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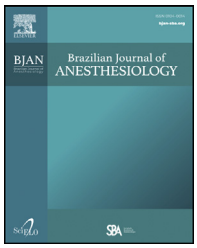

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ORIGINAL INVESTIGATION

Hemodynamic impact of increasing time between fentanyl and propofol administration during anesthesia induction: a randomised, clinical trial

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Abstract
Background and objective: Anesthesia induction can produce severe propofol dose-dependent hypotension. Fentanyl coadministration reduces the catecholaminergic response to orotracheal intubation allowing propofol dose reduction. The aim of this study is to determine whether the hemodynamic response is improved by increasing the time between fentanyl and propofol administration and reducing the dose of the latter without increasing the time to achieve optimal hypnosis.
Methods: After approval by the Research Ethics Committee, patients undergoing non-cardiac surgery with endotracheal intubation were randomized by a computer-generated table into six time-dose groups (1 or 2 minutes/1, 1.5, or 2 $mg.kg^{-1}$ of propofol). Patients with high bronchoaspiration risk, a difficult airway, hemodynamic instability, or anesthetic allergies were excluded. After giving intravenous fentanyl (2 $\mu g.kg^{-1}$), each group received different doses of propofol after 1 or 2 minutes. Non-invasive blood pressure (BP) and heart rate (HR) were measured at pre-induction, pre-intubation, and post-intubation. Time to hypnosis (bispectral index < 60) was also recorded.
Results: Of the 192 recruited patients, 186 completed the study (1 min group n = 94; 2 min group n = 92). It was observed that HR and BP decreased after propofol administration and increased after intubation in all groups ($p < 0.0001$). In patients over 55 years, the 2 min – 2 $mg.kg^{-1}$ group showed the greatest systolic BP reduction (36 ± 12%) at pre-intubation, while the 1 min – 1.5 $mg.kg^{-1}$ group showed the least hemodynamic alteration between pre- and post-intubation (-4 ± 13%). No significant differences were found in younger patients or in the time to reach hypnosis between the six groups. While no cases of severe bradycardia were recorded, 5,4% of the sample required vasopressors.
Conclusion: Increasing the time between the administration of fentanyl and propofol by up to two minutes results in greater hypotension in patients over 55 years.

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Introduction

Propofol is the most commonly used hypnotic in non-cardiac surgery due to its pharmacokinetic characteristics, such as short onset time, high metabolism and elimination, and short half-life. However, it leads to a series of unwanted hemodynamic effects (decrease in systemic vascular resistance, negative inotropism, and bradycardia).[1,2]

Older patients are more sensitive to propofol because of a decreased central compartment and a lower concentration of plasma proteins, which result in a reduced distribution volume and cardiac output.[3] These physiological changes led manufacturers to suggest a reduction in the induction dose, to 1 mg.kg^{-1}, in patients over 55 years or those with a high anesthetic risk.

Concomitant administration of fentanyl during anesthesia induction aims to reduce the catecholaminergic response to laryngoscopy, as post-intubation hypertension increases the risk of myocardial infarction, heart failure, pulmonary edema, intracranial hemorrhage, etc.[4] The prior administration of opioids has been proposed in order to decrease the need for propofol, mainly due to pharmacological synergy.[5,6] Taking into account that propofol-associated hypotension is dose-dependent, a dose reduction based on opioid coadministration would result in less hemodynamic instability.[7]

No studies have been found that assess the optimal time between the administration of both drugs to enhance this supra-additive relationship and allow the maximum reduction of propofol doses. The aim of this study is to determine whether increasing the time between fentanyl and propofol administration and reducing the dose of the latter, improves the hemodynamic response in different age groups without increasing the time required to achieve optimal hypnosis.

Methods

This prospective, randomized clinical trial was approved by the Research Ethical Committee of the Hospital Central de la Defensa ''Gómez Ulla'' in October 26th 2017 (approval nº: 09/17), registered at clinicaltrials.gov (NCT04194151) and was conducted after obtaining written consent from all participants.

All adults who were scheduled for general anesthesia with endotracheal intubation for non-cardiac surgery in our hospital between November 2017 and October 2018 were considered eligible. Patients with an increased risk of bronchoaspiration (absence of fasting, stomach retention, intestinal obstruction, etc.), a difficult airway, allergies to anesthetic drugs, or baseline systolic blood pressure (SBP) $\leq$ 90 mmHg were excluded.

Study protocol

Sample size was calculated with a power of 80% (beta risk 20%) to detect an expected minimal significant SBP difference of 5 mmHg between groups, an overall two-sided alpha level of significance of 0.05, assuming a pooled standard deviation of 22 mmHg and maintaining a group ratio of 1:1:1:1:1:1. A minimum of 162 patients were required (27 in each group). We raised this to 192 patients, estimating a possible loss of 15% and keeping the group proportion (32 in each group).

Table 1 Study groups.

Group	Time until propofol (min)	Propofol dose (mg.kg^{-1})
1	2	2
2	2	1.5
3	2	1
4	1	2
5	1	1.5
6	1	1

Two time-groups were established (1 and 2 minutes), and these were each divided into three dose subgroups (1, 1.5, and 2 mg.kg^{-1}), resulting in six time-dose groups (Table 1). Randomization was achieved using a computer-generated randomization table, leading to six groups of 32 patients. Each subject who met the inclusion criteria and accepted participation was assigned to the corresponding group according to his/her order number (1 to 192). Because the grouping was established prior to data collection, age, sex, and American Society of Anesthesiologist (ASA) physical status risk were not randomized. Only the anesthesiologist and the data collector were aware of the allocated group.

In the operating room (OR), monitoring included electrocardiogram, pulse oximetry, non-invasive blood pressure (BP), and bispectral index (BIS – Covidien Complete Monitor System P/N 185-0151, USA). After preoxygenation (expired oxygen fraction $\geq$ 80%), 2 μg.kg^{-1} of intravenous fentanyl were administered. After 1 or 2 minutes (depending on the study group), 1, 1.5, or 2 mg.kg^{-1} of propofol were given. We registered the time until the BIS value dropped below 60. Muscle relaxation was performed with rocuronium 0.6 mg.kg^{-1}, and endotracheal intubation was achieved by the same experienced anaesthesiologist.

The primary outcome was to identify hemodynamic alteration through SBP or heart rate (HR) during the different phases of anesthesia induction. SBP and HR were collected manually and set as follows: baseline (SBPb and HRb) was recorded before fentanyl administration; the pre-intubation value (SBP1 and HR1) was recorded after propofol administration and once the BIS value had reached 60; and the post-intubation value (SBP2 and HR2) was recorded 15 seconds after endotracheal tube placement. In cases where hypotension was observed (SBP < 90 mmHg or SBP reduction > 30%), vasopressors, such as ephedrine or phenylephrine were administered.

Statistical analysis

Values are reported as absolute and relative (percentages) frequencies for categorical variables and mean $\pm$ standard deviation (SD) for quantitative ones. To assess categorical variables, such as presence of hypertension, extra doses of propofol, use of vasopressors, and cardiovascular treatment, chi-square test or Fisher's exact test were used, depending on the sample size. Student's t-test for independent samples was employed to compare parametric data, such as vasopressor use with respect to age, hypertension and antihypertensive treatment with respect to baseline

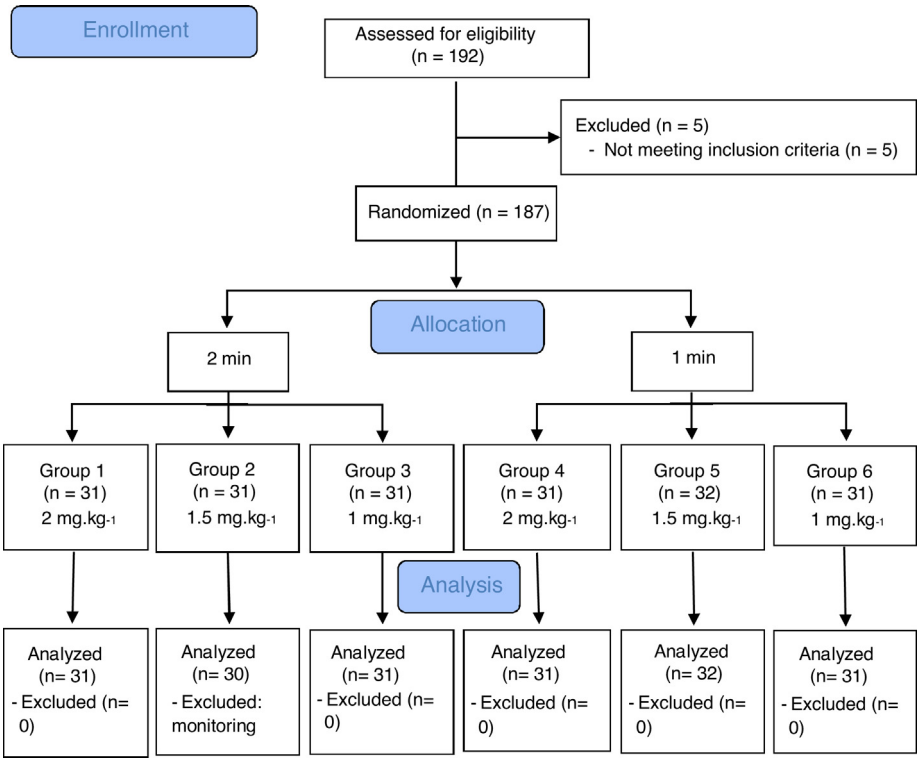

Figure 1 CONSORT flow diagram.

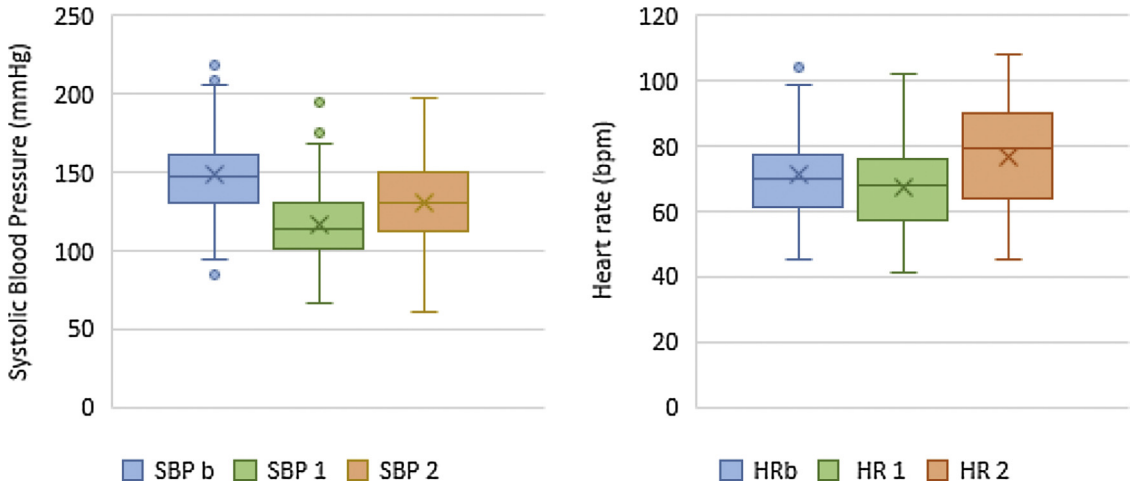

Figure 2 Systolic blood pressure (mmHg) and heart rate (bpm) variation during the study. SBP, systolic blood pressure; HR, heart rate; b, baseline; 1, pre-intubation; 2, post-intubation.

SBP and β blockers treatment with respect to baseline HR, provided a normal distribution could be assumed. ANOVA and Bonferroni correction were used for comparison of hemodynamic values between the groups. Non-parametric statistical tests (Mann-Whitney U-test or Kruskal-Wallis test) were applied when necessary. To analyze data distribution, Shapiro-Wilks or Kolmogorov-Smirnov with Lilliefors correction were conducted for small or large samples, respectively. Boxplots were used to represent quantitative data such as SBP and HR. To compare and represent time to hypnosis between the groups, a Kaplan-Meyers curve was used. A *p*-value of < 0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 22.00 (IBM Corp., Armonk, NY, USA).

Results

From November 2017 to October 2018, we recruited the 192 required patients of whom 6 were removed, generating a sample of 186 subjects in the 6 groups (Fig. 1). No demographic differences were found in age, sex, weight, ASA, or

Table 2 Demographic characteristics of the studied patients.

Group	1 (n = 31)	2 (n = 30)	3 (n = 31)	4 (n = 31)	5 (n = 32)	6 (n = 31)
Age (year)	59 ± 20	61 ± 17	60 ± 19	59 ± 17	64 ± 18	55 ± 16
Female	15 (48,4)	14 (46,7)	17 (54,8)	17 (54,8)	18 (56,3)	14 (45,2)
Weight (kg)	73 ± 16	77 ± 17	70 ± 15	71 ± 15	71 ± 15	73 ± 15
ASA risk,						
I-II	20 (64,5)	19 (63,3)	17 (54,8)	21 (67,7)	13 (40,6)	21 (67,7)
III-IV	11 (35,5)	11 (36,7)	14 (45,2)	10 (32,3)	19 (59,4)	10 (32,3)
Hypertension	15 (48,4)	9 (30)	15 (48,4)	13 (41,9)	16 (50)	13 (41,9)
Hypotensive treat	9 (29)	9 (30)	12 (38,7)	10 (32,3)	12 (37,5)	11 (35,5)
BBlock/Ca Block	11 (35,5)	7 (23,3)	10 (32,3)	9 (29)	11 (34,4)	3 (9,7)

Values are mean ± standard deviation or frequency (percentage). ASA, American Society of Anesthesiologist physical status; Treat, treatment; BBlock, beta blocker; Ca Block, calcium blocker.

in the distribution of hypertensive patients or those undergoing treatment for hypotension or HR control (Table 2).

Thirty-three patients required an extra 0.5 mg.kg^{-1} dose of propofol, 81.8% of whom belonged to the 1 mg.kg^{-1} groups (group 3 – 39.5% and group 6 – 42.3%, $p < 0.0001$). An additional dose was required by 22% of low-risk patients and only 11% of ASA III-IV patients ($p = 0.038$).

There were no cases of severe bradycardia that required anticholinergic treatment. However, 5.4% of the sample showed hypotension that required vasopressors. The mean age of patients requiring its use was 76 ± 13 years, while the mean age of the non-vasopressors group was 59 ± 18 years (p = 0.003). The use of vasopressors was more frequent in those undergoing treatment with HR blockers alone (13.7% vs. 2.2%; $p = 0.006$) or associated with hypotensive drugs (15% vs. 3%; $p = 0.015$), in contrast with the patients with no treatment.

No statistically significant differences were found between baseline BP or HR values between the different groups. However, the mean SBPb was significantly higher in hypertensive patients (156 mmHg, 95% CI 151 – 162 vs. 139 mmHg, 95% CI 138 – 146; $p < 0.0001$) and in those with hypotensive treatment (159 mmHg, 95% CI 152 – 166 vs. 143 mmHg, 95% CI 139 – 147; $p < 0.0001$). On the other hand, the HRb was lower in patients treated with heart rhythm control drugs (71 bpm, 95% CI 67 – 75 vs. 76 bpm, 95% CI 74 – 79; $p = 0.045$). The general tendency was a decrease in BP and HR before intubation and an increase afterwards ($p < 0.0001$), as can be seen in Fig. 2.

No statistically significant differences between the study groups were found with respect to the baseline BIS value or the time required for the BIS to drop below 60, once the patients who required an extra dose were removed from the sample (Fig. 3).

To assess the percentage of BP reduction, the population was divided by patients over the age of 55 and those younger than 55 years, obtaining significant demographic differences between both age groups with respect to ASA ($p < 0.0001$), the incidence of hypertension ($p < 0.0001$) and the use of hypotensive and HR blockers ($p < 0.0001$). In patients under 55 years old, no statistically significant differences were found in the percentages of arterial reduction ($p = 0.99$ for b-1, $p = 0,964$ for b-2 and $p = 0,975$ for 2-1) whereas, in the older population, statistically significant results were obtained (Table 3).

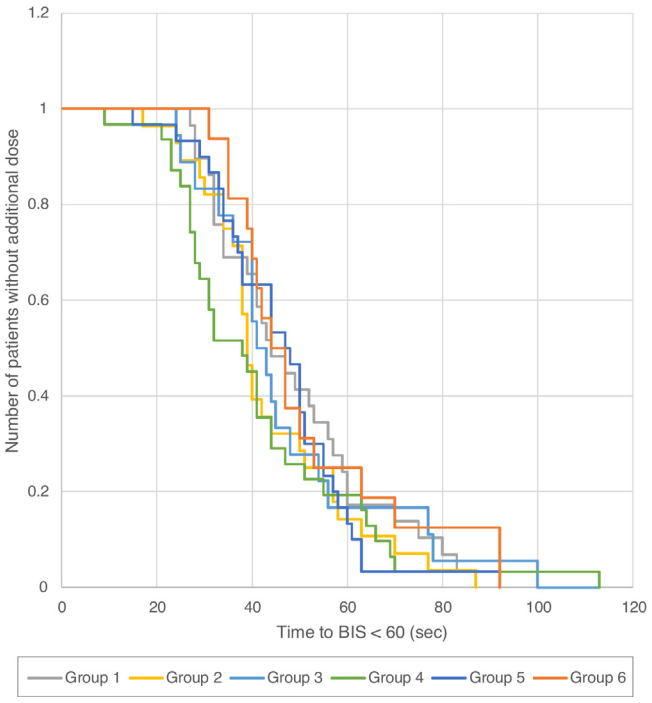

Figure 3 Time (seconds) required for BIS to drop under 60 in the different groups, excluding patients who required an additional propofol dose. BIS, Bispectral Index.

Discussion

This study showed that extending the time between fentanyl and propofol to 2 minutes during anesthesia induction produces more hypotension in adults older than 55 years, even when propofol doses are reduced.

The baseline SBP exceeded the cut-off diagnostic hypertension value established by the latest guidelines of the American College of Cardiology (ACC).[8] However, the OR measurement conditions (decubitus, fasting, and stress) are not those recommended for diagnosis.[9] Despite this, hypertensive patients and those under hypotensive treatment presented higher systolic values than the rest of the sample. When subjected to maintained high tension, the arterial wall suffers pathophysiological changes, such as insensitivity to endogenous vasodilators and a higher response to cate-

Table 3 Percentage of blood pressure reduction in older patients (> 55 years).

Systolic bp	GROUP	BP reduction (%)	group	BP reduction (%)	*p* value
b-1	**1** (n = 18)	36 ± 12	**3** (n = 18)	21 ± 13	0.006
			5 (n = 22)	21 ± 13	0.003
			6 (n = 13)	22 ± 13	0.033
2-1	**5** (n = 22)	- 4 ± 13	**1** (n = 18)	15 ± 25	0.014
			2 (n = 24)	15 ± 17	0.01

Values are mean ± standard deviation. BP, blood pressure; b-1, comparative between baseline and pre-intubation blood pressure; 2-1, comparative between post and pre-intubation blood pressure.

cholamines and stress.[10] On the other hand, the inhibition of β1 receptor activity caused by beta blockers and the voltage and use-dependent blockage of calcium channels generated by calcium antagonists would explain why the HRb was lower in patients under these treatments.[11,12]

Although the propofol manufacturer 's recommendation is that the induction dose could be reduced to 1 mg.kg^{-1} in older patients or those with a high anesthetic risk, in this study the 1 mg.kg^{-1} groups required an extra propofol dose more often, regardless of age. However, we found that ASA I and II patients required an additional hypnotic dose more frequently. The latter is consistent with Schnider et al., who described that those older than 75 years are up to twice as sensitive to propofol as those under 25 years old.[13]

Regarding the use of vasopressors, our incidence is surprisingly lower than that found by Mehandale and Rajasekhar, whose patients reached 24% after administering 2 μg.kg^{-1} of fentanyl and a titrated dose of propofol until loss of consciousness.[14] The main difference was in our propofol administration method (weight-based single bolus). In addition, their study did not specify whether hemodynamically unstable patients or those with an increased risk of hypotension were included.[14] In accordance with a review by Hug et al. which included 25,000 patients of a wide age range, older patients showed a higher incidence of severe hypotension, which supports the greater lability we found in this group.[15] Surprisingly, chronic hypotensive treatment did not present a greater need for vasopressors; however, beta blockers/calcium blockers alone or in association with antihypertensives did. This could be explained by the fact that the latter were suspended 24 hours before surgery, as recommended in the latest perioperative hypertension management guidelines, to reduce cardiovascular complications and, therefore, their half-life was exceeded.[8,16] On the other hand, beta blockers and calcium blockers were administered on the day of the intervention following the same guidelines. As a consequence, these patients have a reduced ability to respond to hypotensive stimulus with tachycardia, peripheral vasoconstriction, and inotropism.

BP variation during induction were as expected, based on the action of propofol on the autonomic nervous system and vascular endothelium, which causes a decrease in preload and peripheral vascular resistance.[14,17] On the other hand, the stress generated by laryngoscopy and orotracheal intubation causes an adrenergic discharge that reverses the hypotensive effects.[18] Multiple studies report a fall after propofol and a rise post-intubation.[14,19,20] Möller Petrun and Kamenik studied cardiovascular changes in 46 ASA III patients who, after a 3 μg.kg^{-1} fentanyl bolus, received propofol or etomidate.[21] Their hypotension peak was 5 minutes after intubation, contrasting with our study where the peak occurred during the pre-intubation period. This could be due to the fact that they initiated sevoflurane straight after intubation, which produces hypotension by itself, adding to the hypotension caused by the other anesthetics administered.[22] HR variations can be understood on the same basis: a slight decrease that was reversed with intubation.[18,23]

Given that the additional hypnotic doses were administered after 120 seconds, when BIS remained above 60, these patients were eliminated when studying the time to hypnosis. We found no significant differences, indicating that waiting 2 minutes between fentanyl and propofol does not increase the risks of prolonging the time to guarantee the airway. Lysakowski et al. found that, in the presence of fentanyl, alfentanil, remifentanil, and sufentanil, the loss of consciousness occurred at a lower concentration of propofol and at a higher BIS compared to the hypnotic as a single drug.[24] These authors used Target Controlled Infusion (TCI) for opioids and propofol, and the loss of consciousness was assessed subjectively based on the response to verbal orders or slight shaking, which can lead to bias. In addition, their objective was to compare propofol with propofol plus different opioids; therefore, they did not study different hypnotic doses as in our study.

We divided the sample into two age groups because propofol manufacturers suggest that the induction dose can be reduced in patients over 55 years and because it has been unequivocally demonstrated that age is a relevant factor in hypnotic needs.[25]

As expected, older patients presented a higher anesthetic risk, higher incidence of hypertension, and higher consumption of hypotensive drugs and HR blockers. This may be due to age-related degenerative processes of the cardiovascular system, which alter inotropic regulatory mechanisms, metabolic alterations, and oxidative stress.[26]

Regarding the decrease in SBP at pre-intubation (b-1), we observed that the hypotensive effect of propofol is greater when the dose is higher, supporting the idea that vasodilation and subsequent hypotension are dose-dependent.[7] Likewise, we found significant differences when adding the time variable (group 1 vs. group 5/6). Our results showed that, when waiting one minute, the maximum peak of the opioid effect has not been reached; therefore, there is less hypotension. A study of 120 patients produced similar findings, whereby fentanyl itself did not cause cardiovascular changes but caused greater hypotension when associated

with propofol.[5] In this study, there was a time period of 5 minutes between the administration of both drugs; therefore, the plasma concentration was higher, obtaining a reduction percentage of 40% for a propofol dose of 2 mg.kg^{-1}.

When comparing SBP variation before and after airway management, group 5 showed better control of post-intubation hypertension, and the 2-minute groups showed the highest percentage of decline. These results confirm a synergistic relationship between fentanyl and propofol. It has been suggested that fentanyl increases the volume of distribution and reduces the clearance of propofol, resulting in an increase in plasma concentration of 25%.[6] When studying the hemodynamic response to intubation, Billard et al. found that the magnitude of post-intubation hypertension is significantly reduced with increasing doses of fentanyl. They also reported that administration should be carried out in close proximity so that the concentration of the biophase and hypotension occur at the same time, avoiding the hypertensive response of the laryngoscopy.[5] In our study, all patients received the same dose of fentanyl (2 μg.kg^{-1}) but, by increasing the time between the administration of both drugs, we allowed a greater blood peak, thus increasing its analgesic capacity. By this, we do not mean that fentanyl generates hypotension per se but that the increase in peripheral vascular resistance caused by the adrenergic response decreases by better controlling the pain produced by the laryngoscopy, and the risk of hypotension caused by the propofol increases.

As this study includes a sample with a wide age range and ASA risk, its results could be easily extrapolated to the general population. However, it has several limitations. First, we did not measure the plasmatic concentrations of both drugs due to lack of means. Further research is needed to specify if, after 2 minutes, the fentanyl plasmatic peak is achieved before intubation allowing a better control of the hypertension associated with intubation. Second, the use of invasive pressure would have decreased measurement bias. We try to reduce them by adjusting the size of the cuff. Third, we did not collect the type of surgical procedure. Although the initial motivation for surgery can influence the baseline state of the patient, this would hardly generate differences during anesthetic induction.[15] Last, type of vasopressors used (ephedrine or phenylephrine) was not recorded. Although this could have altered the HR data obtained, the criteria for its use was based on patients' comorbidities, and both drugs have shown efficiency in the prevention and treatment of hypotension related to anesthetic induction.[19,20,27]

In conclusion, BP falls following administration of the hypnotic and rises after intubation, regardless of the time elapsed between the two drugs or the propofol dose. Despite this, increasing the time between the administration of fentanyl and propofol to two minutes does not generate hemodynamic benefits in patients under 55 years of age. In the older population, increasing this time results in greater BP variation. If greater hemodynamic stability with a decrease in propofol dose in this age group is desired, it is advisable to wait one minute from administration of fentanyl 2 μg.kg^{-1} and to reduce the dose to 1.5 mg.kg^{-1}.

Conflicts of interest

The authors declare no conflicts of interest.

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