

ARTIGO ORIGINAL

Does Intravenous Midazolam Induce Hyperalgesia? A Retrospective Observational Study in Ambulatory Surgery

Será o Midazolam Hiperalgésico? Um Estudo Observacional Retrospectivo em Cirurgia de Ambulatório

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Keywords

Midazolam; Pain, Postoperative

Palavras-chave

Dor Pós-Operatória; Midazolam

ABSTRACT

Introduction: Benzodiazepines are frequently prescribed to surgical patients as anxiolytic premedication. Evidence suggests that midazolam also impacts on nociception, however, conflicting results have been published reporting both antinociceptive and hyperalgesic effects. Our aim was to assess how intravenous midazolam affects pain and functional outcome after ambulatory knee arthroscopy.

Methods: We conducted an observational retrospective cohort study. All patients submitted to arthroscopic knee surgery under spinal anesthesia in our ambulatory surgery center between January 2011 and December 2015 were analyzed. We recorded demographic and clinical data, anesthetic drugs administered, and post-operative pain scores and functional limitations obtained through a telephone interview conducted 24 hours after surgery. The association between midazolam dose and pain, as well as limitations, was estimated by logistic regression, adjusting for age, ASA, opioids and local anesthetics.

Results: We included 270 patients. Mean age was 52.2 ± 9.6 years, 55.9% of patients were male and 95,9% ASA status 1 or 2. At

postoperative day one, 41.8% of patients reported mild or moderate pain, and 58.9% complained of functional limitations. Women reported pain more frequently than men ($p = 0.001$). Higher doses of midazolam were independently associated with postoperative pain at 24 hours in men, but not in women, with multivariate analyses showing an adjusted OR of 1.73 (IC 95% 1.26–2.37).

Conclusion: Our results suggest an association between higher midazolam doses and more frequent report of postoperative pain, in men only. Further studies are needed to evaluate whether this association is due to a true causal relation between midazolam and pain.

RESUMO

Introdução: As benzodiazepinas são frequentemente prescritas como pré-medicação ansiolítica no contexto cirúrgico. Apesar de existir evidência que o midazolam possa interferir na nociceção, os resultados são contraditórios, com estudos sugerindo efeitos antinociceptivos enquanto outros apontam para efeitos de hiperalgesia.

Objetivo: Determinar o impacto do midazolam endovenoso na dor e limitação funcional após artroscopia do joelho em ambulatório.

Métodos: Neste estudo observacional retrospectivo avaliámos os doentes submetidos a artroscopia do joelho sob bloqueio subaracnoideu em regime de ambulatório, entre janeiro 2011 e dezembro 2015. Foram analisados dados demográficos e clínicos,

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fármacos administrados, intensidade da dor pós-operatória e limitação funcional, através de contacto telefónico 24 horas após a cirurgia. A associação entre a dose de midazolam e intensidade de dor e limitação funcional foi estimada usando modelos de regressão logística ajustada para a idade, ASA, uso de opióides e anestésicos locais.

Resultados: Foram incluídos 270 doentes, com idade média de $52,2 \pm 9,6$ anos, 55,9% do sexo masculino e 95,9% ASA 1 ou 2. Às 24 horas, 41,8% referiam dor ligeira a moderada e 58,9% referiam limitação funcional. As doentes do sexo feminino referiram mais frequentemente dor ($p = 0,001$). Doses mais altas de midazolam associaram-se a maior probabilidade de dor às 24 horas, mas apenas no sexo masculino, com um *odds ratio* ajustado de 1,73 (IC 95% 1,26–2,37).

Conclusão: O nosso estudo sugere uma associação entre aumento da intensidade da dor pós-operatória após administração de maiores doses de midazolam, no sexo masculino. Contudo, mais estudos serão necessários para comprovar esta associação.

INTRODUCTION

The role of an anxiolytic premedication in the ambulatory surgical population is under constant debate. Premedication practices with benzodiazepines vary greatly amongst geographic areas and even within providers at a given institution, being often prescribed to surgical patients in this context.¹

Midazolam is the most popular benzodiazepine used prior to surgery due to its rapid onset, short half-life and acceptable safety profile.¹ It exerts its pharmacological effects by binding to benzodiazepine receptors that modulate γ -aminobutyric acid receptor type A (GABA-A), the major inhibitory neurotransmitter in the central nervous system. These receptors are found in several sites, such as cerebral cortex, hippocampus, cerebellum, brain stem and along the spinal cord, with the highest density in *lamina II* of the dorsal horn.^{2,3} Furthermore, midazolam may interact with other receptors, namely DOP receptors in the spinal cord, that can contribute to its antinociceptive effect when administered intrathecally.^{4,5} The supraspinal mode of action, however, is not clear.³⁻⁶

Studies in both animals and humans have shown that intravenous midazolam decreases the intra-operative requirements of volatile agents,^{7,8} and might as well exert a central antiemetic effect, although this mechanism is not well established.¹ Nevertheless, its effect on nociception is still unknown.

In animal studies, midazolam has ambiguous effects on nociception depending on the route of administration and the method used to assess pain: while intrathecally administered midazolam consistently attains an analgesic result,⁹⁻¹¹ intraperitoneal midazolam has been shown to

promote both antinociceptive and nociceptive effects^{6,11}; intracerebroventricular injection may also be associated with hyperalgesia.¹² This nociceptive effect is believed to be due to a supraspinal mechanism.⁹⁻¹²

In humans, similar antinociceptive results of regional administration of midazolam have been published: intrathecal, epidural, intra-articular or brachial plexus administration of midazolam improved postoperative analgesia and reduced rescue analgesics, without adding any significant side effects.^{13,14}

Nevertheless, the effect of intravenous midazolam on human nociception has not become evident yet, with studies showing conflicting results.¹⁵⁻¹⁷ Evidence from animal studies suggests that midazolam could also have hyperalgesic effects in humans, with one study in volunteers demonstrating increased pain perception with midazolam.¹⁵

We have, however, found this association between midazolam and pain (in men only) as an unexpected result in a previous study addressing a different research question.¹⁸

Therefore, with this uncertainty whether systemically administered midazolam is analgesic or hyperalgesic, we conducted a retrospective study to address the effect of different intravenous midazolam doses on postoperative pain and ambulation scores of outpatients submitted to arthroscopic knee surgery.

We hypothesize that midazolam increases pain perception in patients submitted to ambulatory surgery, and that this effect might be different amongst genders.

MATERIAL AND METHODS

Ethics Approval

Ethical approval was obtained from the Hospital Ethics Committee, number 91/2015. The need for patient consent was waived since the study was retrospective and only documented existing clinical practice.

Study Population

For this retrospective cohort study we included all adult patients submitted to elective arthroscopic knee surgery under spinal anesthesia in the Ambulatory Surgery Center of our hospital, between January 2011 and December 2015.

Data Collection

All data were retrospectively collected between January and April 2016 by reviewing patient files and anesthesia records. Demographic data included sex and age. The American Society of Anesthesiology (ASA) physical status, duration of surgery, type of anesthesia (spinal or combined spinal-femoral block) and doses of administered drugs were also recorded. Pain and functional status scores had been obtained and previously recorded into patient files on routine

basis during a telephone interview conducted by a nurse at the first postoperative day.

Exclusion Criteria

Patients with incomplete data or patients that received combined spinal-femoral block were excluded from the study.

Definition of Variables

The main exposure variable was total midazolam dose administered intravenously in the theatre, immediately before the spinal block or during surgery.

The primary outcome was pain, classified as none, mild, moderate or severe, according to the patients' self-report during the telephone interview 24 hours postoperatively. Secondary outcomes were: postoperative limitations, defined as difficulties in walking or carrying out daily activities at the time of the telephone interview, and other postoperative complications.

We consider there might be a different effect among genders; concomitant use of opioids, different doses of local anesthetic, ASA status and age were also deemed potential confounders or effect modifiers, because they might affect the individual perception of pain.

Statistical Analysis

We used a convenience sample that included all cases during the 5-year study period, and this determined the sample size. Categorical variables were presented as frequencies and percentages and continuous variables as means and standard-deviation (mean \pm SD).

In univariate analyses, categorical variables were compared by chi-square tests. The mean values of continuous variables were compared between groups using t-tests.

The odds ratios (OR) with 95% confidence intervals (CI) for the association between midazolam dose and pain or limitations were estimated by logistic regression models, adjusting for age, ASA status, dose of local anesthetic and opioid use. The analyses were performed separately for each gender. All reported *p* values are two-tailed, with a *p* value less than 0.05 indicating statistical significance.

All statistical analyses were performed with StataCorp®.

RESULTS

Participants

Over 5 years, a total of 314 patients were submitted to arthroscopic knee surgery under spinal anesthesia in the Ambulatory Surgery Center. A flowchart of patient entry into the study is shown in Fig. 1.

There were no significant differences between included and excluded subjects regarding age, gender, ASA status, local anesthetic dose, opioid dose and readmission rate. However,

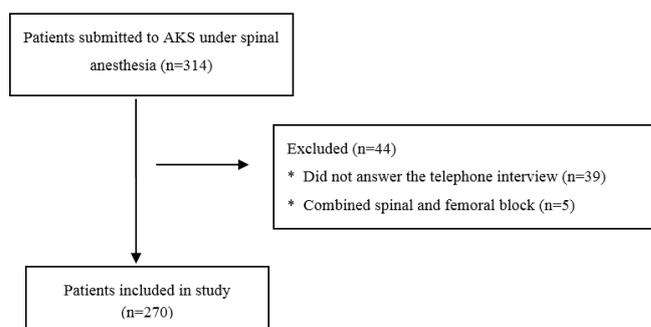


Figure 1. Flowchart of patients in the study

the mean dose of midazolam was significantly higher among excluded patients ($p = 0,041$). Among the 270 patients included in the study, 55.9% were male, the mean \pm SD age was 52.2 ± 9.6 years and 95.9% of the patients were classified as ASA status 1 or 2.

Table 1 lists the characteristics of patients in the study, according to gender.

Female patients were older ($p = 0,002$), but there were no significant differences between male and female patients regarding ASA status, midazolam dose, local anesthetic dose, opioid use and limitations. However, women reported more frequent and more severe pain than men (52.1% versus 34.5%, respectively, $p = 0,001$).

All spinal anesthetics, except one, were performed in the lateral position with hyperbaric bupivacaine (mean \pm SD: 9.2 ± 1.46 mg); one patient received levobupivacaine. Seventeen patients also received intrathecal sufentanil (1-2.5 μ g), and thirteen received intravenous fentanyl (0.05-0.1 mg) as pre-medication. Intravenous midazolam was administered as one or more boluses before induction of spinal anesthesia, or during surgery; the total dose for each patient varied between 0 and 8 mg (mean \pm SD: 3.3 ± 1.43 mg). All surgeries lasted less than 2 hours.

Outcome

At the first postoperative day, 114 (42.2%) patients reported mild or moderate pain, and 159 (58.9%) complained of some functional limitation.

Higher doses of midazolam were associated with more frequent postoperative pain in men ($p = 0.008$) but not in women (Fig. 2), and this effect was independent of other variables. The adjusted OR for reporting pain was 1.73 (95% CI 1.26–2.37). Higher doses of midazolam were also linked to more postoperative functional limitations, but without statistical significance ($p = 0.070$).

On the univariate analysis there was no statistical difference regarding the use of opioid and postoperative pain ($p = 0.692$ and $p = 0.845$, for male and female, respectively) or limitations ($p = 0.958$ and $p = 0.280$, for male and female, respectively). However, in the multivariate analysis, adding

Table 1. Characteristics of patients included in the study, analyzed according to gender

Variable	Male Patients (n=151)	Female Patients (n=119)	P value
Age			
years – mean ± SD	50.5 ± 10.5	54.3 ± 8.2	0.002
ASA status			
1 – no. (%)	42 (27.8)	20 (16.8)	0.101
2 – no. (%)	103 (68.2)	94 (79.0)	0.101
3 – no. (%)	6 (4.0)	5 (4.2)	0.101
Midazolam dose			
mg – mean ± SD	3.19 ± 1.42	3.40 ± 1.45	0.213
Local anaesthetic dose			
mg – mean ± SD	9.12 ± 1.18	9.17 ± 1.73	0.780
Opioid use			
None – no. (%)	131 (86.8)	109 (91.6)	0.211
Sufentanil – no. (%)	13 (8.6)	4 (3.4)	0.211
Fentanyl – no. (%)	7 (4.6)	6 (5.0)	0.211
Pain at 24h PO			
None – no. (%)	99 (65.5)	57 (47.9)	0.001
Mild – no. (%)	51 (33.8)	54 (45.4)	0.001
Moderate – no. (%)	1 (0.7)	8 (6.7)	0.001
Severe – no. (%)	-	-	-
Limitations at 24h PO			
No – no. (%)	64 (42.4)	47 (39.5)	0.632
Yes – no. (%)	87 (57.6)	72 (60.5)	0.632

quantile 1: [0-2.5 mg]; no. = 96; quantile 2: [2.5-4 mg]; no. = 115; quantile 3: [4-8 mg]; no. = 59

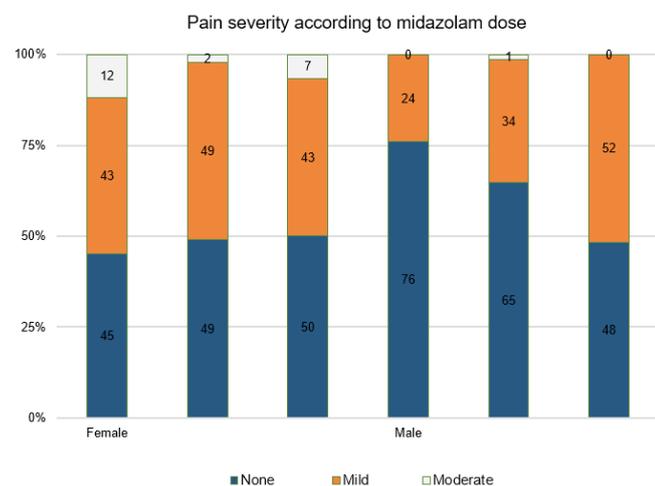


Figure 2. Relation between midazolam dose (quantiles) and pain severity, stratified for gender

the effect of midazolam to the age-, ASA-, local anesthetic use-adjusted model, intrathecal opioids even seemed to increase postoperative pain among men (OR=3.99, 95% CI 1.07–14.91).

There was no statistical difference between different doses of local anesthetic and postoperative pain or limitations.

Tables 2 and 3 present the odds ratios (95% CI) for multivariate

analyses exploring the association between opioid use and midazolam doses and pain or limitations, respectively, according to gender.

Regarding postoperative complications, only one patient

Table 2. Odds ratio (95% CI) for the association between opioid use or midazolam dose and pain, men and women

	Model 1	Model 2	Model 3	Model 4	Model 5
	OR (95% CI)				
Men	No.=151	No.=151	No.=151	No.=151	No.=151
	1.00 (ref)				
Sufentanil use	1.64 (0.52–5.16)	1.63 (0.52–5.15)	1.63 (0.52–5.16)	1.57 (0.49–5.00)	3.99 (1.07–14.91)
Fentanyl use	0.32 (0.04–2.73)	0.32 (0.04–2.81)	0.32 (0.04–2.81)	0.31 (0.04–2.73)	0.42 (0.04–4.13)
Midazolam dose	1.39 (1.08–1.79)	1.40 (1.08–1.80)	1.40 (1.08–1.80)	1.54 (1.16–2.05)	1.73 (1.26–2.37)
Women	No.=119	No.=119	No.=119	No.=119	No.=119
	1.00 (ref)				
Sufentanil use	0.91 (0.12–6.71)	0.97 (0.13–7.23)	0.65 (0.08–5.19)	0.64 (0.08–5.19)	0.63 (0.07–5.38)
Fentanyl use	0.91 (0.18–4.72)	0.92 (0.18–4.78)	0.80 (0.15–4.18)	0.81 (0.15–4.26)	0.80 (0.15–4.35)
Midazolam dose	0.94 (0.73–1.21)	0.95 (0.74–1.22)	1.01 (0.78–1.32)	1.01 (0.76–1.33)	0.99 (0.74–1.32)

OR, odds ratio; 95%CI, 95% confidence interval;
 Model 1: crude;
 Model 2: adjusted for age;
 Model 3: adjusted for age and ASA status;
 Model 4: adjusted for age, ASA status and local anaesthetic dose;
 Model 5: adjusted for age, ASA status, local anaesthetic dose and opioid use or midazolam dose.

Table 3. Odds ratio (95% CI) for the association between opioid use or midazolam dose and limitations, men and women

	Model 1	Model 2	Model 3	Model 4	Model 5
	OR (95%CI)				
Men	No.=151	No.=151	No.=151	No.=147	No.=147
	1.00 (ref)				
Sufentanil use	0.84 (0.27–2.65)	0.82 (0.26–2.61)	0.84 (0.26–2.65)	0.83 (0.26–2.67)	1.36 (0.39–4.75)
Fentanyl use	0.96 (0.21–4.49)	1.08 (0.23–5.12)	1.04 (0.22–4.99)	1.04 (0.22–4.99)	1.39 (0.27–7.21)
Midazolam dose	1.24 (0.98–1.58)	1.26 (0.99–1.59)	1.26 (0.99–1.60)	1.32 (1.01–1.71)	1.36 (1.02–1.80)
Women	No.=119	No.=119	No.=119	No.=119	No.=119
	1.00 (ref)				
Sufentanil use	0.20 (0.02–1.99)	0.21 (0.02–2.16)	0.10 (0.01–1.24)	0.10 (0.01–1.20)	0.11 (0.01–1.35)
Fentanyl use	0.60 (0.12–3.13)	0.61 (0.12–3.17)	0.48 (0.09–2.52)	0.44 (0.08–2.46)	0.43 (0.08–2.41)
Midazolam dose	0.93 (0.72–1.20)	0.94 (0.73–1.21)	1.02 (0.77–1.34)	1.06 (0.79–1.41)	0.97 (0.71–1.33)

OR, odds ratio; 95%CI, 95% confidence interval;
 Model 1: crude;
 Model 2: adjusted for age;
 Model 3: adjusted for age and ASA status;
 Model 4: adjusted for age, ASA status and local anaesthetic dose;
 Model 5: adjusted for age, ASA status, local anaesthetic dose and opioid use or midazolam dose.

required urgent observation in the emergency room, due to uncontrolled pain (a woman having received 1 mg of midazolam).

DISCUSSION

In our study, men that were administered higher midazolam doses were more likely to report pain at the first postoperative day, suggesting a possible hyperalgesic effect of this drug. Midazolam, prescribed as an anxiolytic, might be aggravating pain in the postoperative setting, with a differential effect on each gender.

Anxiety control is indeed desirable in the perioperative context, and midazolam has proved to be effective in reducing perioperative anxiety without delaying discharge in outpatient surgery.^{1,5} On the other hand, premedication with benzodiazepines has been implicated in the development of postoperative behavioral disturbances, such as delirium and negative effects on cognitive function.¹⁹ This evidence is reinforced by the European Society of Anaesthesiology evidence-based and consensus-based guidelines on postoperative delirium that suggest avoiding routine premedication with benzodiazepines except for patients with severe anxiety.²⁰

Animal studies have suggested both analgesic and hyperalgesic effects of midazolam, and different results seem to be dependent of dose and/or site of administration, whether acting predominantly on the spinal cord or brain.^{6,9-12} Ito and colleagues²¹ showed that intracerebroventricular administration of midazolam alone produced hyperalgesia, by interfering with antinociception at the supraspinal level; this effect was flumazenil-reversible.

Still, clear evidence of the effect of systemic midazolam in human nociception is missing.

In 1992, Coulthard and Rood²² attributed analgesic properties to midazolam in the setting of induced pain in volunteers, but later concluded that this reduction of pain in sedated patients was probably due to a suppression of brain cortical activity, responsible for the motivational-affective dimension of pain. After them, other authors failed to show any antinociceptive effect of midazolam in volunteers.

In 2000, Kain *et al*¹⁶ concluded that patients treated with midazolam before surgery reported a greater reduction in pain throughout the first postoperative week and a greater decrease of anxiety throughout the first postoperative month. In this study, however, outcome was measured as the reduction of Visual Analogue Scale (VAS) pain score compared to postoperative day 1, and not as the absolute VAS score. In fact, the midazolam group had greater opioid consumption both intraoperatively and at the post-anesthesia care unit.¹⁶ Shortly after, the same authors conducted a randomized controlled trial in women submitted to hysterectomy and did not find any significant effect of midazolam premedication

on postoperative pain.¹⁷

Three other human studies found the same antinociceptive effect,²³⁻²⁵ with patients under midazolam needing less and later postoperative rescue analgesics. However, pain was measured in the early postoperative period when patients were still under the sedative effect of midazolam.

Curiously, in our population, higher doses of midazolam increased the likelihood of reporting pain at day 1, but only in men, and this effect was independent of other variables: the OR of reporting pain increased 1.73 with each mg of administered midazolam. Higher doses of midazolam tended also to associate to more postoperative functional limitations. The causality of this association, however, is still to be clarified.

Our results point out a significant difference among genders. Sex-related differences in the experience of both clinical and experimentally induced pain have been widely reported, with women expressing significantly higher baseline pain ratings.^{15,26} Previous studies have also specifically addressed a possible gender difference concerning midazolam pharmacokinetics and pharmacodynamics in humans, with women having a significantly increased midazolam clearance due to greater CYP3A activity.²⁷ When compared to men, women also show higher levels of anxiety both before and after anxiolytic premedication, and develop less sedation when administered the same age and weight adjusted doses of midazolam.⁵

Several speculative factors have been discussed in an attempt to explain these gender differences: social and cultural beliefs with different expressiveness towards pain, psychological factors, and alterations in endogenous pain control systems.¹⁵ On the other hand, female hormones seem to directly interfere on neurotransmission, through the binding of certain metabolites of progesterone to the GABA-A receptor complex, where they exert a facilitating effect on inhibitory neurotransmission, thus modulating pain.²⁸

Midazolam significantly impairs psychomotor function. This sedation can confound pain ratings because of reduced vigilance and cognition, especially when using reaction time-dependent tests. Midazolam also causes amnesia and affects the emotional perception of pain. This could help explain inconsistent results of previous animal and human studies. On the other hand, the apparently opposite results showing an antinociceptive effect during anesthesia and a hyperalgesic effect in the following postoperative days, reflect different time points and different settings. Thus, the two observations are not conflicting and both effects could actually coexist. We must then consider that midazolam might truly increase pain perception, at least at some point in time.

Studies considering a possible hyperalgesic effect of intravenous sedatives on human pain perception have emerged in the last years, namely the GABA receptor agonists

midazolam and propofol.^{15,29} Frölich *et al*¹⁵ showed that, in volunteers, midazolam increased cold, heat and electrical pain ratings. This suggests that midazolam might be hyperalgesic across several pain modalities, that usually combine clinically in the physiopathology of acute postoperative pain. However, the hyperalgesic mechanisms of midazolam are poorly understood. A possible explanation is that midazolam could attenuate the stress response induced by surgery or trauma, thus decreasing the release of endogenous opioids in the brain, that play a role in supra-spinal nociceptive inhibitory mechanisms.¹⁶ In fact, Maieawski *et al*³⁰ have demonstrated that the secretion of β -endorphins by the anterior pituitary in rats is mediated by a benzodiazepine receptor, and that this secretion can be increased by administering a benzodiazepine antagonist, or decreased by administering an agonist.

Trials using intrathecal opioids in ambulatory arthroscopic knee surgery have shown a reduction of postoperative pain scores and decreased analgesic requirements.³¹ In our study we did not find a direct association between the use of opioid (either intrathecal or intravenous) and postoperative pain, but when adding the effect of midazolam, intrathecal opioids even seemed to increase postoperative pain. Research has shown that adding an opioid to local anesthetic increases the success of spinal anesthesia, the duration and quality of anesthesia without any effect on motor blockade. Nevertheless, we did not find an association between the use of opioid and postoperative limitations, neither between the use of intravenous opioids and pain. These results might be explained by the small number of patients who were given opioids in our series.

There are a number of caveats in our study, inherent to its retrospective nature. We did not evaluate chronic benzodiazepine consumption nor perioperative anxiety levels. Anxiety might be a confounder in this setting, leading to both increased administration of midazolam by the anesthetist and increased report of pain by the patient. Pain was also not evaluated preoperatively, and the existence of previous pain could contribute to both anxiety and postoperative pain. Pain had been registered in patient files as categorical data, so we could not analyze pain as a numeric scale, as we know would have been desirable. Few patients have received opioids, so the lack of association with pain intensity might result from the lack of statistical power. Although most arthroscopic knee surgery patients follow the same analgesic protocol, we did not individually analyze all administered medication. We also did not evaluate the technique of surgery, that could contribute to the development of postoperative pain. Any information bias resulting from the retrospective nature of data collection would probably be non-differential and so might not have influenced the direction of results. However, all the aforementioned limitations could affect the external validity of our results.

The retrospective nature of this study does not permit us to prove causality but only association. Nevertheless, some of Hill criteria³² for inferring about causality could apply: midazolam was administered before evaluation of pain; there is similar evidence from animal studies; there is a dose-response relationship; and there could be a biological plausibility, although not obvious.

Our study suggests an association between midazolam and pain in the clinical setting. We think this effect, if true, would apply to other surgical settings, like major invasive surgery, but possibly only to male patients. Prospective studies applying standardized anesthetic techniques for control of confounders and accurate evaluation of preoperative pain and anxiety could possibly bring new evidence about the topic. Until then, Anesthesiologists should be aware of possible hidden effects of midazolam.

CONCLUSION

Higher doses of midazolam were independently associated with postoperative pain at 24 hours in men, suggesting a possible hyperalgesic effect of this drug. Further studies are needed to evaluate whether this association is due to a true causal relation between midazolam and pain.

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Ethical Disclosures

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Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Proteção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsinquia da Associação Médica Mundial.

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