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Effectiveness of Atenolol in Preventing Perioperative Hypertension in Hypertensive Patients During Endoscopic Cholecystectomy

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Abstract: Introduction: Perioperative hypertension represents one of the leading alterations detected performing endoscopic cholecystectomy. It is presumed that atenolol has a protective effect able to reduce this morbid condition, likely due to its beta-blocking action. Objective: To assess the efficacy of atenolol on preventing perioperative hypertension performing laparoscopic cholecystectomy in the surgical unit of the Hospital Clínico Quirúrgico "Lucía Íñiguez Landín" of Holguín. Method: An observational, analytical, longitudinal and prospective cohort study was conducted with two study groups at the same time, experimental group and control group, from January to December, 2018. A total of 697 patients (N = 697) evaluated in the preoperative consultation were involved in the study, the sample included 183 hypertensive patients (n = 183) who underwent endoscopic surgery for gallbladder lithiasis, of whom 95 were randomized to the atenolol treatment group and 88 to the control group. Patients in the treatment group were administered atenolol at 25 mg daily for 15 days before surgery. Leading variables used were systolic, diastolic and mean arterial pressures, and specific indicators were used to evaluate treatment effectiveness. Results: Preoperative arterial pressures decreased significantly with the use of atenolol in the treatment group. Perioperative hypertension was more frequent in the control group. Atenolol is a selective beta 1 receptor blocker, who causes a hypertensive effects in the central level, depressing the bulbar vasomotor center. Conclusions: The results of this investigation show that the use of atenolol in treatment was an effective alternative, thus effectively reducing the rate of perioperative hypertension.

Key words: laparoscopic cholecystectomy; hypertension; atenolol; perioperative medicine

1. Introduction

High blood pressure (HBP) is one of the main public health problems worldwide. It is estimated that approximately 691 million people suffer from it. However, a large proportion of hypertensive patients remain undetected, many untreated, and others uncontrolled. [1] The distribution of blood pressure (BP) in the population and its relationship with cardiovascular risk are continuous. There is an association between HBP as a risk factor and the development of all clinical manifestations of atherothrombotic disease, coronary artery disease, cerebrovascular disease, and peripheral arterial disease.

The incidence of this disease in the general population ranges between 20% and 25%. In Cuba, it affects over 20% of the adult population. The overall mortality rate is 8.1 per 100,000 inhabitants. The number of undiagnosed patients has increased to 33%. [2]

The association of uncontrolled hypertensive patients with the need for surgical treatment reaches nearly 25%. It is associated with the leading cause of cancellations of elective surgical procedures and with an increase in morbidity and mortality during the perioperative period. [3] 4% of patients undergoing surgery in our setting develop perioperative complications. [2]

On the other hand, there is gallbladder stones, which are one of the most common medical problems. It affects 10% to 20% of the world's population, with a prevalence between 11% and 36%. [4] In Cuba, the incidence ranges between 2% and 30%, more common in women, and increases with age. [2] If it produces symptoms, its treatment is surgical.

The video-endoscopic approach to gallbladder stones revolutionized its treatment. The main advantages of this procedure are minimal scarring, improved postoperative recovery with reduced postoperative ileus and decreased parietal pain, reduced hospital stay, and a faster return to work. This type of outpatient surgery is a feasible economic and social option that reduces the risk of hospital-acquired infections and costs, as it eliminates prolonged hospitalization. It is currently the treatment of choice for symptomatic patients.

More than 40% of cholecystectomies performed worldwide are performed using video endoscopy. [4, 5] In Cuba, of the 1,159,392 operations carried out in 2018, 67,730 were performed in this way, including 1,717 in the province of Holguín. [2]

During endoscopic cholecystectomy, there are some specific situations that can favor the development of hypertension, such as antiphysiological (extreme) positions and their repercussions, as well as the use of carbon dioxide and a history of hypertension in some individuals. [4]

In compensated hypertensive patients, perioperative hypertension is one of the main abnormalities detected during this type of surgery, with a reported incidence of between 30% and 40% worldwide. [5] In Cuba, incidences of between 20% and 30% have been reported. [2] Therefore, all efforts to improve the prevention of perioperative hypertension are justified.

Blood pressure (BP) depends on cardiac output (CO) and peripheral resistance (PR) according to the equation BP = CO × PR; and CO, in turn, depends on stroke volume (SV) and heart rate (HR), according to the formula CO = SV × HR. At a constant SV, a decrease in HR decreases CO. In turn, at a constant PR, a decrease in CO decreases BP. [6] Therefore, a decrease in HR and myocardial contractility indirectly decrease BP.

During the perioperative period, a significant release of catecholamines occurs, resulting in an increase in heart rate and myocardial contractility, and an increase in cardiac metabolic demand.

The main reason for the use of beta-blockers in the perioperative period is to decrease myocardial oxygen consumption by reducing heart rate and myocardial contractility, which results in a decrease in blood pressure.

Several studies demonstrate the protective effect of beta-blockers in reducing perioperative cardiac morbidity and mortality. [7, 8] Some authors have obtained absolute reductions in the risk of developing cardiac complications of up to 30%. [8, 9]

The incidence of perioperative hypertension found in compensated hypertensive patients during endoscopic cholecystectomy is 34% at the aforementioned institution, high compared to the incidence of 30% reported in Cuba in the last 5 years.

For all the above reasons, it was decided to conduct this research, the objective of which is to evaluate the effectiveness of atenolol in preventing perioperative hypertension during video-endoscopic cholecystectomy in the surgical unit of the "Lucía Íñiguez Landín" Clinical and Surgical Hospital in Holguín, Cuba, in 2018.

2. Method

A prospective, analytical, case-control study was conducted in the surgical unit of the "Lucía Íñiguez Landín" Clinical and Surgical Hospital in Holguín, from January to December 2018.

The study population consisted of 697 hypertensive patients (N = 697), of both sexes, over 30 years of age, proposed for elective video-endoscopic cholecystectomy. The sample consisted of 183 patients who agreed to participate in the study (n = 183). Patients with contraindications to atenolol use and those receiving regular atenolol treatment were excluded.

Two parallel study groups were formed: a treatment group and a control group:

- Treatment group: comprised of 95 patients from the sample who were assigned to atenolol treatment using a simple randomization system. These patients received 25 mg/day of oral atenolol for 15 days before elective video-endoscopic gallstone surgery.
- Control group: comprised of 88 patients from the sample who were not assigned to atenolol treatment.

Patients in both groups continued their baseline antihypertensive treatment.

The independent variables analyzed were age, sex, baseline systolic blood pressure (SBP), baseline mean arterial pressure (MAP), baseline diastolic blood pressure (DBP), and study groups. The dependent variables were perioperative SBP, perioperative MAP, perioperative DBP, and perioperative hypertension.

After peripheral venous catheterization with an 18G or 20G plastic catheter, preferably in the left upper extremity, all patients were premedicated with ondansetron at 0.15 mg/kg and midazolam at 0.05 mg/kg. Preoxygenation was provided at a rate of 3 to 5 L/min via a face mask. Monitoring was performed using a Doctus VII multiparameter monitor, including systolic, diastolic, and mean blood pressure every 5 minutes, peripheral oxygen saturation, respiratory rate, heart rate, expired carbon dioxide concentration, and electrocardiogram in leads DII and V5. In all cases, total intravenous anesthesia was administered via infusion syringes. Anesthesia was inducted with propofol 1.5 to 2.5 mg/kg, fentanyl 2 to 8 µg/kg, and lidocaine 1 mg/kg. Muscle relaxation was achieved with succinylcholine 1 mg/kg before tracheal intubation, and maintenance was achieved with propofol 4 to 12 mg/kg, fentanyl 1 to 3 mcg/kg, and rocuronium 0.15 mg/kg. Analgesia was administered with tramadol 1 mg/kg/dose.

To evaluate the efficacy of atenolol treatment, the primary and secondary efficacy indicators were calculated. The primary efficacy indicators were compared between the two study groups, and indicators with statistically significant differences between the groups were considered effective. Secondary efficacy indicators were estimated by comparing the two groups based on the presence or absence of perioperative hypertension.

The primary efficacy indicators calculated were the following:

(1) SBP reduction of up to 20%: number of patients whose systolic blood pressure decreased during the study.

(2) MAP reduction of up to 20%: number of patients whose mean arterial pressure decreased during the study.

(3) DBP reduction of up to 20%: number of patients whose diastolic blood pressure decreased during the study.

(4) Mean reduction: mean value between the differences in mean arterial pressure at baseline and perioperatively.

The secondary efficacy indicators calculated were as follows:

(1) Treatment group incidence risk: ratio of the number of treated patients who developed perioperative hypertension to the total number of cases in the treatment group. The estimated value was multiplied by 100 and quantified as a percentage.

(2) Control group incidence risk: ratio of the number of patients not treated with atenolol who developed perioperative hypertension to the total number of cases in the control group. The estimated value was multiplied by 100 and quantified as a percentage.

(3) Absolute risk reduction: difference between the risk of perioperative hypertension incidence between the two treatment groups. The estimated value was multiplied by 100 and quantified as a percentage. [9]

(4) Relative risk of the treatment group compared to the control group: ratio of the risk of incidence in the treatment group to the risk of incidence in the control group. The estimated value was rounded to the nearest decimal point.

(5) Relative risk reduction: one minus the relative risk of the treatment group compared to the control group. The estimated value was rounded to the nearest decimal point.

(6) Number of people needed to treat to prevent one case of perioperative hypertension: one divided by the absolute risk reduction. The estimated value was rounded to the nearest whole number.

Treatment with atenolol was considered effective in preventing perioperative hypertension if at least two primary indicators were significant with a $p < 0.05$. Treatment was considered ineffective if one or none of the indicators was significant. Secondary effectiveness indicators were used as a measure of the treatment effect in preventing perioperative hypertension.

The following inferential techniques were used:

- Independent samples t-test: This test was used for the quantitative variables age, baseline SBP, baseline MAP, baseline DBP, perioperative SBP, perioperative MAP, perioperative DBP, and for the effectiveness indicator of mean reduction. Differences with a $p < 0.05$ were considered significant.
- Chi-square (X2) test: This test was used for the analysis of the qualitative variables sex, study groups, perioperative hypertension, and for the effectiveness indicators of SBP reduction, MAP reduction, and DBP reduction. The null hypothesis, H0, was established as the absence of a significant association between two variables, and the dependency hypothesis, H1, was established as the existence of an association. Associations with a $p < 0.05$ were considered significant.

The exact limits of the 95% confidence interval were estimated. The results were presented in tables and figures and expressed as numbers and percentages. They were compared with national and international studies, and conclusions and recommendations were made. The approval of the institution's Scientific Committee and the informed consent of the patients were obtained for the study. The principles established in the Declaration of Helsinki were followed.

3. Results

Table 1 identifies the preoperative blood pressures by study group. The mean preoperative SBP was higher in the control group at 142.23 mmHg. Likewise, the mean preoperative MAP was 99.09 mmHg. Finally, the mean preoperative DBP in the control group was 77.52 mmHg. The difference in means between the groups was significant for each of the preoperative pressures identified.

Table 1. Perioperative blood pressures by study group

Preoperative blood pressures	Study groups		Significance (p)
	Treatment group (with atenolol) $n_1 = 95$	Control group (without atenolol) $n_2 = 88$	
Preoperative SBP	133.44	142.23	0.000
Preoperative MAP	94.03	99.09	0.000
Preoperative DBP	74.33	77.52	0.010

Note: SBP: Systolic blood pressure. MAP: Mean arterial pressure. DBP: Diastolic blood pressure. (Source: Anesthesia medical records)

The incidence of perioperative hypertension in the control group was 20.2% (Table 2). It was much lower in the treatment group, at 11.6% of the total cases. The differences between groups were significant. The odds ratio for the treatment group was 0.52, and for the control group, 1.66. As measures of treatment effect, the ARR (Absolute Risk Reduction) was 17.9%, the RR (Incidence Rate in Exposed/Incidence Rate in Unexposed) was 0.4, the RRR (Relative Risk) was 60%, and the NNT (Number of Patients Needed to Treat) was 6.

Table 2. Patients with perioperative hypertension by study group

Perioperative hypertension	Study groups				Total	
	Treatment group (with atenolol)		Control group (without atenolol)			
	No.	%	No.	%	No.	%
Yes	11	11.6	26	29.5	37	20.2
No	84	88.4	62	70.5	146	79.8
Total	95	100	88	100	183	100

Source: Anesthetic medical records.

In the treatment group, MAP decreased by 86.3% and DBP by 85.3%. The differences between the two groups in terms of reduction in SBP, MAP, and DBP were statistically significant. The mean reduction in the treatment group was 11.89 mmHg. The mean difference of 2.40 mmHg more in the treatment group was significant. The odds ratio for the treatment group in relation to the reduction in SBP was 1.82, for the reduction in MAP, 1.71, and for the reduction in DBP, 1.57.

When analyzing the main indicators of the effectiveness of atenolol treatment in Table 3, all showed significant differences between the groups. The greatest reduction occurred in SBP and MAP, with 86.3% of the total cases in the group. The mean reduction in the treatment group was 2.40 mmHg greater than in the control group. The treatment group was 1.92 times more likely to experience a decrease in SBP than the control group, 1.82 times more likely to experience a decrease in MAP, and 1.57 times more likely to experience a decrease in DBP.

Table 3. Main indicators of atenolol treatment effectiveness by study group

Indicators	Study groups		Significance p (ORt)
	Treatment group (with atenolol) $n_1 = 95$	Control group (without atenolol) $n_2 = 88$	
SBP reduction	82 (86.3%)	60 (68.2%)	0.003 (1.82)
MAP reduction	82 (86.3%)	62 (70.5%)	0.009 (1.71)
DBP reduction	81 (85.3%)	63 (71.6%)	0.024 (1.57)
Mean reduction	11.89	9.49	0.034

Note: SBP: Systolic blood pressure. MAP: Mean arterial pressure. DBP: Diastolic blood pressure. ORt: Odds ratio of the treatment group. (Source: Anesthesia clinical records)

4. Discussion

Atenolol is a selective beta-1 receptor blocker that exerts its hypotensive effect centrally by depressing sympathetic cardiovascular centers such as the bulbar vasomotor system. It decreases heart rate and myocardial contractility, thereby reducing blood pressure. [6] These could be the main reasons for the results found in the present study.

HBP occurs in 25% of surgical patients, and 4% of these cases develop complications. In this study, the treatment group significantly reduced SBP by 8.79 mmHg, MAP by 5.06 mmHg, and DBP by 3.20 mmHg, compared to the control

group. Preoperative blood pressures were higher in the control group.

Cáceres et al. [11] found that treatment with atenolol reduces the incidence of complications in non-cardiac surgery. Zaidel [12] demonstrated that the beta-blockade strategy with atenolol attenuates the systemic cardiocirculatory response, providing protection against cardiac events and perioperative death. This is consistent with our results, as significant blood pressure reductions only occurred in the atenolol treatment group.

Several studies have demonstrated an incidence between 30% and 40%. Jacomelli et al. [3] found an incidence of 34% in patients undergoing video-endoscopic surgery. This is inconsistent with our results, where the incidence was between 10% and 30%.

Patients in the control group had an incidence of 29.5%, closer to the incidence reported in the literature. However, the incidence in the treatment group was much lower, at 11.6%. The differences between groups were significant. The odds ratio in the treatment group of less than 1 constitutes a protective factor. However, the odds ratio for the control group suggests that perioperative hypertension is 1.66 times more common in the control group than in the treatment group.

Regarding the analysis of secondary indicators of atenolol's effectiveness as measures of treatment effect, the positive effect it had in reducing the incidence of perioperative hypertension is demonstrated. Hazzi and Mayock [8] in their study used beta-blockers prior to anesthetic induction and found a significant reduction in the risk of ischemia, non-fatal postoperative infarction, and cardiovascular and total death at 2 years. Meanwhile, Poldermans et al. [9] obtained an absolute reduction in the risk of ischemic cardiac complications of 30% with the use of preoperative beta-blockers. Both studies agree with our results regarding the reduction of perioperative events with the use of beta-blockers. In the case of the current study, the incidence of perioperative hypertension was significantly reduced in the atenolol treatment group.

The antihypertensive effects of atenolol may have influenced the results by reducing heart rate and decreasing myocardial contractility, decreasing sympathetic outflow to the peripheral vasculature, and inhibiting renin release from the kidney.

Teixido-Tura et al. [7] found that hypertensive patients with a MAP $\geq$ 129.5 mmHg have a higher incidence of myocardial ischemia during surgery. In our study, MAP was reduced by 11.87 mmHg in patients taking atenolol, with a mean perioperative MAP of 94.03 mmHg in the treated group. The observed MAP reduction decreased the incidence of perioperative hypertension by 17.9%.

The primary indicators of atenolol's effectiveness were significant, and the secondary indicators showed a positive effect. All of this demonstrates that atenolol was effective in reducing the incidence of perioperative hypertension.

Despite the study's limitations related to the small sample size and the short observation time of the cases, studies such as the current one provide an effective therapeutic option, such as atenolol, for preventing perioperative hypertension during endoscopic cholecystectomy in hypertensive patients.

5. Conclusions

Preoperative treatment with atenolol is an effective treatment for hypertensive patients undergoing video-endoscopic surgery for gallstones.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Supplementary File (Open Data)

Database of the Efficacy of Atenolol for the Prevention of Perioperative Hypertension in Hypertensive Patients During Endoscopic Cholecystectomy, https://zenodo.org/records/8147174

Statistical Evidence of the Efficacy of Atenolol for the Prevention of Perioperative Hypertension in Hypertensive Patients During Endoscopic Cholecystectomy, https://zenodo.org/records/8147210

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