

COMPARISON BETWEEN THE USE OF REMIMAZOLAM AND PROPOFOLEM GENERATING ARTERIAL HYPOTENSION DURING ANESTHETIC INDUCTION: AN INTEGRATIVE REVIEW

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Abstract: Worldwide, more than 300 million major surgeries are performed per year, with the majority of these using general anesthesia. Among the most used anesthetics is propofol, a drug that inhibits the neurotransmitter gamma-aminobutyric acid (GABA). However, despite being widely used, the administration of propofol induces intraoperative hypotension, mainly due to the reduction in vascular resistance. Another anesthetic, Remimazolam, is a new emerging medication with a similar effect to propofol, being an ultra-short-acting benzodiazepine. Compared to propofol, remimazolam has fewer hemodynamic side effects, and may play an important role in preventing intraoperative hypotension. Considering the great impact on the health of those affected by intraoperative hypotension and postoperative damage, this work aims to analyze in recent literature the best evidence regarding the hypotensive effect of two drugs used in anesthetic induction, remimazolam and propofol, in order to compare them and verify which one presents the best benefit, among the different surgeries and patient profiles, with the aim of avoiding hypotensive effects. This is a qualitative, retrospective and cross-sectional study carried out through an integrative literature review. The databases used were the National Library of Medicine (PubMed) and Virtual Health Library (VHL). Among the studies analyzed, several procedures from different surgical categories were compared, such as: EDA, bronchoscopy, conization, colonoscopy, hysteroscopy, orthopedic surgery, valve replacement and endoscopic retrograde cholangiopancreatography. In all cases, it was possible to perceive the same outcome: a greater degree of arterial hypotension related to the use of Propofol during anesthetic induction when compared to Remimazolam. Therefore, it can be concluded that, from a hemodynamic point of view, there is a

clear advantage of using the combination of Remifentanyl with Midazolam in relation to the exclusive use of Propofol for anesthetic induction, with smaller variations in MAP, HR and, consequently, Cardiac Output. in the groups in which Remidazolam was used.

Keywords: Propofol, Remidazolam, Hypotension, hemodynamics

INTRODUCTION

Worldwide, more than 300 million major surgeries are performed each year, the majority of which use general anesthesia. ¹ During this procedure, there is a frequent occurrence of hemodynamic instability, which among the unstable variables, presents the so-called intraoperative hypotension (IOH), present in 18–50% of surgeries. ² OHI occurs due to the depressant effects of anesthetic agents on the cardiovascular and central nervous system and is highly prevalent and associated with harmful patient outcomes. ³

Risk factors for OHI include induction regimen, age, routine medications such as angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs), and patient medical comorbidities. ⁴, such as cardiovascular diseases ⁵ and obstructive jaundice. ⁶ The threshold for harm appears to be a mean arterial pressure of about 65 mmHg and systolic blood pressure of 90 mmHg, with increased risk at lower pressures and longer exposure times. ⁷

A sudden drop in blood pressure (BP) below the lower limit can lead to ischemia of vital organs, causing myocardial injury, stroke and acute kidney injury ⁸, with a time of approximately five minutes with systolic BP less than 90 mmHg conducive to associated myocardial and renal injury. ⁹ Furthermore, IOH is closely related to postoperative cognitive dysfunction caused by impaired cerebral perfusion. ¹⁰, longer hospital stay, morbidity after surgical outcome ¹¹ and even

mortality. ¹²

Gregory et al ¹³ reported that:

[...] We believe that hypotension in the operating room is a serious public health problem and must not be ignored in any age group. We suggest that there is an urgent and currently unmet need for prospective interventional studies focusing on its prevention.

Therefore, one of the measures that could be adopted would be the use of an appropriate hypnotic agent, in order to minimize the incidence of hypotension and prevent adverse complications in these patients.

Among the most used anesthetics is propofol, a drug that inhibits the neurotransmitter gamma-aminobutyric acid (GABA), which acts through GABA receptors and is considered a potent anesthetic, with rapid intravenous hypnotic action combined with an ultra-short half-life. ¹⁴ Being one of the most used anesthetics in the world, it promotes a quick and lucid recovery, in addition to reducing the generation of pro-inflammatory cytokines and exerting a neuroprotective effect. ¹⁵ However, despite being widely used, the administration of propofol induces intraoperative hypotension, mainly due to the reduction in vascular resistance. ¹⁶

Another anesthetic, Remimazolam, is a new emerging medication with a similar effect to propofol, being an ultra-short-acting benzodiazepine that also acts on γ -aminobutyric acid A (GABA A) receptors to induce sedation. ¹⁷ This is an ester-based compound, with a rapid onset of action and good aqueous solubility, its metabolism being independent of liver and kidney function ¹⁸ and, therefore, not prone to body accumulation and cardiorespiratory inhibition. Furthermore, the sedative effect of remimazolam can be quickly reversed by its antagonist, flumazenil, demonstrating greater safety. ¹⁹ Compared to propofol,

remimazolam has fewer hemodynamic side effects, and can play an important role in preventing intraoperative hypotension, with less adverse damage.²⁰

GOAL

Considering the great impact on the health of those affected by intraoperative hypotension and postoperative damage, this work aims to analyze in recent literature the best evidence regarding the hypotensive effect of two drugs used in anesthetic induction, remimazolam and propofol, in order to compare them and verify which one presents the best benefit, among the different surgeries and patient profiles, with the aim of avoiding hypotensive effects.

METHODOLOGY

This is a qualitative, retrospective and cross-sectional study carried out through an integrative literature review. The databases used were the National Library of Medicine (PubMed) and Virtual Health Library (VHL). The search for articles was carried out considering the descriptors “propofol”, “remimazolam” and “hypotension”, using the Boolean operator “AND”. The literature review was carried out following the following steps: establishment of the theme; definition of eligibility parameters; definition of inclusion and exclusion criteria; verification of publications in databases; examination of the information found; analysis of the studies found and presentation of the results. The study included articles published in the last 2 years (2021-2023); controlled clinical trial-type studies and freely available articles. Articles that did not have a clear definition of theoretical and thematic basis in line with the objects of the study and articles outside the topic covered were excluded.

RESULTS

The search resulted in a total of 123 works. 58 articles were found in the PubMed database and 65 articles in the VHL. After applying the inclusion and exclusion criteria, 18 articles were selected from the PubMed database and 11 from the VHL, with 21 articles being removed due to being duplicates, as shown in Figure 1.

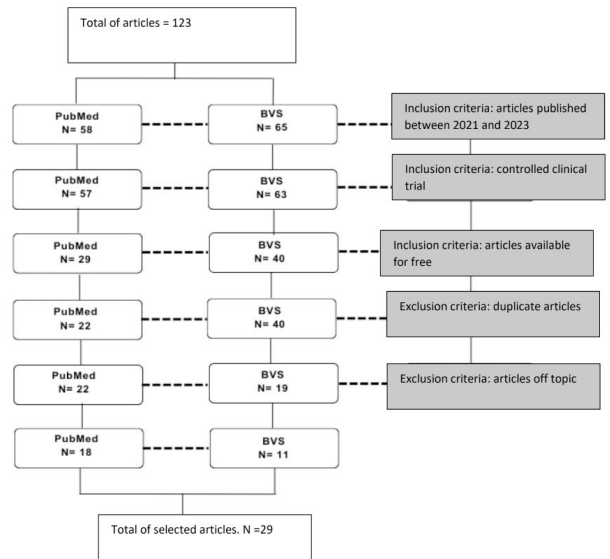


Figure 1: Flowchart of identification and selection of articles selected from the PubMed and VHL databases.

Source: Authors (2023).

The selected articles are of the controlled clinical trial type, with 29 studies unanimously demonstrating greater efficacy of remimazolam in relation to propofol in terms of intraoperative hypotension. 4 studies showed a better benefit of remimazolam with regard to previously hypertensive patients, 1 of which considered the regular use of angiotensin axis blocking drugs. Hypotension was lower with remimazolam in the elderly age group in 6 studies. Furthermore, 6 studies showed less use of vasoactive drugs, such as phenylephrine and ephedrine, with the choice of using remimazolam. The main results are described in Table 1 and the surgical

procedures in which remimazolam was more effective compared to propofol are highlighted in Figure 2.

LIST OF ABBREVIATIONS AND ACRONYMS

DC Cardiac output

EDA Upper gastrointestinal endoscopy

Group P Group that received propofol

Group R Group that received remimazolam

RP Group with propofol and remimazolam combined

CI Cardiac Index

DBP Diastolic blood pressure

MAP Mean arterial pressure

SBP Systolic blood pressure

DISCUSSION

Among the studies analyzed, several procedures from different surgical categories were compared, such as: EDA, bronchoscopy, conization, colonoscopy, hysteroscopy, orthopedic surgery, valve replacement and endoscopic retrograde cholangiopancreatography. In all cases, it was possible to perceive the same outcome: a greater degree of arterial hypotension related to the use of Propofol during anesthetic induction when compared to Remimazolam. Between the two, the combination between the benzodiazepine and the opioid was reportedly more cardiostable in the groups of patients tested, both for the elderly and young populations 3,4,32.

As a consequence, the need for vasoactive drugs was lower in the groups in which Remimazolam was used, requiring a smaller number of interventions and MAP corrections throughout the peri-operative period. This fact culminated in a post-operative period with fewer complications, with a similar awakening time after a drug session between the two, as well as a sedative effect, but again with greater hemodynamic stability in the

groups in which Remimazolam was used, with hypotension also being evident. more frequent postoperative period with the use of Propofol 12,13,29.

A significant benefit was observed from the use of Remimazolam associated with dexmetomidine in cardiac surgeries, where a greater cardiac output could be maintained throughout the surgical procedure, consequently with better tissue perfusion and a lower risk of postoperative complications for these patients 2,5, 9. The studies also indicated superiority in the use of Remidazolam in elderly patients with mild hypertension or using angiotensin axis blockers, considering that such individuals would benefit more from more discreet changes in MAP as they have a body that is less capable of large reductions. pressure 6,34,36.

Finally, the association between the use of Propofol and hypotension is widely known and well established in the literature, and its use is contraindicated in situations of hemodynamic instability. However, with the analysis of the selected studies it was possible to reiterate this relationship and present another alternative to the use of propofol with fewer changes in blood pressure: Remimazolam.

CONCLUSION

Therefore, it can be concluded that, from a hemodynamic point of view, there is a clear advantage of using the combination of Remifentanyl with Midazolam in relation to the exclusive use of Propofol for anesthetic induction, with smaller variations in MAP, HR and, consequently, Cardiac Output. in the groups in which Remimazolam was used.

The groups of patients who benefited most from the combination of benzodiazepines and opioids were those undergoing heart surgery and the elderly with mild hypertension or using angitensin axis blockers, managing to maintain greater blood pressure stability with

Authors	Year	Sample	Main conclusions
Cui X, Cheng Z, Li H, Zhang X, Luan H, Zhao Z, et al	2023	N=218	The incidence of hypotension during EDA was lower in the R groups than in the propofol group. A lower rate of hypotension was also found post-operatively with Remimazolam.
Xu Q, Wu J, Shan W, Duan G, Lan H.	2023	N=60	MAP, HR, CO and IC were significantly lower with the use of propofol compared to remimazolam combined with sufentanil. Remimazolam has been shown to be effective for elderly patients with mild hypertension.
Choi EK, Jang Y, Park SJ.	2023	N=96	MAP, SBP, DBP and HR were lower in group P than in group R, with remimazolam being preferable for anesthetic induction in hypertensive patients.
Zhang L, Yu L, Xu L, Wang JF, Li JY, Chen ZJ.	2023	N=192	Remimazolam combined with alfentanil for bronchoscopy may reduce the incidence of hypotension compared to propofol.
Kuang Q, Zhong N, Ye C, Zhu X, Wei F.	2023	N=84	SBP and MAP were significantly lower in group P than in group R, the incidence of hypotension was significantly lower in group R than in group P and remimazolam significantly reduced the number of doses of vasoactive drugs used.
Song SW, Kim S, Park JH, Cho YH, Jeon YG.	2023	N=81	There was lower MAP, SBP and DBP in group R compared to group P. Remimazolam resulted in less frequent post-induction hypotension than propofol in patients regularly using angiotensin axis blockers.
Wang C, Gao Y, Li J, Zhang L, Li Q, Li Y, et al	2023	N=256	The proportion of sedative hypotension was significantly lower in group R and group RP than in group P in patients undergoing EDA.
Wang L, Wang Y, Ma L, Wang Y, Mu X, Huang Z, et al	2023	N=204	The incidence of hypotension and use of vasoactive drugs in group R was significantly lower than in group P in patients undergoing conization.
Luo W, Sun M, Wan J, Zhang Z, Huang J, Zhang J, et al	2023	N=115	Lower percentages of patients in group R developed hypotension during anesthesia compared to group P and consequently fewer vasoactive drugs were required in group R.
Liu F, Cheng X, Wang Y, Li K, Peng T, Fang N, et al	2023	N=216	Elderly patients sedated with remimazolam had a lower risk of hypotension compared to propofol during EDA.
Dong SA, Guo Y, Liu SS, Wu LL, Wu LN, Song K, et al	2023	N=518	Patients sedated with remimazolam had a lower percentage of hypotension than patients sedated with propofol during endoscopic retrograde cholangiopancreatography.
Sekiguchi R, Kinoshita M, Kawanishi R, Kakuta N, Sakai Y, Tanaka K	2023	N=40	Group R presented less hypotension compared to group P, in anesthetic induction of middle-aged and elderly patients.
Yang JJ, Lei L, Qiu D, Chen S, Xing LK, Zhao JW, et al	2023	N=300	Elderly patients undergoing orthopedic surgery in group R had a lower incidence of hypotension after induction compared to group P and consumed fewer vasoactive drugs.
Zhang F, Chang H, Qing W, Yu R, Liao Q, Tong J.	2022	N=193	The incidence of intraoperative hypotension during hysteroscopy in groups R and RP was significantly lower than that in group P.
Hu B, Jiang K, Shi W, Xiao S, Zhang S, Zhang Y, et al	2022	N=346	The incidences of hypotension and hypotension requiring treatment were significantly higher in the propofol group than in the R group in patients undergoing EDA.
Lu K, Wei S, Ling W, Wei Y, Ran X, Huang H, et al	2022	N=400	Remimazolam was associated with a lower rate of hypotension in elderly patients undergoing EDA under deep sedation/anesthesia than propofol.
Gao S, Wang T, Cao L, Li L, Yang S.	2022	N=90	The incidence of hypotension during bronchoscopy was significantly lower in the remimazolam and remimazolam combined with dexmedetomidine groups than in the propofol control group.
Zhou YY, Yang ST, Duan KM, Bai ZH, Feng YF, Guo QL, et al	2022	N = 154	The incidence of hypotension and hypotension requiring treatment during bronchoscopy was significantly lower in the remimazolam group than in the propofol group.
Wang X, Hu X, Bai N, Li L, Zhang M, Cheng Z, et al	2022	N=480	The incidence of hypotension was more frequent in patients receiving propofol compared to patients receiving remimazolam, in patients undergoing colonoscopy.

Xu C, He L, Ren J, Zhou J, Guo H, Chen N, et al	2022	N=914	There was a higher rate of hypotension in group P compared to group R, and the difference was statistically significant in patients undergoing EDA.
Qiu Y, Gu W, Zhao M, Zhang Y, Wu J.	2022	N=56	The incidence of hypotension, number of vasoactive drugs used and CD was lower in group R compared to group P. Cardiac output was preserved much better in group R compared to group P.
Xin Y, Chu T, Wang J, Xu A.	2022	N=120	The incidence of hypotension decreased significantly and mean MAP was higher in groups R than in group P in patients undergoing colonoscopic polypectomy.
Yao Y, Guan J, Liu L, Fu B, Chen L, Zheng X.	2022	N=132	The occurrence of hypotension was lower in the group that received remimazolam compared to the group that received propofol, in patients undergoing colonoscopy.
Cao Y, Chi P, Zhou C, Lv W, Quan Z, Xue FS	2022	N=148	A significantly smaller number of patients in group R developed hypotension when compared to group P in cirrhotic patients undergoing EDA.
Shi W, Cheng Y, He H, Fang Q, Hu Y, Xu X, et al	2022	N=161	The incidence of hypotension was lower in group R compared to group P in patients undergoing EDA.
Liu T, Lai T, Chen J, Lu Y, He F, Chen Y	2021	N=60	The variation in MAP, incidence of hypotension and doses of vasoactive drugs used were significantly lower in group R than in group P in patients undergoing valve replacement.
Dai G, Pei L, Duan F, Liao M, Zhang Y, Zhu M, et al	2021	N=189	The groups that used remimazolam had lower rates of hypotension compared to the group that used propofol.
Zhang X, Li S, Liu J.	2021	N=82	The incidence of hypotension in Group R was lower than in Group P, in patients undergoing hysteroscopy
Chen SH, Yuan TM, Zhang J, Bai H, Tian M, Pan CX, et al	2021	N=384	The incidences of hypotension were significantly lower in group R compared to group P in patients undergoing EDA.

Table 1. Characterization of articles and main conclusions

Source: Authors (2023).

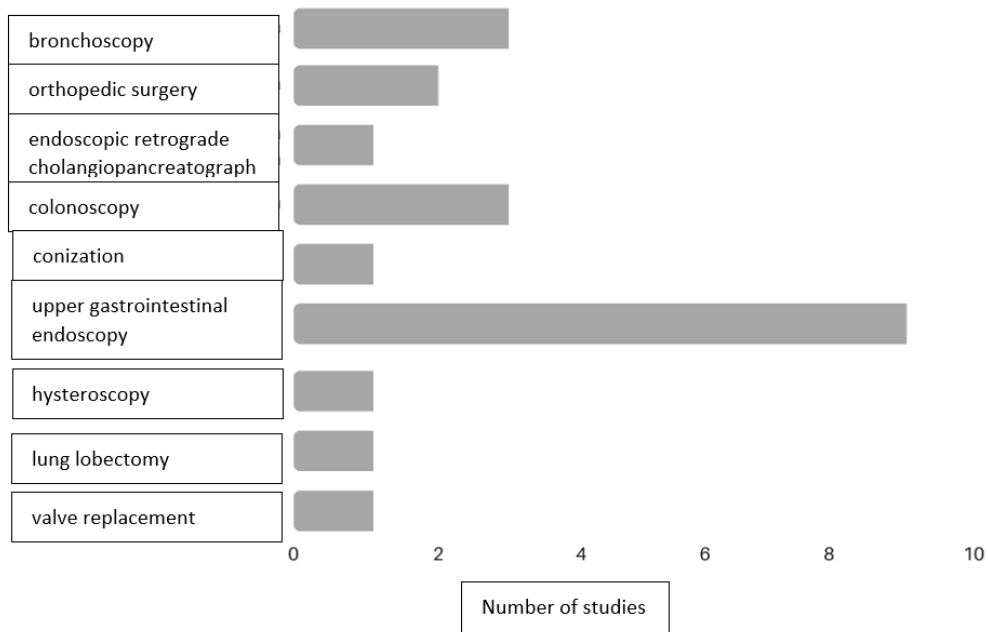


Figure 2. Characterization of surgical procedures

Source: Authors (2023).

fewer systemic repercussions.

Therefore, there is a greater risk of pressure reduction and hemodynamic instability with the use of propofol during anesthetic induction, with remidazolam being a safe alternative with lower pressure repercussions

and a similar sedative effect, with the advantage of less need for the use of vasoactive drugs throughout the period. surgical procedure and fewer adverse effects in the postoperative period.

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