-anestésica de um grande centro universitário em setor terciário de cuidados pós-cirurgia sob anestesia geral entre 1º de janeiro de 2010 e 30 de abril de 2015 foram identificados e pareados com dois controles cada por idade, sexo e procedimento cirúrgico. Flumazenil foi administrado na fase de recuperação imediatamente após a anestesia geral, de acordo com a avaliação clínica do anestesiológico. Os dados demográficos, dos procedimentos e dos desfechos foram extraídos do registro eletrônico de saúde. A regressão logística condicional para os desenhos do estudo de caso-controle pareado em 1:2 foi utilizada para avaliar as características associadas ao uso de flumazenil.

Resultados: A incidência da administração de flumazenil em sala de recuperação pós-anestésica foi de 9,9 por 10.000 (95% IC: 8,4-1,6) anestésias gerais. História da apneia obstrutiva do sono (razão de chances [OR] = 2,27; IC 95%: 1,02-5,09), anestesia de longa duração (OR = 1,13; IC 95%: 1,03-1,24 por 30 minutos), uso de anestesia intravenosa total (OR = 6,09; IC de 95%: 2,60-14,25) e uso de benzodiazepínicos (OR = 8,17; IC 95%: 3,71-17,99) foram associados a risco para a administração de flumazenil. Entre os pacientes que receberam midazolam, os casos tratados com flumazenil receberam uma dose mediana mais alta (intervalo interquartil) do que os controles: 3,5 mg (2,0-4,0 mg) vs. 2,0 mg (2,0-2,0 mg), respectivamente ($p < 0,001$). O uso de flumazenil foi correlacionado com uma taxa maior não prevista de ventilação não invasiva com pressão positiva, permanência mais longa em sala de recuperação pós-anestésica e aumento da taxa de admissões em unidade de terapia intensiva.

Conclusões: Os pacientes que precisaram de flumazenil no pós-operatório receberam uma dose maior de benzodiazepínicos e usaram mais recursos de cuidados da saúde no pós-operatório. O uso mais conservador de benzodiazepínicos no período perioperatório pode melhorar a recuperação e o uso de recursos de cuidados da saúde no pós-operatório.

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Introduction

Benzodiazepines are a class of psychoactive drugs used as anxiolytic and amnestic agents before or during anesthesia or as a component of conscious sedation. Excess administration, altered pharmacodynamics or pharmacokinetics, and coadministration of respiratory depressants all can potentiate the adverse effects of benzodiazepines. In oversedated patients, flumazenil may be used to antagonize those adverse effects. Intravenous flumazenil, with a peak effect in 6–10 minutes, acts as a competitive inhibitor at the benzodiazepine binding site on the γ -aminobutyric acid Type A (GABA_A) receptor. Because flumazenil has a shorter

duration of action than benzodiazepines, re sedation may occur after the initial reversal effect dissipates.

The implications of antagonizing the effects of benzodiazepines after general anesthesia are unclear: Some studies have associated flumazenil use with higher composite scores on cognitive function tests and shortened recovery time, and others have described no difference in recovery time and adverse events.^{1–5} Further, although flumazenil reliably reverses benzodiazepine-induced sedation, it has complex effects on benzodiazepine-altered central ventilatory drive (it restores tidal volume but not respiratory rate), and it paradoxically decreases the ventilatory response to hypercarbia.⁶

Information is limited on the effects of flumazenil administration during recovery after general anesthesia to treat respiratory depression or oversedation. Additionally, clinical outcomes among patients after receiving flumazenil during recovery from anesthesia are abstruse. The primary aim of the present study was to determine risk factors associated with flumazenil administration during postanesthesia recovery. A secondary aim was to describe outcomes among patients who received flumazenil.

Materials and methods

This study was approved by the Institutional Review Board. Only patients who had provided written authorization for the use of their medical records in research were included (in accordance with Minnesota Statute 144.295). A retrospective case-control study design was used to assess the preoperative and procedural characteristics associated with flumazenil administration during recovery after undergoing general anesthesia.

Study population

This study was performed at a large, academic tertiary care facility. Institutional medical records from January 1, 2010, to April 30, 2015, were screened electronically for adult patients administered flumazenil during the recovery phase after undergoing general anesthesia. For each index patient who had received flumazenil, 2 control patients (who received general anesthesia during the same year but did not receive flumazenil) were identified from the electronic health record database. Matching between cases and controls included age (within 5 years), sex, and procedural type according to International Classification of Diseases, Ninth Revision (ICD-9) procedural codes.

Intervention

Flumazenil was administered in the recovery phase immediately after general anesthesia. This phase extended from the end of the surgical procedure to discharge from the Postanesthesia Care Unit (PACU). The PACU was staffed with registered nurses qualified in phase 1 postanesthesia recovery. If additional expertise was required, the attending anesthesiologist was readily available. Administration of flumazenil was determined according to the clinical judgment of the anesthesiologist. Common criteria for discharge from phase 1 recovery were used⁷ along with additional screens for respiratory depression.^{8,9} Further, discharge necessitated acceptable control of nausea and a numeric pain score less than 5 (on a scale from 0 to 10, where 10 is the worst pain). If patients had a known history of Obstructive Sleep Apnea (OSA), continuous positive airway pressure devices were used during recovery if indicated.

Data collection

Data extracted from the electronic health record included patient demographics, comorbid conditions, perioperative variables (including postoperative course), and

postprocedural complications. Collected metrics included patient age, sex, body mass index, American Society of Anesthesiologists (ASA) Physical Status score, history of consumption of benzodiazepines or opioids (or both), chronic lung disease, and history of OSA or positive results for OSA from a standardized screening tool.¹⁰

The surgical records were used to determine the type of surgical procedure. Anesthetic records were reviewed for (1) Anesthetic technique (general anesthesia with or without neuraxial analgesia); (2) Anesthetic type (Volatile or Total Intravenous Anesthesia [TIVA]); (3) Duration of anesthesia; and (4) Dose of midazolam, ketamine, nondepolarizing muscle relaxants, reversal with neostigmine if indicated, and use of systemic opioid analgesics. TIVA included only patients who received exclusively intravenous anesthesia (without volatile agents). Systemic opioid doses were converted to intravenous morphine equivalents according to published guidelines.^{11,12} Phase 1 recovery duration was considered to extend from PACU admission to the time when discharge criteria were met. PACU nursing records were examined for administration of opioids, midazolam, neostigmine, flumazenil, or naloxone and for admission to the Intensive Care Unit (ICU) from the PACU. Length of hospital stay, postoperative complications, unplanned transfer from PACU to the ICU, and 30-day mortality were abstracted from the medical records.

Statistical analysis

Data from continuous variables were expressed as mean (SD) or median (interquartile range); categorical variables were summarized as frequency and percentage. Conditional logistic regression, taking into account the 1:2 matched-set case-control study design, was used to assess characteristics potentially associated with flumazenil administration. Body mass index, anesthesia duration, and intraoperative opioid dose were modeled as continuous variables; all other characteristics were modeled as nominal variables. Outcomes were appraised with administration of flumazenil as the explanatory variable for univariate comparisons; 2 sample methods (*t*-test or rank sum test as appropriate) were used for continuous variables, and the Fisher exact test was used for categorical variables. Although not adjusted for multiple comparisons, 2 tailed *p*-values were reported. A *p*-value less than 0.05 was considered significant. Analyses were performed with SAS statistical software (Version 9.2; SAS Institute Inc.).

Results

Demographics

A total of 152,197 patients underwent general anesthesia and were admitted to the PACU during the study period. Of those, 151 received flumazenil, yielding an incidence of flumazenil administration of 9.9 per 10,000 (95% CI 8.4–11.6) general anesthetics in the PACU. Of the 151 patients who received flumazenil, 20 denied research authorization for review of their medical records and were therefore excluded from subsequent analyses.

Table 1 Matching variables for patients who received flumazenil during anesthesia recovery and matched controls.^a

Variable	Cases (n=131)	Controls (n=262)
Age, y	57.7 (13.3)	57.9 (12.6)
Males	53 (40.5)	106 (40.5)
<i>Surgical specialty</i>		
Cardiac	3 (2.3)	6 (2.3)
General	19 (14.5)	38 (14.5)
Head and neck	13 (9.9)	26 (9.9)
Neurosurgical	16 (12.2)	32 (12.2)
Ophthalmologic	2 (1.5)	4 (1.5)
Orthopedic	11 (8.4)	22 (8.4)
Plastic	7 (5.3)	14 (5.3)
Thoracic	25 (19.1)	50 (19.1)
Urologic and gynecologic	33 (25.2)	66 (25.2)
Vascular	1 (0.8)	2 (0.8)
Interventional pain	1 (0.8)	2 (0.8)

^a Continuous data are presented as mean (SD); categorical data as number of patients (percentage of sample).

Analysis

Table 1 summarizes appropriate matching between index cases and controls by age, sex, and procedural type. Univariable comparisons and adjusted multivariable modeling of baseline clinical factors and intraoperative course of cases and controls are shown in **Table 2**. In adjusted multivariable analysis, history of OSA, longer anesthetic duration, maintenance of anesthesia with TIVA, and the use of benzodiazepines were associated with increased flumazenil administration (**Table 2**). Subgroup analysis showed that patients maintained with TIVA received a higher mean midazolam dose and a lower median opioid dose (**Table 2**). Of the subset of patients (cases and controls) who received midazolam, those who were treated with flumazenil received higher median doses of midazolam compared to the controls: 3.5 mg (2.0–4.0 mg) vs. 2.0 mg (2.0–2.0 mg) ($p < 0.001$).

Outcomes

The phase 1 and postoperative courses of cases and controls are summarized in **Table 3**. The administration of flumazenil was correlated with a higher incidence of noninvasive positive pressure ventilation in those without OSA, a longer PACU stay, and an increased rate of ICU admission.

Discussion

As expected, the main finding from this study was that more liberal administration of midazolam was associated with increased rates of flumazenil administration. Additional associations included OSA history (or screen) and 2 components of perioperative care: the use of TIVA for anesthetic maintenance and longer anesthetic duration. The administration of flumazenil was infrequent but comparable to our previous report of the incidence of naloxone

administration during phase 1 recovery of 2.5 per 1000 (95% CI 7–6.5) anesthetics.^{13,14} The patients administered flumazenil required more health care resources as manifested by longer phase 1 anesthesia recovery, increased need for unanticipated noninvasive positive pressure ventilation, and higher rates of ICU admissions.

The use of benzodiazepines, specifically midazolam, as part of the induction of general anesthesia is common in contemporary practice. Yet, with the exception of a potentially favorable decrease in phase 1 recovery time vis-à-vis antiemetic property,^{15,16} the effects of midazolam on phase 1 recovery have not received extensive attention in the medical literature. Some evidence has shown that midazolam is associated with longer phase 1 recovery time and episodes of hypoxemia in elderly surgical patients¹⁷ and with postoperative sedation in younger adults undergoing outpatient surgery.¹⁸ We previously observed that midazolam trended toward an association with an increased rate of respiratory depressive episodes during anesthesia recovery.¹⁹ We have also observed that higher doses of midazolam during spinal anesthetics were associated with increased rates of respiratory depression during anesthesia recovery.²⁰

The association between TIVA and an increased risk for receiving flumazenil was unexpected. This higher rate of respiratory events or oversedation occurred despite the substantially lower use of opioids in patients undergoing TIVA. We speculate that this relationship reflects that patients anesthetized with TIVA were administered midazolam more frequently and at higher doses than those anesthetized with inhalational volatile agents. Although the reason for greater midazolam administration with TIVA cannot be determined retrospectively, it may result partly from a need to ensure amnesia out of concern about a higher incidence of recall with TIVA than with a balanced volatile anesthetic.²¹ Another possible explanation is that the elimination of inhalational agents with breathing may more predictably lead to anesthetic recovery when compared to the polypharmacy that is sometimes used during TIVA.

Also unexpected was the association between longer anesthetic duration and flumazenil administration. Logically, a longer anesthetic would allow the effects of the benzodiazepine administered during anesthetic induction to subside and thus be protective. It is unclear why the opposite relationship was observed, but it could be due to the cumulative effects of a longer anesthetic on phase 1 recovery.

More resources were required for the care of patients administered flumazenil compared to their matched controls. Therefore, a reduction in the need for flumazenil administration should have a favorable effect on the efficiency of the perioperative practice. We previously observed that PACU efficiency was improved and phase 1 recovery time reduced with a practice initiative that included less perioperative midazolam administration.¹⁹ This suggests that more conservative administration of perioperative benzodiazepine may improve immediate postoperative outcomes. Our observations that TIVA, longer surgery, and history (or positive screen) for OSA were associated with increased flumazenil administration can help the anesthesiologist assess individual risk and guide midazolam use. Fortunately, patients administered flumazenil did not have

Table 2 Potential risk factors for receiving flumazenil during anesthesia recovery.^a

Characteristic	Cases (n = 131)	Controls (n = 262)	Univariable analysis ^b			Multivariable analysis ^b		
			OR	95% CI	p	OR	95% CI	p
<i>Medical comorbidity or condition</i>								
BMI	28.3 (6.8)	29.0 (7.5)	0.93	0.80–1.08	0.37	0.96	0.92–1.01	0.09
Lung disease	10 (7.6)	27 (10.3)	0.73	0.35–1.53	0.40	0.77	0.31–1.92	0.57
Long-term use of opioid or benzodiazepine	40 (30.5)	81 (30.9)	0.98	0.60–1.61	0.93	0.78	0.41–1.48	0.44
OSA ^c	31 (23.7)	40 (15.3)	1.83	1.04–3.20	0.04	2.27	1.02–5.09	0.046
<i>ASA PS score</i>								
I or II	67 (51.1)	153 (58.4)	1.00	–	–	–	–	–
≥III	64 (48.9)	109 (41.6)	1.48	0.90–2.41	0.12	1.28	0.68–2.41	0.44
<i>Anesthetic agent</i>								
Volatile	63 (48.1)	195 (74.4)	1.00	–	<0.001	–	–	<0.001
TIVA ^d	68 (51.9)	67 (25.6)	5.72	3.07–10.66	–	6.09	2.60–14.25	–
Anesthetic duration, min ^e	169 (104–296)	171 (92–268)	1.08	1.01–1.16	0.03	1.13	1.03–1.24	0.01
<i>Preoperative medication</i>								
Gabapentin	21 (16.0)	26 (9.9)	2.67	1.11–6.42	0.03	1.63	0.47–5.64	0.44
Benzodiazepine ^f	119 (90.8)	160 (61.1)	6.74	3.41–13.31	<0.001	8.17	3.71–17.99	<0.001
Sustained-release opioid	20 (15.3)	21 (8.0)	2.68	1.23–5.82	0.01	2.60	0.88–7.68	0.08
<i>Intraoperative medication</i>								
Neuraxial opioid	4 (3.1)	13 (5.0)	0.45	0.11–1.87	0.27	0.26	0.04–1.80	0.17
Systemic opioid (ME), mg	19 (5–30)	23.3 (10–31.5)	0.89	0.82–0.98	0.02	0.94	0.81–1.08	0.38
Ketamine ^g	31 (23.7)	45 (17.2)	1.57	0.91–2.73	0.11	1.77	0.85–3.71	0.13
Nondepolarizing muscle relaxants	64 (48.9)	133 (50.8)	0.86	0.48–1.55	0.62	1.31	0.56–3.07	0.53

ASA-PS, American Society of Anesthesiologist Physical Status; BMI, Body Mass Index calculated as weight in kilograms divided by height in meters squared; ME, morphine equivalents; OR, Odds Ratio; OSA, Obstructive Sleep Apnea; TIVA, Total Intravenous Anesthesia.

^a Continuous data are presented as mean (SD) or as median (interquartile range); categorical data as number of patients (percentage of sample).

^b Analyses were completed with conditional logistic regression factoring in the matched-set (1:2) study design. In addition to univariable analysis, all variables were included in the multivariable model. The odds ratio is presented for a 5 kg·m⁻² increase in BMI, 30 min increase in anesthetic duration, and 5-ME increase in intraoperative systemic opioid.

^c Diagnosis from a documented history or a positive screen for OSA.

^d Secondary analysis for patients maintained with TIVA, compared to those who received inhalation agents, showed an increased frequency of receiving midazolam (number of instances), an increased median (SD) dose of midazolam (in milligrams), and a decreased median dose (interquartile range) of intraoperative systemic opioid (ME in milligrams): 110 (84.0%) vs. 169 (64.5%); 3.23 (0.24) vs. 1.65 (0.17); and 10 (5.0–15.3) vs. 25 (17.9–35.0), respectively (all $p < 0.001$).

^e Multivariate analysis with 95% confidence in units of 30 minutes.

^f Among patients who received midazolam, index cases received a median dose (interquartile range) of 3.5 mg (2.0–4.0 mg), and controls received 2.0 mg (2.0–2.0 mg) ($p < 0.001$).

^g Secondary analysis for patients who received ketamine showed no difference between the median perioperative dose (interquartile range) for index cases (20 mg [10–20 mg]) and controls (20 mg [10–20 mg]) ($p = 0.88$).

longer hospital stays or increased rates of adverse events, unlike patients who required naloxone administration during phase 1 anesthesia.^{13,14}

Postoperative oversedation from benzodiazepine administration has been considered by others. Specifically, to eliminate elements of excessive postoperative sedation, some have suggested the planned use of flumazenil after anesthesia; however, the clinical effect of this preemptive treatment is controversial. Some have reported higher composite scores for cognitive function with the

administration of flumazenil after general anesthesia maintained with midazolam and fentanyl,² significant shortening of recovery time after conscious sedation with midazolam,¹ and expedited recovery after sevoflurane-remifentanyl anesthesia.³ In contrast, others have reported no difference in recovery time with flumazenil reversal after sevoflurane-sufentanil despite a partial reversal of hypnotic effects⁴ and an association with adverse events from flumazenil treatment for suspected benzodiazepine intoxication (overdose).⁵

Table 3 Postoperative outcomes among patients administered flumazenil and matched controls.

Outcome	Cases (n = 131) ^a	Controls (n = 262) ^a	p
<i>Recovery room</i>			
Respiratory depressive events	10 (7.6)	14 (5.3)	0.38
Noninvasive positive pressure ventilation in those without OSA ^b	5 (5.0)	1 (0.5)	0.01
Duration of stay, min ^c	106 (65–155)	71 (43–106)	<0.001
ICU admission	25 (19.1)	20 (7.6)	0.001
Inpatient length of stay, days	3 (1–7)	2 (1–4)	0.15
Death	1 (0.8)	4 (1.5)	0.67

ICU, intensive care unit; OSA, obstructive sleep apnea.

^a Categorical data are summarized as number of patients (percentage of sample) and compared with the Fisher exact test; continuous data are summarized as median (interquartile range) and compared with the rank sum test.

^b Analysis was restricted to 100 cases and 222 controls who did not have a history of OSA.

^c Analysis excluded 19 cases and 28 controls who bypassed phase 1 recovery in the postanesthesia care unit for various reasons, including direct transfer to ICU, to a general care ward, or to a subsequent procedural care area.

The retrospective nature of the study design has several inherent limitations, including a potential for incomplete data and a potential for biases affecting the selection of controls, which limit its predictive ability. In addition, the administration of flumazenil was used as a marker for respiratory depression or excess sedation requiring intervention, and it may be an imperfect surrogate. Possibly cases of less severity were treated with more conservative methods, and so were not identified with our data collection. Another source of bias is that the decision to administer flumazenil was left to the judgment of the attending anesthesiologist. Consequently, this study may have underreported the true rate of benzodiazepine-associated postoperative sedation or respiratory depression. Limitations also exist for the routine use of personal positive pressure airway equipment as necessitated for diagnosed OSA and the deployment of these personal devices during anesthesia recovery. This introduces a limitation in the interpretation of documented unanticipated noninvasive positive pressure ventilation for the treatment of respiratory depression in the PACU. Finally, the matched design of this study prevented an assessment for potential associations with age, sex, or surgical type.

Conclusions

Flumazenil administration during anesthetic recovery was found to be a marker of respiratory depression secondary to higher benzodiazepine usage. The requirement for flumazenil administration was associated with a history of OSA, TIVA, and longer anesthetic duration and resulted in higher rates of unanticipated noninvasive positive pressure ventilation, more time in the recovery room, and increased rates of ICU admission. Reduced use of perioperative benzodiazepines, especially during TIVA, may decrease the need for postoperative flumazenil interventions and may decrease the use of health care resources.

Conflicts of interest

The authors declare no conflicts of interest.

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