

**Original Research****The Effect Of Oral Clonidine On Hemodynamic Status During Laparoscopic Cholecystectomy**

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**Abstract:**

**Background:** Hemodynamic changes during laparoscopic surgery are important categories in laparoscopic cholecystectomy. Therefore, the aim of this study was to evaluate the effect of oral clonidine on hemodynamic status during laparoscopic cholecystectomy.

**Method:** In this randomized double-blind clinical trial study, 50 patients with class I and II anesthesia underwent laparoscopic cholecystectomy. Patients were randomly divided into oral clonidine and control groups. Systolic and diastolic blood pressure, mean arterial pressure (MAP) and intraoperative heart rate were recorded.

**Results:** The results showed that in the third and fourth periods, a significant difference was observed in the mean systolic blood pressure between the two groups ( $P < 0.05$ ). Mean diastolic blood pressure was significantly different between the two groups only in the fourth period ( $P < 0.05$ ) and was lower in the clonidine group than the control group. In the clonidine group, the mean trend of systolic and diastolic blood pressure was significant from the first 30 minutes to the fifth 30 minutes ( $P < 0.001$ ). But in the control group was not significant ( $P = 0.137$ ). The results showed that the mean heart rate between The control group and clonidine were not significant, but in the clonidine group the heart rate increased up to the second 30 minutes but then decreased ( $P < 0.05$ ). In the control group the heart rate increased up to the second 30 minutes but it has fluctuated since then.

**Conclusion:** The results of the present study showed that oral clonidine was able to stabilize hemodynamics during laparoscopic cholecystectomy. It seems that the use of oral clonidine in laparoscopic cholecystectomy can stabilize hemodynamic symptoms during surgery.

**Keywords:** Clonidine Hemodynamic symptoms, Cholecystectomy, Laparoscopy.

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## Introduction

Laparoscopic cholecystectomy was introduced by Philip Mort in 1987 and is now the gold standard method for treating gallstones (1). Laparoscopy is a diagnostic and therapeutic surgery that is performed to replace laparotomy because it has a shorter recovery time, smaller scar site, shorter surgery time, lower surgery cost, and less adhesive bandage complication. Other common problems during laparoscopy include hemodynamic changes when gas is blown into the peritoneum, which include decreased cardiac output, increased systemic vascular resistance, hypertension, changes in heart rate, decreased respiratory capacity, and increased airway pressure (3-7). While the heart rate, heart rate and heart rate increase compared to the time after induction of anesthesia and CO<sub>2</sub> injection into the peritoneal cavity (8). Sympathetic responses to changes in body position during laparoscopy include increased heart rate, increased blood pressure, and tachyarrhythmia. These responses are associated with an acute increase in plasma concentrations of norepinephrine and epinephrine (9-10). There are several ways to reduce the cardiovascular effects of increased sympathetic activity, including the use of beta-blockers, alpha-two agonists, calcium channel blockers, nitroglycerin, nystatin, and aspirin (11-14). Clonidine is approximately a selective stimulator of the  $\alpha_2$ -adenoreceptor receptor with an approximately 200: 1 affinity for the  $\alpha_2$ -receptor relative to  $\alpha_1$  (15-17). Clonidine is a specific  $\alpha_2$ -agonist whose most important role is to inhibit the sympathetic system (18). Studies on the role of  $\alpha_2$ -agonist drugs have shown that these drugs can improve and stabilize hemodynamic symptoms in laparoscopic cholecystectomy (19-20). Due to the increasing technique of laparoscopic surgery and the importance of proper hemodynamic control during surgery, this study was performed to investigate the effect of oral clonidine on hemodynamic status during laparoscopic cholecystectomy.

## Methods

### Study design:

The present study is a double-blind randomized clinical trial that was performed during a four-month period from August 2016 to November 2016 in patients aged 18 to 65 years who referred to Shahid Mohammadi Hospital in Bandar Abbas for laparoscopic cholecystectomy.

### Ethical considerations:

Before the inclusion of patients in this study, the research process was explained and informed consent was obtained from them. Throughout the study, researchers adhered to the principles of the Helsinki Declaration and the confidentiality of patient information. All costs of the project were covered by the researchers and no additional costs were incurred by the patients. This study has been approved by the ethics committee of Hormozgan University of Medical Sciences under the ethical code IR.HUMS.REC.1399.079.

### Sampling:

The study population was patients undergoing laparoscopic cholecystectomy. The sample size was obtained using the formula  $\alpha = 0.01$ ,  $\beta = 1 - 0.9$ ,  $z_{(1-\alpha/2)} = 2.57$  and  $z_{(1-\beta)} = 1.28$  in each group of 20 people with a probability of shedding. 25 people were considered in each group. Then, to have an equal chance of being in the intervention group or control group, the samples were randomly assigned to study groups (25 people in each group) using a table of random numbers. Subjects were randomly divided into two groups of oral and control clonidine based on the inclusion and non-exclusion criteria. Patients in the groups were randomly assigned. To do this, numbers from 1 to 50 were written on similar cards and the cards were placed in an envelope. A card was then randomly selected from the envelope and assigned to each patient. The patient was then randomly assigned to one of two groups. The patients were assigned to two random groups using black and white cards. For patients who received a white card, the person in charge of blinding studied oral clonidine and for patients who received a black card, the drug was used as a

placebo (Figure 1) (Figure 1). Sampling was performed to achieve agreement between the two groups in terms of basic characteristics.

#### **Inclusion and Exclusion criteria:**

**Inclusion criteria:** Patients aged 18 to 65 years and class I and ASA II who are candidates for elective laparoscopic cholecystectomy in Shahid Mammadi Hospital.

**Exclusion criteria:** Patients with a history of asthma, Breastfeeding, renal failure, heart failure, history of addiction and sensitivity to clonidine.

#### **Intervention:**

After signing an informed written consent to participate in the study, patients were treated equally (25 people in each group) using Block Randomization method based on inclusion and exclusion criteria. One hour before the operation, the intervention was performed for the patients. The first group received 0.2 mg of oral clonidine and the second group received placebo. All patients underwent careful monitoring including ECG, pulse oximetry and BP after being placed on the operating table. Peripheral intravenous access (IV Line) was established for all of them. 3 cc/kg of body weight of ringer lactate solution and to provide initial oxygenation (preoxygenation), patients received 3-5% per minute 100% oxygen through the face mask for 3 minutes with normal breathing. Then, as a prodrug, all patients were prescribed 2 mg midazolam (0.03 mg / kg) and fentanyl (2 mcg / kg) intravenously and general anesthesia by intravenous induction by 5 mg/Kg body weight of thiopental sodium was established as the main anesthetic and 0.5 mg / kg body weight of atracurium was established as a neuromuscular relaxant for patients. As soon as induction drugs were prescribed, patients underwent mask ventilation (BMV). After about 3-5 minutes and ensuring the onset of muscle relaxation and ensuring the proper depth of anesthesia, a direct laryngoscopy in the Sniff position was performed by an anesthesia assistant. Anesthesia was maintained for all patients at 100  $\mu$ g / kg body weight of propofol and 0.1  $\mu$ g / kg body weight of remifentanil. During the operation, 10 mg of

atracurium was administered every 30 minutes. 20 minutes before the end of the operation, the infusion of remifentanil was stopped. If the patient's blood pressure increased to more than 180, if there was sufficient depth of anesthesia, the dose of remifentanil infusion was increased to keep the blood pressure in the range below 160/90 and this dose increase was recorded in the questionnaire. The type of anesthesia and how to do it was performed by the anesthesia assistant and all conditions related to anesthesia were the same for all patients and the medication was given to the patient 1 hour before the start of surgery. None of the above individuals knew about the grouping of patients and the drug prescribed in the intervention and were only responsible for performing anesthesia and recording the required symptoms in the questionnaire. After surgery, patients were transferred from the operating room to recovery. The duration of surgery was considered from the beginning of the patient to the end of the dressing. With the help of monitoring, blood pressure (SBP / DBP / MAP) and heart rate of patients were recorded immediately after intubation during the operation at intervals of 30 minutes.

#### **Data analysis:**

Data were analyzed using SPSS software version 21 and descriptive statistics (mean, percentage, frequency and standard deviation) and inferential tests (t-test, Mann-Whitney, Friedman) and at a significant level  $P <0.05$ .

#### **Results**

Fifty patients aged 18 to 65 years (in two groups of 25) were evaluated. One hour before the operation, subjects in the first group received 0.2 mg of oral clonidine and the second group received placebo. 22 patients (88%) were clonidine group and 18 patients (72%) were female control group. The results in Table 1 showed that the study groups were similar in terms of demographic variables of age, weight, height, body mass index and gender ( $p <0.05$ ). The mean duration of surgery was  $77.06 \pm 19.69$  minutes in the clonidine group and  $85.42 \pm 18.93$  minutes in

the control group, which showed no significant difference ( $P = 0.437$ ) (Table 1).

The results showed that in the third and fourth periods, a significant difference was observed in the mean systolic blood pressure between the two groups ( $P < 0.05$ ) (Table 2). Mean systolic blood pressure in the third and fourth periods was lower in the clonidine group than in the control group. Also, the mean diastolic blood pressure was significantly different between the two groups only in the fourth period ( $P < 0.05$ ) and in the clonidine group was lower than the control group. In the clonidine group, the mean trend of systolic and diastolic blood pressure was significant from the first 30 minutes to the fifth 30 minutes ( $P < 0.001$ ). But in the control group was not significant ( $P = 0.137$ ). The results showed that the mean heart rate between the control and clonidine groups was not significant, but in the clonidine group the heart rate increased up to the second 30 minutes but then decreased ( $P < 0.05$ ). In the control group, the heart rate increased until the second 30 minutes but fluctuated after that (Table 2).

## Discussion

Maintaining cardiovascular stability can reduce the cardiovascular risks of increased sympathetic activity that occur during surgery or when the patient wakes up after anesthesia (20-22).  $\alpha_2$  agonist drugs act on central and pre-synaptic receptors and inhibit the central output of the sympathetic system, reducing the environmental impact of the sympathetic system. These drugs are able to dilate the coronary arteries after stenosis, reducing hemodynamic abnormalities near the time of operation (23). The effect of the oral prodrug clonidine to inhibit sympathetic responses during other open surgeries has long been demonstrated (24-29). hemodynamic changes during laparoscopy are a combination of the effects of pneumoperitoneum and the patient's position and anesthesia and hypercapnia due to CO<sub>2</sub> uptake, which in addition to pathophysiological changes, increases Vaginal tonic reflex and the possibility of arrhythmia (30).

The results of the present study showed that clonidine was able to stabilize the hemodynamic symptoms during laparoscopic cholecystectomy compared to the control group. Rafiei et al. (2011) in their study, which aimed to investigate the effect of Premedication with oral clonidine on hemodynamic status during laparoscopic cholecystectomy, showed that the effect of Premedication with oral clonidine on systolic blood pressure and heart rate during laparoscopic surgery in comparison with the control group was a modification in increasing systolic and diastolic blood pressure and heart rate, which reduces the need for adjuvant drugs to control hemodynamic symptoms during surgery. Modulation of hemodynamic symptoms during laparoscopic surgery was used (19). Kholdebarin et al. (2014) conducted a study to investigate the effect of oral clonidine on intraoperative hemodynamic changes and pain after laparoscopic cholecystectomy. The results of this study showed that clonidine was able to stabilize the hemodynamic symptoms in laparoscopic cholecystectomy (20). Hassani et al. (2006) conducted a study to investigate the effect of the oral drug clonidine on hemodynamic responses during laparoscopic surgery in women under general anesthesia. The results of this study showed that clonidine was able to stabilize hemodynamic symptoms during the study compared to the control group (31). The study of Sane et al. (2019) investigated the effect of preoperative oral clonidine on shoulder pain in laparoscopic cholecystectomy under general anesthesia. The results of this study showed that clonidine could reduce hemodynamic variables during the study compared to the control group (32). Sung et al. (2000) conducted a study to evaluate the clinical efficacy of preoperative oral clonidine in anesthesia in patients undergoing laparoscopic cholecystectomy. The results of this study showed that clonidine was able to improve Hemodynamics stability during laparoscopic cholecystectomy (33). Singh et al. (2011) in their study, which aimed to investigate the effect of oral clonidine on the stability of hemodynamic

symptoms during laparoscopic cholecystectomy, showed that clonidine improves hemodynamic symptoms during laparoscopic cholecystectomy (34). Masud et al. (2017) conducted a study to investigate the effect of clonidine on hemodynamic symptoms in laparoscopic cholecystectomy. The results of this study showed that oral clonidine can improve and stabilize hemodynamic symptoms during laparoscopic cholecystectomy (35). The present study also showed that the use of clonidine in the preoperative time was able to inhibit the activity of the sympathetic system by controlling systolic blood pressure and preventing an increase in heart rate, without putting the disease at risk for bradycardia. The anti-sympathetic effects of clonidine appear to be effective in causing these results. The sedative effect of  $\alpha_2$  agonists may also explain the difference in hemodynamic symptoms between the two groups.

### Conclusion

The results of the present study showed that oral clonidine was able to stabilize hemodynamics during laparoscopic cholecystectomy. It seems that this drug can be used in patients undergoing laparoscopic cholecystectomy to stabilize hemodynamic symptoms.

### Conflict of interest

The authors declare that they have no conflict of interest.

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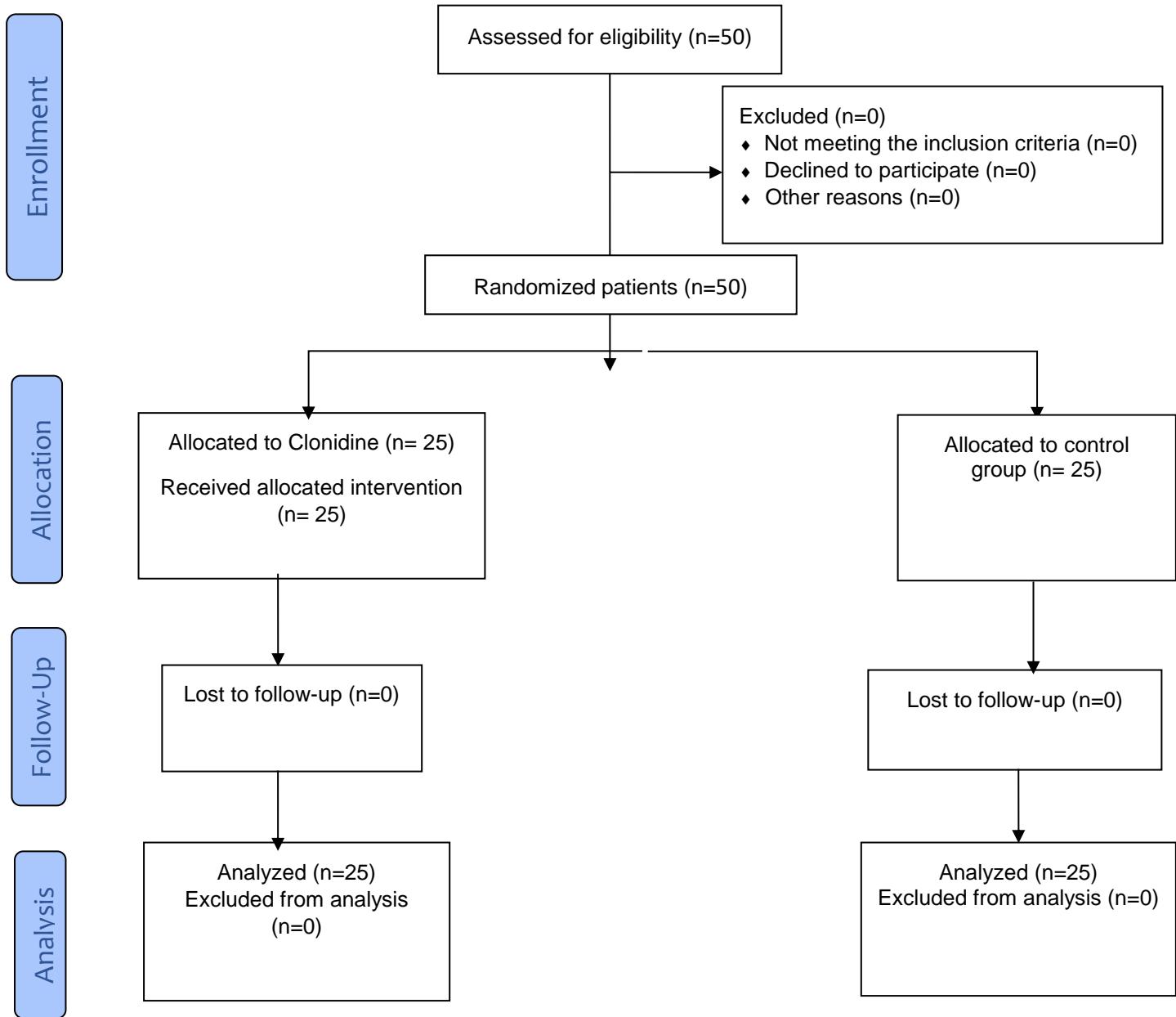
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**Table/ Figure****Figure 1: Study consort diagram**

**Table 1: Descriptive statistics indicators of demographic and clinical variables by two groups**

	Clonidine (25)	Control (25)	P-value
	<b>SD±Mean</b>	<b>SD±Mean</b>	
Age(year)	14.26±38.44	11.48±36.04	0.349
Weight(kg)	18.77±69.04	11.21±67.24	0.725
Height (cm)	9.95±160.17	5.93±163.12	0.496
BMI	5±26.43	4.30±25.31	0.102
Duration of surgery (minutes)	19.69±77.06	18.93±85.42	0.437
	<b>Frequency (%)</b>	<b>Frequency (%)</b>	
Gender	Male	3(12)	7(28)
	Female	22(88)	18(72)

**Table 2: Changes in hemodynamic variables between the two groups at different times**

	Time	Clonidine (25)		Control (25)		P-value
		SD	Mean	SD	Mean	
<b>SBP<sup>1</sup> (mm Hg)</b>	First 30 m <sup>4</sup>	15.71	135.22	19.35	131.96	0.777
	30 m second	19.82	122.80	24.72	128.48	0.402
	30 m Third	10.63	111.92	17.21	126.04	0.001
	30 m fourth	12.43	126.20	18.68	135.96	0.037
	30 m fifth	8.16	127	15.89	128.44	0.547
	P-value		<0.001		0.137	
<b>DBP<sup>2</sup> (mm Hg)</b>	First 30 minutes	11.64	86.08	13.11	83.92	0.537
	30 m second	15.08	81.20	21.36	86.48	0.468
	30 m Third	10.17	71.48	13.23	81.60	0.205
	30 m fourth	9.66	84.68	14.85	91.88	0.002
	30 m fifth	12.01	85	10.28	82.44	0.058
	P-value		<0.001		0.012*	
<b>HR<sup>3</sup></b>	First 30 minutes	11.07	84.12	12.67	82.32	0.905
	30 m second	12.83	88.63	18.93	92.60	0.677
	30 m Third	13.18	71.33	13.07	81.88	0.023
	30 m fourth	12.44	77.96	12.62	75.84	0.674
	30 m fifth	15.61	80.52	13.34	73.08	0.184
	P-value		<0.001		<0.001*	

SBP<sup>1</sup>: Systolic blood pressure DBP<sup>2</sup>: Diastolic blood pressure HR<sup>3</sup>: Heart Rate M<sup>4</sup>: minutes