Original Research

The Effect Of Oral Clonidine On Hemodynamic Status During Laparoscopic Cholecystectomy

Mehrdad Malekshoar[1], Pourya Adibi[2], Kaveh Hedayati Emami[3], Majid Vatankhah[4*]

1. Associated Professor of Anesthesiology, Intensive Care fellowship, Anesthesiology & Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Orcid: 0000-0002-3361-5429
2. Assistant Professor of Anesthesiology, Intensive Care fellowship, Anesthesiology & Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Orcid: 0000-0003-2296-2166
3. Department of Anesthesiology & Critical Care, Tehran university of Medical Sciences, Tehran, Iran. Orcid: 0000-0001-5920-396X
4. Associated Professor of Anesthesiology, Intensive Care fellowship, Anesthesiology & Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Orcid: 0000-0002-2053-1138

Corresponding Author: Dr Majid Vatankhah, Associated Professor of Anesthesiology, Intensive Care fellowship, Anesthesiology & Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Email: hormozgan91@yahoo.com, Orcid: 0000-0002-2053-1138

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.

Submitted: 28 Jan 2023, Revised: 20 Feb 2023 , Accepted: 27 March 2023

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 CO2 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 α2-adenoreceptor receptor with an approximately 200: 1 affinity for the α2-receptor relative to α1 (15-17). Clonidine is a specific α2-agonist whose most important role is to inhibit the sympathetic system (18). Studies on the role of α2-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 Mohammadi 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 μg / kg body weight of propofol and 0.1 μg / 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 ±19.69 minutes in the clonidine group and 85.42 ±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). α2 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 CO2 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 α2 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.

Acknowledgment

The Vice Chancellor for Research and Technology of Hormozgan University of Medical Sciences is thanked for providing the necessary funds for this study. We would also like to thank the Clinical Research Development Unit of Peymanieh Hospital in Jahrom for the final edition of this article.

References

1. Vecchio R, MacFayden BV, Palazzo F. History of laparoscopic surgery. Panminerva Med 2000; 42(1):87-90.
2. Lundorff P; Hahlin M; Kallfelt B; Thorburn J; Lindblom B. Adhesion formation after laparoscopic surgery in tubal Pregnancy: a randomized trial versus laparotomy. Fertil Steril 1991 May;55 (5): 911-5.
3. Wahba RW, Beique F, Kleiman SJ. Cardiopulmonary function and laparoscopic cholecystectomy. Can J Anaesth 1995; 42(1):51-63.
4. Hirvonen EA, Nuutinen LS, Kauko M. Hemodynamic changes due to trendelenburg positioning and Pneumoperitoneumdurin laparoscopic hysterectomy. Acta Anaesthesiol Scand 1995; 39(7):949-55.
5. Gannedahl P, Odeberg S, Brodin LA, Sollevi A. Effects of posture and pneumoperitoneum during anaesthesia on the indices of left ventricular filling. Acta Anaesthesiol Scand 1996; 40(2):160-6.
6. Odeberg S, Ljungqvist O, Svenberg T, Gannedahl P, Bäckdahl M, von Rosen A, et al. Hemodynamic Effects of pneumoperitoneum and the influence of posture during anaesthesia for laparoscopic suegery. ActaAnaesthesiolScand 1994; 38(3):276-83.
7. Hirvonen EA, Nuutinen LS, Vuoltennaho O. Hormonal responses and cardiac filling pressures in head-up or head-down position and pneumoperitoneum in patients undergoing operative laparoscopy. Br J Anaesth 1997; 78(2):128-33.
8- Jean L Joris. Anesthedia for laparoscopic surgery. Miller RD, Gucchira RF, Miller ED, Gerald Reves J. Anesthesia, 5th ed. Philadelphia: Churchill Livingstone, 2000: 2004-17.
9. Shribman AJ Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with or without tracheal intubation. Br J Aneaesth 1987; 59: 295-9.
10. Wahba RWM, Beique F, Kleiman SJ. Cardiopulmonary function and laparoscopic cholecystectomy. Can J Anesth 1995; 42: 51.

11. Slogoff S, Keats AS. Does chronic treatment with calcium entry blocking drugs reduce perioperative myocardial ischemia? Anesthesiology 1988;68 (5): 676-80.
12. Coriat P, Daloz M, Bousseau D, Fusciardi J, Echter E, Viars P. Prevention of intraoperative myocardial ischemia during noncardiac surgery with intravenous nitroglycerin. Anesthesiology 1984;61 (2): 193-6.
13. Dunkelgrum M, Schouten O, Feringa HH, Vidakovic R, Poldermans D. Beneficial effects of statins on perioperative cardiovascular outcome. Curr Opin Anaesthesiol 2006; 19 (4): 418-22.
14. Schouten O, Bax JJ, Dunkelgrun M, Feringa HH, Van UH, Poldermans D. Statins for the prevention of perioperative cardiovascular complications in vascular surgery. J Vasc SURG 2006;44(2): 419-24.
15. De Vos H, Bricca G, De Keyser J, De Backer JP, Bousquet P, Vauquelin G. Imidazoline receptors, Non-adrenergic idazoxan binding sites and α2-adrenoceptors in the human central nervous system. Neuroscience 1994; 59(3): 589-98.
16. Hamilton CA. The role of imidazoline receptors in blood pressure regulation. Pharmacol Ther 1992; 54(3): 231-48.
17. Guyenet PG, Cabot JB. Inhibition of sympathetic preganglionic neurons by catecholamines and Clonidine: Mediation by an alpha-adrenergic receptor. J Neurosci 1981; 1(8): 908-17.
18. Perioperative sympatholysis. Beneficial effects of the alpha 2-adrenoceptor agonist mivazerol on hemodynamic stability and myocardial ischemia. McSPI--Europe Research Group. Anesthesiology. 1997 Feb;86(2):346-63.
19. Rafiei M, Hjjat M, Ariana M, Kianersi K. Evaluation of oral clonidine premedication on hemodynamic parameters during laparoscopic cholecystectomy. Ann Mil Health Sci Res. 2012; 10(1):67-71.
20. Kholdebarin A, Jalili S, Godrati M, Rahimzadeh P, Rokhtabnak F, Sayarifard A et al . The effect of oral clonidine on hemodynamics and postoperative pain in laparoscopic cholecystectomy. JAP. 2014; 5 (1) :45-53.
20. Nishina K, Mikawa K, Uesugi T, Obara H, Maekawa M, Kamae I, et al. Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. Anesthesiology 2002; 96(2):323-3.
21. Wallace AW, Galindez D, Salahieh A, Layug EL, Lazo EA, Haratonik KA, et al. Effect of clonidine on Cardiovascular morbidity and mortality after noncardiac surgery. Anesthesiology 2004; 101(2):284-93.
22. Priebe HJ. Perioperative myocardial infarction-a etiology and prevention. Br J Anaesth 2005; 95(1):3-19.
23. Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative Cardiovascular complications: a meta-analysis. Am J Med 2003; 114(9):742-52.
24. Orko R, Pouttu J, Ghighone M Rosenberg Ph. Effects of clonidine on hemodynamic responses to endotrachean intubation and gastric acidity. Acta Anesthesiol Scand 1987; 31: 325-9.
25. Kulka PJ, Tryba M, Zens M. Dose response effective of iv clonidine on stress response during induction of anesthesia in coronary artery bypass graft patoents. Anesth Anal 1996; 80: 263-8.
26. Muzi M Goff DR, Kampine JP. Clonidine sympathetic activity but maintains baroreflex responses in normotensive humans. Anesth 1992; 77: 864-71.
27. Carabine UA, Wright PMC, Moore JA. Preanesthetic medication with clonidine. Br J Anesth 1991; 67: 79-83.
28. Mikawa K, Mackawa N, Nishina K. Efficacy of oral clonidine premedication in

children. Anesthesiology 1993; 79: 926-31.
29. Ghingone M, Cavillo O, Quintin L. Anesthesia and hypertension: the effect of clonidine on perioperative hemodynamics and isoflurane requirements. Anesth 1987; 67: 3-10.
30. Struthers AD, Cuschieri A: Cardiovascular consequences of laparoscopic surgery. Lancet 1998; 352: 568.
31. Hassani V, Mohammad Taheri F, Mehdizadeh A. The Effect of Oral Clonidine Premedication on Hemodynamic Responses during Gynecologic Laparoscopy under General Anesthesia. RJMS. 2006; 13 (50) :39-46.
32. Sane S, Majedi MA, Golmohammadi M, Abedini M, Abbasivash R. The Effect of Preoperative Oral Clonidine on Shoulder Pain in Laparoscopic Cholecystectomy with General Anesthesia. J Isfahan Med Sch 2019; 37(545): 1129-35.
33. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY. Effect of oral clonidine premedication on Perioperative hemodynamic response and postoperative analgesic requirement for patients Undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin 2000; 38(1): 23-9.
34. Singh S, Arora K. Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Indian J Anaesth. 2011 Jan;55(1):26-30.
35. Masud M, Yeasmeen S, Haque AK, Jahan S, Saha NC, Banik D. Role of Oral Clonidine Premedication on Intra-operative Hemodynamics and PONV in Laparoscopic Cholecystectomy. Mymensingh Med J. 2017 Oct;26(4):913-920.

Table/ Figure

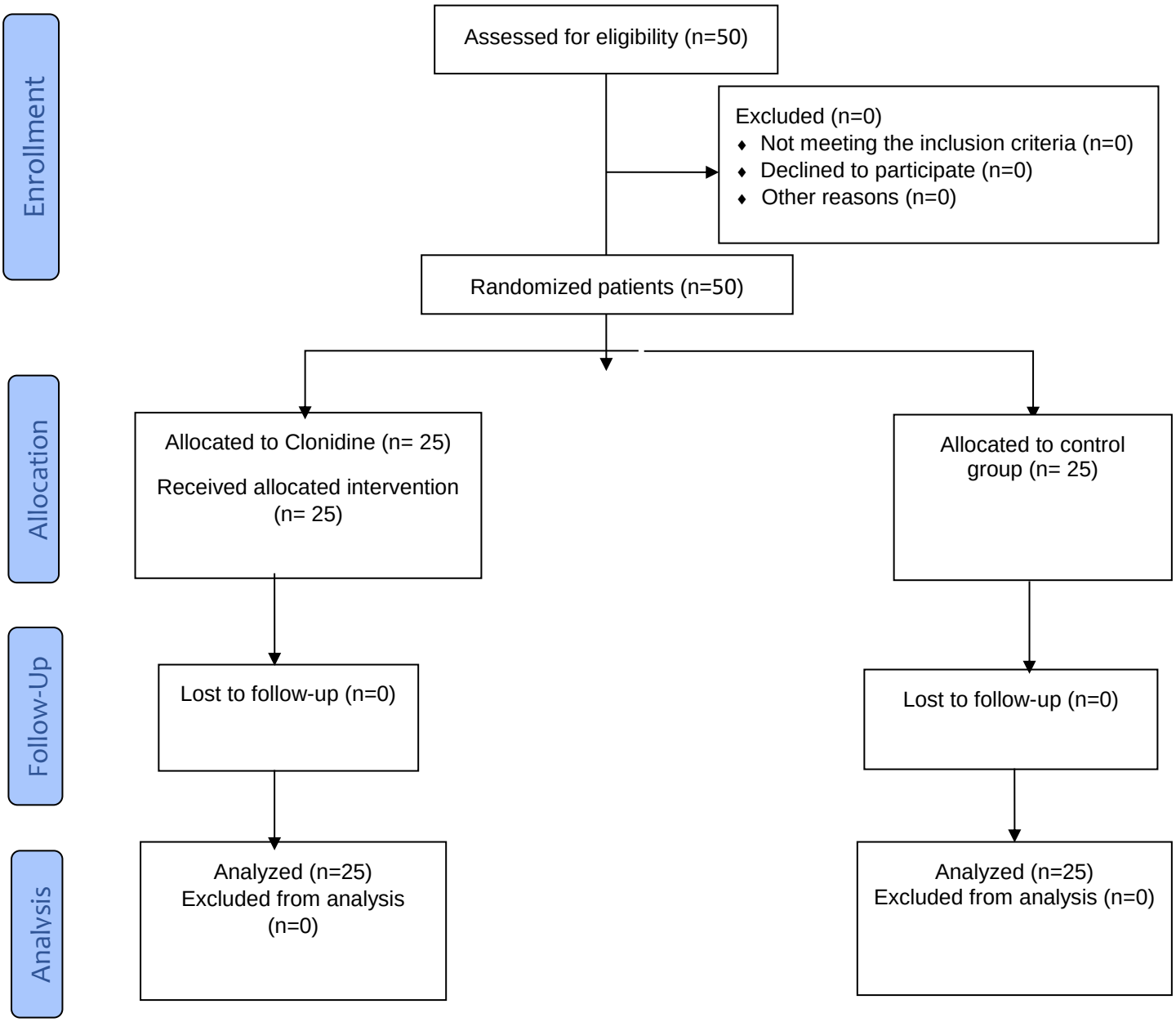

Figure 1: Study consort diagram

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

		Clonidine (25)	Control (25)	P-value
		SD±Mean	**SD±Mean**	
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
		Frequency (%)	**Frequency (%)**	
Gender	Male	3(12)	7(28)	0.145
	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	
SBP[1] (mm Hg)	First 30 m[4]	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	
DBP[2] (mm Hg)	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*	
HR[3]	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[1]: Systolic blood pressure DBP[2]: Diastolic blood pressure HR[3]: Heart Rate M[4]: minutes