Research Paper

INTERNATIONAL JOURNAL OF CURRENT ADVANCED RESEARCH
ISSN: O: 2319-6475, ISSN: P: 2319-6505
Available Online at www.journalijcar.org
Volume 15; Issue 03; March 2026; Page No.650-660
DOI: http://dx.doi.org/10.24327/ijcar.2026.0660.0108

Subject Area : Anaesthesiology

STUDY OF THE EFFECT OF LABETALOL IN ATTENUATION OF PRESSOR RESPONSE TO PNEUMOPERITONEUM DURING LAPROSCOPIC SURGERIES

Dr Sumesha Chakurkar, Dr Sandhya Gujar, Dr Nitin Jadhav

Type 4 Quaters Room No 12, Esic Hospital Campus , Andheri Midc, Mumbai -400093.

ARTICLE INFO

Received 16th February, 2025
Received in revised form 25th February, 2025
Accepted 19th March, 2026
Published online 28th March, 2026

Key words:

Labetalol, Pneumoperitoneum, IAP (Intra-abdominal pressure rresponse, Laparoscopicsurgery, Hemodynamic changes.

ABSTRACT

Though laparoscopic surgery is considered a gentle surgery the procedure is indeed not risk free, because of "Pneumoperitoneum" required, which has significant hemodynamic effect. Pneumoperitoneum during laparoscopic surgeries can induce significant hemodynamic changes, particularly an increase in blood pressure and heart rate, due to elevated intra-abdominal pressure and CO_2 absorption. Attenuating this pressor response is crucial, especially in patients with cardiovascular risk. Labetalol, a combined α- and β-adrenergic blocker, may be effective in blunting this response. The pressor response to pnemoperitoneum is mainly due to sympathetic stimulation, which can be overcome by using various methods like IV drugs like β blockers, dexmeditomidine, clonidine, magnesium sulfate, epidural analgesia and decrease in flow rate of carbon dioxide insufflation. We studied the effect of Labetalol which is an alpha and beta blocker on the haemodynamic changes to CO2 insufflation and desufflation and its complications 2hrs in the postoperative period. This Study shows that the hemodynamic changes varied from baseline, but the change remained insignificant in case of end tidal carbon dioxide and arterial oxygen saturation, but the heart rate, systolic, diastolic and mean arterial blood pressures were significantly increased.

INTRODUCTION

Laparoscopy has shown appreciable growth in its clinical application and popularity, and worldwide acceptance as a frequently performed surgery due to its various advantages over the open technique. The various benefits include small incision, reduced pain, better cosmetic results, quicker recovery, reduced hospital stay, lesser postoperative complications, etc. Though considered a gentle surgery, the procedure is indeed not risk-free, because of 'Pneumoperitoneum' which is having a significant hemodynamic and respiratory effect which increases the risk of anesthesia.

Diminished length of postoperative hospital stay has decreased healthcare costs, and also there is a reduced need for postoperative analgesia and an earlier return to gainful employment. Laparoscopy was first introduced by Kelling in 1901, and he had viewed the abdominal viscera of a living dog using a cystoscope. Ruddock was the first to use peritoneoscopy in the United States. Power and Barnes had performed the first laparoscopic sterilization.Later in the 1960s, this minimally invasive procedure became popular amongst gynaecologists and patients for its effectiveness and simplicity. Recent advances in video imaging, automatic pressure-driven insufflators, powerful light sources, and high-flow suction irrigation technology have made it possible to perform even difficult intra-abdominal maneuvers relatively easily.Gallbladder surgery has been revolutionized using this approach and, unless contraindicated, it is almost exclusively performed by laparoscopy. Because of the improvement of technology, complications of laparoscopic surgeries have decreased tremendously. Hence, elderly persons and patients with significant.

disease and other comorbidities are also being offered this surgical intervention. The creation of pneumoperitoneum is an integral part of laparoscopic procedures and is usually done by insufflation of carbon dioxide for the proper visualisation of abdominal viscera and various manipulations.The main effects are due to raised intra-abdominal pressure leading to respiratory, cardiovascular, and neurologic alterations. The cardiovascular effects at an intra-abdominal pressure (IAP) of less than 15 mmHg augment the venous return due to the emptying of splanchnic vessels, and thus cardiac output and blood pressure are increased. At higher intra-abdominal

*Corresponding author: **Dr Sumesha Chakurkar**

Type 4 Quaters Room No 12, Esic Hospital Campus , Andheri Midc, Mumbai -400093.

pressures of more than 15 mmHg, they compress the inferior vena cava and other collaterals, leading to a decrease in the venous return, thus reducing cardiac output and blood pressure. Various bradyarrhythmias leading to atrioventricular blocks and cardiac arrest have been documented due to vagal stimulation on the insertion of a trocar, peritoneal stretch, or carbon dioxide embolization

Respiratory changes include reduced lung volumes, basal atelectasis, increased intrapulmonary shunting, and raised peak and mean airway pressures, which are attributed to raised intra-abdominal pressures and cephalad migration of the diaphragm. There may also be chances of endobronchial migration of the endotracheal tube, resulting in hypercarbia and hypoxia. Laparoscopic procedures have been traditionally performed under general anesthesia due to the respiratory changes caused by pneumoperitoneum. The precise control of ventilation in general anesthesia has proven it to be ideal for such procedures. However, recently the use of regional anesthesia (RA) has emerged as an alternative choice for laparoscopy. Since RA leads to vasodilation, it reduces blood loss, thereby making the surgical field clear, which helps in easy surgery.The advantages of RA can include: prevention of airway manipulation, an awake and spontaneously breathing patient intra-operatively, minimal nausea and vomiting, effective post-operative analgesia, and early ambulation and recovery. However, it may be associated with a few side effects such as the requirement of a higher sensory level, more severe hypotension, shoulder discomfort due to diaphragmatic irritation, and respiratory embarrassment caused by pneumoperitoneum. Because of the above-mentioned reasons, general anesthesia remains the preferred technique for laparoscopic surgery

Fig.1:Laproscopyprocedure with position of ports in situ

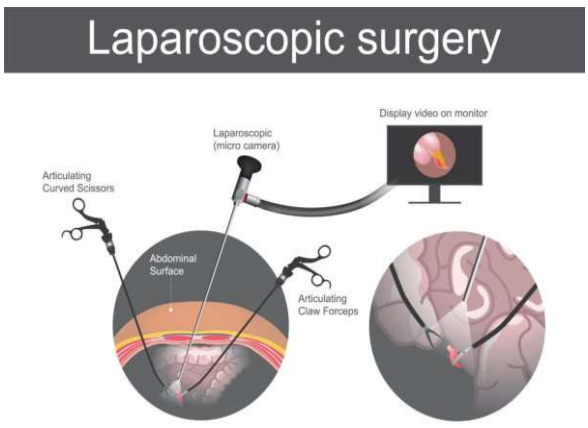

Fig.2

Various pharmacologic drug combinations and methods have been used to partially suppress the cardiovascular response to pneumoperitoneum in laparoscopic surgeries. These drug combinations include intravenous lidocaine, selective and nonselective beta-blockers, selective and nonselective alpha-blockers, calcium channel blockers, adrenergic blockers, vasodilators, narcotics and non-narcotic pain relievers, opioids, clonidine, dexmedetomidine, magnesium sulfate, as well as inhalational agents by increasing the depth of anesthesia. Most workers have used Esmolol (a cardioselective beta-blocker) as a bolus and in infusion and found it to be effective. Other beta-blockers like metoprolol and labetalol have been useful in not only attenuating the response of laryngoscopy and pneumoperitoneum but also in preventing perioperative cardiovascular events.

It is very important to be very cautious of the pressor response of pneumoperitoneum in order to prevent its detrimental effects like tachycardia, arterial hypertension, raised intraocular and intracranial pressures, myocardial ischemia, myocardial infarction, heart failure, etc. The major conditions in which the pressor responses may pose serious challenges are cardiovascular diseases like coronary artery disease, aneurysmal vascular disease, or those with decreased cranial compliance like head injury with extra- or intradural hematoma formation, intracranial tumors, etc.

We considered giving Labetalol for attenuating the pressor response to pneumoperitoneum because it is both a beta as well as an alpha-blocker. Administration of labetalol lowers systemic blood pressure by decreasing systemic vascular resistance (alpha-1 blockade). Blockade of alpha-1 adrenergic receptors inhibits vasoconstriction induced by endogenous catecholamines; vasodilation may occur in both arteriolar resistance vessels and veins. In addition to producing vasodilation by alpha-1 blockade, labetalol may cause vasodilation that is mediated by beta-2 adrenergic agonistic activity. Labetalol attenuates the reflex tachycardia triggered by a fall in blood pressure by simultaneous beta-1 blockade. Since catecholamines have positive chronotropic and inotropic actions, beta-receptor blockade produces a decrease in heart rate and myocardial contractility. Cardiac output, however, remains unchanged.

AIMS AND OBJECTIVES

To study the effect of Labetalol in the attenuation of the pressor response to pneumoperitoneum in patients of ASA I and II grade posted for elective laparoscopic surgeries under general anesthesia.Hemodynamic and respiratory parameters, including:

- Heart rate
- Systolic and diastolic blood pressure
- Mean arterial blood pressure
- EtCO2are to be observed.

REVIEW OF LITERATURE

Laparoscopy mainly involves inspecting the abdomen and pelvis using an endoscope. Carbon dioxide is the gas which is most commonly used to insufflate the abdomen so as to facilitate the view. It was first performed at the beginning of the 20th century by Georg Kelling, Dimitri Ott, and Christian Jacobeus, and it has now become an important tool in patient management. It had

also become popular among gynecologists for its effectiveness and simplicity.Until Lukichev in 1983 and Muhe in 1985, it was only performed for the diagnosis of liver disorders via visualization and biopsy, and abdominal trauma in general surgery. They had used laparoscopy to do cholecystectomy in humans.Over the past two decades, the use of laparoscopy has increased due to the advances in video imaging, automatic pressure-driven insufflators, powerful light sources, and high-flow suction-irrigation technology, making it possible to perform difficult intra-abdominal maneuvers more easily. Advantages of laparoscopy include less postoperative pain and analgesia use, reduced pulmonary complications, rapid recovery of bowel function, less intra-operative bleeding, less postoperative wound infection, and fewer metabolic derangements. This helps in reducing hospital stay with significant cost reduction. Additionally, small incisions heal well and provide an improved cosmetic appearance. This helps in doing more extensive procedures even in older patients with multiple comorbidities, including those with significant cardiopulmonary disease

Laparoscopic techniques had been attempted for multiple types of surgeries, some with proven benefit, some with possible benefit and some with uncertain benefit[17].

Surgeries with Proven Benefit

- Diagnostic & staging laparoscopy for malignancy
- Cholecystectomy
- Adrenalectomy
- Splenectomy
- Anti-reflux surgery
- Cardiomyotomy for achalasia
- Obesity surgery
- Laparoscopic colonic surgeryLive donor nephrectomy [1, 2]

Surgeries with Possible Benefit

- Laparoscopic abdominal aneurysm surgery
- Laparoscopic distal and central pancreatic surgery
- Laparoscopic left hepatic resections
- Laparoscopic rectal surgery (anterior resection)
- Appendectomy
- Laparoscopic hernia surgery [1]

Surgeries with Uncertain Benefit

- Right hepatectomy
- Pancreatoduodenectomy [1]

Common Gynecologic Procedures

- Tubal surgery (Tubal ligation, Salpingectomy, Salpingostomy)
- Diagnostic surgery (Adhesions, Endometriosis, Pelvic inflammatory disease)
- Ovarian surgery (Ovarian cystectomy)
- Uterine surgery (Myomectomy, Hysterectomy)

GASES USED IN LAPAROSCOPY

The most important aspects of laparoscopy are the use of an optimal insufflating gas to create adequate space for the surgery.

The ideal insufflating gas for creating pneumoperitoneum should be nontoxic, colourless, readily soluble in blood, easily ventilated through the lungs, noninflammable and inexpensive. The gases that had been used in laparoscopic surgery are air, O2, N20, N2, CO2, argon and helium. In early days of laparoscopy, air or oxygen was used for insufflation. The main consideration in choosing a gas is its solubility and its support to combustion.

1. AIR- It is composed of various gases. It is odorless, tasteless colorless, and since it contains oxygen, it will support combustion. It was the first gas to be used.Later it was withdrawn because it has high chance of fatal venous air embolism if there was an inadvertent air entry into a blood vessel.
2. OXYGEN- It is a colourless, odourless, and easily available gas. But it has been abandoned as an insufflating gas, since it supports combustion and has low blood gas solubility coefficient.
3. NITROGEN- It is colourless, tasteless, odourless, and an inert gas. The risk with nitrogen is chance of embolism.
4. NITROUS OXIDE-It is colourless, odourless and non-irritating gas with low solubility in blood. It is very stable and inert chemically at room temperature. Unlike CO2, N2O has no effect on pH and base changes20. It has no effect on MAP and pulse rate but cause a slight decrease in cardiac output. It also results in elevated plasma catecholamine. The N2O has negligible effect on hepatoportal circulation. It also increases intracranial pressure, but less than CO2. 11 Since it is more soluble than air, the transfer rate of N2O into peritoneal cavity, after the creation of pneumoperitoneum with air, has been reported to be rapid. It may support combustion when present with flammable gases and can cause intestinal distension. It permits laparoscopy in awake patients as it produces less peritoneal irritation and less pain.
5. CARBON DIOXIDE- It is the insufflating gas of choice at present. It is inert, readily absorbable gas,does not support combustion and permits the use of electrocautery. It is highly soluble in blood with solubility coefficient of 0.49 at 37 degree. It is carried in body in three forms.99% in the form of bicarbonates, 5-10% dissolved in plasma, and rest combined with proteins mainly hemoglobin. Absorption of CO2 during pneumo-peritoneum causes hypercarbia and acidemia. Mild hypercarbia (45-50) has little impact on hemodynamic while severe hypercarbia (50-60) alter cardiovascular function by stimulating the sympathetic system with elevation in plasma catecholamine, which cause vasoconstriction, rise in heart rate, blood pressure, and even arrhythmias.

   Complications due to CO2 insufflation

   Pain in abdomen-due to peritoneal irritation
   Shoulder pain-due to carbonic acid
   Lowers the threshold for arrhythmias
   Venous gas embolism
   Promotion of port site tumor growth
6. HELIUM- It is the second lightest element which is chemically inert, colorless, odorless, and tasteless gas that changes to liquid at-268.9 degree. Helium has low density, high thermal conductivity, and low solubility. During laparoscopy, it causes minimal hypercarbia

and minimal changes in pH. It has minor effect on the cardiovascular status also. But there is minimal increase in pulse rate, mean arterial pressure, and mean pulmonary arterial wedge pressure. Helium pneumoperitoneum is not associated with significant hypercarbia, and respiratory acidosis. Helium 12 also has no effect on renal blood flow but slightly decrease in the hepatic blood flow28. It may produce a small increase in intracranial pressure.

7. ARGON- It is a monoatomic gas which is colourless, odourless, and chemically inert. It was first of the noble gases. It is 2.5 times as soluble in water as N2 and O2. Argon also has no effect on pH or acid-base status30. One of the drawbacks is that pneumoperitoneum with argon increase vascular resistance and mean arterial pressure more than CO2 peritoneum and reduces stroke volume. It does not have any effect on ICP. Argon induces maximum decrease in hepatic blood flow as compared with other insufflating gases. Renal blood flow is not affected. Argon emboli results in greater hemodynamic effects than other gases. Due to decreased solubility in blood, there is rapid respiratory and metabolic acidosis resulting in death.

IDEAL IAP DURING LAPAROSCOPY

In 1901, Kelling performed abdominal endoscopy on a dog using air to fill abdominal cavity5. He also coined the term "Celioscopy" for this technique. Later a Swedish physician, Jacobaeus in 1910 used this procedure in humans for the first time. Goetz and Veres developed the automatic insufflating needle to establish pneumoperitoneum. In 1944, Raoul Palmer had advocated the importance of monitoring intra abdominal pressure. Later Kurt Semm had developed an automatic insufflation device that monitored the abdominal pressure and gas flow. The IAP is the steady pressure within the abdominal cavity and it varies with respiration. The normal values are 0-5 mmHg, and values greater than 12 mmHg are considered to be increased. The physiological changes observed during pneumoperitoneum are related to biochemical changes caused by insufflating gas, patient position, and mechanical changes caused by raised intra-abdominal pressure. Physiological Effect at Low IAP (7-10 mmHg).

The hemodynamic and metabolic parameter does not change significantly up to 10mmHg IAP34. Hepatic blood flow, hepatic arterial,portal and micro vascular perfusion are all reduced, in flow occurring with intra abdominal pressures as low as 10mmHg. Barczynski and et al demonstrated in their study that , keeping intra abdominal pressure as low as 7mmHg are associated with lower pain scores, lower incidence of shoulder pain, and better quality of life within 7 days following laparoscopic surgery.

Physiological Effect at Standard IAP (12-15 mmHg)

Various studies had demonstrated that up to IAP 15mmHg, the cardiac output does not change much although the dp/dt values get significantly reduced.There is reduction in the stroke volume due to the rise in afterload and depressant effect of carbon dioxide on the myocardial contractility. There is reduction in blood flow velocity in the femoral vein during laparoscopic surgery at 14mmHg, which can disturb venous return and stagnant blood flow predisposing to thromboembolism.

Due to shunting of blood away from the abdominal cavity, Mean arterial blood pressure may rise initially till an IAP 15mmHg but thereafter normalizes or decrease. Heart rate may rise transiently in response to increase in systemic vascular resistance and arterial blood pressure to maintain cardiac output. But most studies have reported that there is no significant long term change in heart rate with laparoscopy. In a small subset of otherwise normal healthy patients, bradycardia and asystole can occur during CO2 insufflation and pneumoperitoneum. Even though the exact mechanism is not clear, it is believed that direct pressure on the vagus nerve cause a stimulatory parasympathetic effect that lead to a drop in heart rate. Pneumoperitoneum causescephalad shift of the diaphragm, which lead to reduced lung expansion, reduced diaphragmatic excursion causing a pattern of restrictive lung disease. There is a fall in functional residual capacity, minute ventilation and tidal volume. Pulmonary vascular resistance increases, uneven distribution of ventilation to non dependent parts of lungs produces ventilation perfusion mismatch, hypercarbia and hypoxia. An IAP of 15mmHg also raises the PaCO2 by 10mmHg and decrease lung compliance by 25%.

Physiological Effect at high IAP (greater than15mmHg)

At 20mmHg, the cardiac output decreases and the systemic vascular resistance increases due to the collapse of the capacitance vessels. As IAP approaches 20 mmHg, there is decrease in blood flow due to the compression of the inferior vena cava56, resulting in hypotension. Pulmonary capillary wedge pressure, right and left side cardiac filling pressure and CVP usually increase with IAP greater than 20mmHg. Pneumoperitoneum at IAP of 15-20 mmHg is associated with increase in peak and plateau alveolar pressure as much as 50 and 80% respectively.

Decreased FRC promotes ventilation perfusion mismatch and an intrapulmonary shunting which may result in hypoxemia. IAP greater than 20mmHg, result in decrease in portal venous blood flow which result in liver dysfunction. Prolonged renal hypo-perfusion due to raised IAP carries the risk of acute tubular necrosis.

Effect of pneumoperitoneum

With pneumoperitoneum there is a cephalad displacement of diaphragm, limiting the movement of diaphragm and abdominal wall, decrease lung volumes, increase in peak airway pressure, atelectasis and dead space ventilation. After the induction of anesthesia, the functional residual capacity is reduced which is further reduced after the creation of pneumoperitoneum. Respiratory compliance is reduced due to the decrease in lung and chest wall compliance.

Increase in PaCO2.

The rise in intracranial pressure is mainly due to engorgement of cerebral veins, mainly because of increase in vena caval pressure during intra-abdominal insufflation. Hypercarbia also cause intracranial arteriolar dilation which results in increased cerebral perfusion.

During pneumoperitoneum, there is decrease in renal perfusion which leads to reduction in glomerular filtration rate,urinary output, sodium excretion and clearance. Even though renal function deteriorates at an IAP of 10mmHg, these changes are more at an IAP greater than 15mmHg.

COMPLICATIONS OF PNEUMOPERITONEUM

Arrhythmias and alteration in blood pressure that can be hypotension or hypertension, Brady arrhythmias occur due to increased vagal tone due to peritoneal stretching usually at light plain of anesthesia while tachyarrhythmias are due to hypercarbia. Subcutaneous Emphysema, Capnothorax and Capnomediastinum, Gas Embolism.

THE ANATOMY AND PHYSIOLOGY OF SYMPATHETIC NERVOUS SYSTEM

The sympathetic nervous system originates from the spinal cord in the thoracolumbar region, from the first thoracic through the second or third lumbar segment. The preganglionic sympathetic neurons have cell bodies within the horns of the spinal gray matter. Nerve fibres from these cell bodies extend to three types of ganglia grouped as paired

The drug is a modification of conventional beta adrenoceptor blocking drugs in which the isopropyl group has been replaced by an alkyl substitution and there is a salicymide moiety on the aromatic terminus. Labetalol has two chiral carbons and consequently exists as four stereoisomers110. Two of these isomers, the (S,S)- and (R,S)- forms are inactive. The third, the (S,R)-isomer, is a powerful α1 blocker. The fourth isomer, the (R,R)-isomer which is also known as dilevalol, is a mixed nonselective β blocker and selective α1 blocker.

Labetalol is one-fifth to one-tenth as potent as phentolamine in its ability to block alpha receptors and is approximately one-fourth to one-third as potent as propranolol in blocking beta receptors. In humans, the beta to alpha blocking potency ratio is 3:1 for oral and 7:1 for IV labetalol.

MATERIAL AND METHODS

A randomised prospective study of 81 patients undergoing elective Laproscopic surgery were randomly allocated into study (labetalol) and control (normal saline) group.

Duration of study: 2yrs.

Eligibility Criteria:

INCLUSION CRITERIA

1. Age between 15-60 yrs of either sex.
2. Weight of 40-80kg.
3. ASA Grade I and II.
4. Patient posted for Laparoscopic surgeries with a duration less than 120min.

EXCLUSION CRITERIA

1. ASA Grade III and IV.
2. Patients with respiratory disease.
3. Patients with cardiovascular disease.
4. Patients with renal disease.
5. Obese patients.
6. Pregnancy.

PREANAESTHETIC EXAMINATION AND PREPARATION

Approval from institutional ethics committee was obtained. Pre-anesthetic checkup was done one day prior to the surgery. Patients were examined for any systemic diseases and laboratory investigations recorded. The procedure of general anaesthesia and study protocol was explained to the patients and written informed consent was obtained. Patients were advised overnight fasting and premedicated with Tab. Ranitidine 150mg and Tab Alprazolam 0.5mg. Patients were assigned randomly by chit method to either of two groups based on the agents used for the study.

1. Group 1 (n=40) = Inj. Labetalol 0.5mg/kg diluted upto 10ml
2. Group 2 (n=41) = Normal saline 10 ml.

METHODOLOGY

Preparation of operating room

Anaesthesia machine was checked. Appropriate size endotracheal tubes, working laryngoscope with medium and large size blades, stylet, magillforcep and working suction machine was kept ready before the procedure.

On arrival in the operation theatre, standard monitors (NIBP, Pulse oximeter, ECG, Capnography) were attached to each patient. Baseline recording of the heart rate, systolic, diastolic, mean arterial blood pressures, EtCO2 and SPO2 were made. Intravenous access was established and slow infusion of crystalloids commenced.

Premedication with InjGlycopyrrolate 0.004mg\kg and InjEmset 0.1mg\kg, Inj Midazolam 0.03-0.05mg\kg, InjFortwin 0.3-0.5mg\kg was given. Vitals of all patients were monitored. Pre oxygenation with 100% O2 was done for 3 min and all patients were induced with InjPropofol 2mg\kg and intubation performed with appropriate sized portex cuffed endotracheal tube after Inj Succinylcholine 2mg\kg. Anaesthesia was maintained with 60% N20 in O2 with Isoflurane /Sevoflurane and relaxation maintained with Injvecuronium.

Inj Labetalol (0.5mg/kg) was given to the patients of group (L) 5 mins before CO2 insufflation. CO2 pnuemoperitoneum is established and maintained by an automatic insufflation unit throughout the laparoscopicsurgery . During surgery iv fluids were 43 administered in accordance with fasting volumes, maintenance volumes and blood losses.

Monitoring

The following parameters were recorded in all the patients.

- Heart rate (HR)
- Systolic blood pressure (SBP) in mm Hg
- Diastolic blood pressure (DBP) in mm Hg
- Mean arterial pressure (MAP) in mm Hg
- ETCO2
- SPO2

The haemodynamic response is recorded 5 mins (baseline) just before pneumoperitoneum (P0); and at 5min(P5), 10min(P10), 15min(P15), 30min(P30), 45min(P45), 60min(P60), 75min(P75), 90min(P90) after pneumoperitoneum commencement (post pneumoperitoneum); and 30mins after desufflation of pneumoperitoneum. Intra-operatively tidal volume was kept between 8-10ml\kg and respiratory rate 12-16\min. Peak airway pressure was maintained below 35. Intraabdominal pressure was kept between 12-15mmHg and flow rate of C02 at 5 10L/min. InjDiclofenac sodium was given as analgesic. Intraoperative monitoring was done with pulse oximetery, NIBP and Capnography. 30 mins after desufflation,

the haemodynamic response is recorded in similar way as in before the CO2 insufflation period and analyzed . Vital parameters were monitored. Residual effect of neuromuscular blockade was reversed by Inj Neostigmine 0.05mg\kg and InjGlycopyrrolate 0.008mg\kg. Patient was extubated after return of power, tone, reflex, respiration and proper suctioning.

Patients were observed for complications like nausea/vomiting, bradycardia and hypotension.

We defined the following terms for study

- Hypotension - defined as SBP < 25% of the baseline value or 90mmhg, whichever is lower.
- Bradycardia - defined as HR<60 /min.

OBSERVATIONS AND RESULTS

This was a prospective, randomised study. 81 patients aged between 20 and 60 years belonging to ASA grade I and II were divided into two groups.

Group 1(N-40)-Patients received Inj. Labetalol 0.5mg/kg diluted up to 10ml, 5 minutes prior to CO2 insufflation.

Group 2(N-41)-Patients received Normal saline 10ml, 5 minutes prior to CO2 insufflation.

Minimum age in both groups is 20 yrs. Maximum age is 58 yrs in group 1 and 59 yrs in group 2. Mean age in group 1 is 38.90 yrs and in group 2 is 38.88 yrs. Above data reveals no significant difference in both groups (p=0.992); so both groups are comparable.

In group 1, 17 male and 23 female patients were included. In group 2, 17 male and 24 female patients were included. Above data reveals no significant difference in both groups (p=0.925); so both groups are comparable.

In Group 1: ASA grade l 24 patients and ASA grade ll 28 patients were included. In Group 2: ASA grade l 16 patients and ASA grade ll 13 patients were included. Above data reveals no significant difference (p=0.436) and both groups are comparable.

	Group	N	Mean	Std. Deviation	Unpaired T test	P value
HRBase	Labetalol	40	81.95	12.343	0.476	0.636
	Control	41	80.78	9.658		
InjLabet/NS HR	Labetalol	40	79.88	11.161	-1.725	0.088
	Control	41	83.71	8.713		
HR5min	Labetalol	40	82.58	11.227	-1.552	0.125
	Control	41	86.29	10.328		
HR10min	Labetalol	40	85.25	12.733	-2.516	0.014
	Control	41	94.29	18.936		
HR15min	Labetalol	40	82.88	10.818	-6.571	0
	Control	41	97.95	9.818		
HR30min	Labetalol	40	79.83	10.488	-7.813	0
	Control	41	96.15	8.202		
HR45min	Labetalol	40	78.88	9.351	-10.04	0
	Control	41	98	7.736		
HR60min	Labetalol	40	77.03	8.778	-9.748	0
	Control	41	95.15	7.942		
HR75min	Labetalol	40	76.35	7.879	-8.18	0
	Control	41	92.54	9.801		
HR90min	Labetalol	40	69.83	7.795	-5.957	0
	Control	41	86.78	16.27		
HR30minpost desufflation	Labetalol	40	72.55	5.482	-9.065	0
	Control	41	88.49	9.711		

	Group	N	Mean	Std. Deviation	Unpaired T test	P value
SBPBase	Labetalol	40	124.9	9.032	0.806	0.422
	Control	41	122.68	14.924		
InjLabet/NS SBP	Labetalol	40	124.28	13.224	0.502	0.617
	Control	41	122.68	15.245		
SBP5min	Labetalol	40	121.38	10.539	-0.856	0.395
	Control	41	124	16.36		

SBP10min	Labetalol	40	119.23	10.876	-9.027	0
	Control	41	146.98	16.204		
SBP15min	Labetalol	40	113.7	10.403	-10.114	0
	Control	41	143.71	15.699		
SBP30min	Labetalol	40	109.1	9.094	-9.195	0
	Control	41	137.71	17.505		
SBP45min	Labetalol	40	106.55	9.941	-7.915	0
	Control	41	131.29	17.16		
SBP60min	Labetalol	40	103.2	8.413	-7.849	0
	Control	41	129.24	19.268		
SBP75min	Labetalol	40	101.33	7.364	-7.921	0
	Control	41	128.68	20.595		
SBP90min	Labetalol	40	101.15	7.095	-7.024	0
	Control	41	122.37	17.769		

	Group	**N**	**Mean**	**Std. Deviation**	**UnpairedT test**	**P value**
DBPBase	Labetalol	40	77.98	5.304	0.329	0.743
	Control	41	77.51	7.201		
InjLabet_/ NS DBP	Labetalol	40	79.58	7.049	0.254	0.8
	Control	41	79.07	10.388		
DBP5min	Labetalol	40	77.58	5.715	-0.766	0.446
	Control	41	79.02	10.549		
DBP10min	Labetalol	40	84.65	5.903	-3.175	0.002
	Control	41	90.8	10.785		
DBP15min	Labetalol	40	80.98	6.674	-4.5	0
	Control	41	89.07	9.277		
DBP30min	Labetalol	40	75.35	6.225	-5.185	0
	Control	41	86.05	11.509		

The Meanbasal systolicbloodpressurein Group1 was(124.90 ±9.03)mm Hgand in Group 2 was (122.68 ±14.92) mm Hg, the difference was statistically not significant (p> 0.05). During the time of giving inj Labetalol 0.5mg/kg 5min before pneumoperitoneum there was stastically no significant difference between the two groups. The mean systolic blood pressure 10min after the creation of pneumoperitoneum in group 1 was (119.23±10.87) and in group 2 was (146.98 ± 16.20) with p<0.005. So the difference in the systolic blood pressure at 10min of giving inj Labetalol between the groups was statistically significant. Thereafter both the groups were observed till 90min and 30min post desufflation. It was thus

	Group	N	Mean	Std.Deviation	UnpairedT test	P value
DBPBase	Labetalol	40	77.98	5.304	.329	.743
	Control	41	77.51	7.201		
InjLabet_/NS DBP	Labetalol	40	79.58	7.049	.254	.800
	Control	41	79.07	10.388		
DBP5min	Labetalol	40	77.58	5.715	-.766	.446
	Control	41	79.02	10.549		
DBP10min	Labetalol	40	84.65	5.903	-3.175	.002
	Control	41	90.80	10.785		
DBP15min	Labetalol	40	80.98	6.674	-4.500	.000
	Control	41	89.07	9.277		
DBP30min	Labetalol	40	75.35	6.225	-5.185	.000
	Control	41	86.05	11.509		

DBP45min	Labetalol	40	73.43	5.574	-4.817	.000
	Control	41	82.46	10.512		
DBP60min	Labetalol	40	72.85	4.650	-3.804	.000
	Control	41	80.29	11.490		
DBP75min	Labetalol	40	71.60	4.187	-3.918	.000
	Control	41	79.68	12.374		
DBP90min	Labetalol	40	70.65	3.386	-3.400	.001
	Control	41	77.34	11.989		
DBP30minpost desufflation	Labetalol	40	71.38	3.513	-3.257	.002
	Control	41	77.68	11.744		

concluded that there was a stastically significant difference in the systolic blood pressure up to 90min and 30min post desufflation (p<0.005) between group 1 and group 2.

The Mean basal diastolic blood pressure in Group 1 was (77.98 ±5.30) mm Hg and in Group 2 was (77.51 ±7.20) mm Hg, the difference was statistically not significant (p> 0.05). During the time of giving inj Labetalol 0.5mg/kg 5min before pneumoperitoneum there was stastically no significant difference between the two groups. The mean diastolic blood pressure 10min after the creation of pneumoperitoneumin group 1 was (84.65±5.90) andingroup2 was (90.80 ±10.78) with p<0.005. So the difference in the diastolic blood pressure at 10min of giving inj Labetalol betweenthegroups wasstatisticallysignificant. Thereafterboththegroups were observed till 90min and 30min post desufflation. It was thus concludedthat there was a stastically significant difference in the diastolic blood pressure up to 90min and 30min post desufflation (p<0.005) between group 1 and group 2.

The Mean arterial pressure in Group 1 was (91.08±6.54) mm Hg and in Group 2 was (91.22 ±7.32) mm Hg, the difference was statistically not significant (p> 0.05). During the time of giving inj Labetalol 0.5mg/kg 5min before pneumoperitoneum there was stastically no significant difference between the two groups. The mean arterial pressure 10min after the creation of pneumoperitoneum in group 1 was (94.15±7.14) andin group 2was (107.10 ±10.07) withp<0.005. Sothe differencein the mean arterial pressure at 10min of giving inj Labetalol between the groups was statistically significant. Thereafter both the groups were observed till 90min and 30min post desufflation. It was thus concludedthat there was a stastically significant differenceinthe meanarterial pressureupto90minand30minpos tdesufflation (p<0.005) between group 1 and group 2.

	Group	**N**	**Mean**	**Std.Deviation**	**UnpairedT test**	**P value**
MAPBase	Labetalol	40	91.08	6.549	-.094	.926
	Control	41	91.22	7.326		
InjLabet/NSMAP	Labetalol	40	92.80	8.645	.445	.657
	Control	41	91.85	10.382		
MAP5min	Labetalol	40	91.83	7.179	-.544	.588
	Control	41	92.93	10.662		
MAP10min	Labetalol	40	94.15	7.145	-6.655	.000
	Control	41	107.10	10.079		
MAP15min	Labetalol	40	89.90	7.801	-6.703	.000
	Control	41	104.44	11.349		
MAP30min	Labetalol	40	85.23	7.298	-7.121	.000
	Control	41	102.29	13.333		
MAP45min	Labetalol	40	84.13	7.690	-5.804	.000
	Control	41	97.29	12.172		
MAP60min	Labetalol	40	82.25	5.638	-5.738	.000
	Control	41	95.41	13.398		
MAP75min	Labetalol	40	81.50	4.696	-5.534	.000
	Control	41	93.71	13.155		
MAP90min	Labetalol	40	79.95	4.218	-5.651	.000
	Control	41	91.32	12.018		
MAP30minpost desufflation	Labetalol	40	79.68	4.843	-5.261	.000
	Control	41	89.93	11.356		

	Group	N	Mean	Std.Deviation	UnpairedT test	P value
ETC02Base	Labetalol	40	31.78	2.759	-2.632	.010
	Control	41	33.15	1.851		
InjLabet / NS_ETCO2	Labetalol	40	31.85	2.666	-3.161	.002
	Control	41	33.68	2.554		
ETCO25min	Labetalol	40	33.03	2.778	-.428	.670
	Control	41	33.29	2.848		
ETCO210min	Labetalol	40	33.58	2.099	.081	.936
	Control	41	33.54	2.181		
ETCO215min	Labetalol	40	33.20	2.584	-.079	.937
	Control	41	33.24	2.406		
ETCO230min	Labetalol	40	32.73	2.375	-1.781	.079
	Control	41	33.68	2.464		
ETCO245min	Labetalol	40	32.25	2.085	-1.963	.053
	Control	41	33.34	2.851		
ETCO260min	Labetalol	40	31.95	1.934	-3.722	.000
	Control	41	33.68	2.241		
ETC0275min	Labetalol	40	32.08	1.685	-1.818	.073
	Control	41	32.73	1.566		
ETC0290min	Labetalol	40	31.65	1.673	-3.547	.001
	Control	41	33.20	2.205		
ETCO230minpost desufflation	Labetalol	40	32.93	1.927	-.170	.865
	Control	41	33.00	2.037		

The End tidal carbondioxide in Group 1 was (31.78± 2.75) mm Hg and in Group 2 was (33.15 ±1.85) mm Hg, the difference was statistically not significant (p> 0.05). During the time of giving inj Labetalol 0.5mg/kg 5min before pneumoperitoneum

there was stastically no significant difference between the two groups. The end tidal carbondioxide 10min after the creation of pneumoperitoneum in group 1 was (33.58± 2.09) and in group 2 was (33.54 ± 2.18) with p>0.005. So the difference in the end tidal carbondioxide at 10min of giving inj Labetalol between the groups was statistically not significant. Thereafter both the groups were observed till 90min and 30min post desufflation. It was thus concluded that there was stastically no significant difference in the end tidal carbondioxide up to 90min and 30min post desufflation (p<0.005) between group 1 and group

COMPLICATIONS

ThepatientsinGroup1andGroup2wereobservedintraoperatively forBradycardia and Hypotension after giving injection Labetalol/Normal saline, up to two hours. It was observed thatintraoperatively, 2 patients in Group 1 developed bradycardia while no bradycardia occurred in Group 2 and 3 patients developed hypotension in Group 1and no hypotesion occurredin Group2. Thedifference was statistically not significant.Nobradycardiaandhypotensionwasobservedinbotht hegroupsduring rest of the study period.

Table: ComparisonofchangesinIntraoperativecomplicationsbothgroups

			Labetalol	Control	Total	Unpaired T test	P value
Intra-op complications	Bradycardia	Count	2	0	2		
		%within Group	5.0%	0.0%	2.5%		
	Hypotension	Count	3	0	3		
		%within Group	7.5%	0.0%	3.7%		
	Nil	Count	35	41	76		
		%within Group	87.5%	100.0%	93.8%		
Total	Count	40	41	81			
	% within Group	100.0%	100.0%	100.0%			
PearsonChi-Square					5.462	.065	

DISCUSSION

A primary goal in the administration of general anaesthesia is the maintenance of normal cardiovascular dynamics. The creation of pneumoperitoneum in any laproscopic surgery is considered to be the most critical event during the proceedure. It is invariably associated with certain cardiovascular changes due to activation of the sympathetic system resulting in bizarre

complications such as tachycardia,rise in blood pressure and a wide variety of cardiacarrhythmias. These responses may pose serious challenges majorly in conditions of cardiovascular diseaseslikehypertension,coronaryarterydisease,aneury smal vasculardiseaseor those with decreasedintracranial compliancelike headinjury with extra orintradural hematoma formation, intracranial tumors, etc. A sudden rise in blood pressure can result in left ventricular failure, myocardial ischemia, and cerebral hemorrhage.

These complications are more likely in the presence of coronary or cerebral atheromaorhypertension.Itmayalsoprecip itateconvulsionsinpreeclampticpatients.

Various pharmacologic drug combinations and methods have been used to partially suppress the cardiovascular response to pneumoperitoneum. The pharmacological methods are aimed at efferent, afferent, or both limbs of response e.g. volatile inhalationalagents 61, lignocaine 62, opioids 63, sodiumnitro prusside64,nitroglycerine65, calcium channel blockers66, and adrenergic blockers67.

Inhalationalagentswereusedintheearlysixtiestobluntthecirculato ryresponsesto Pneumoperitoneum in laproscopic surgeries. But these agents had their own disadvantages like arrhythmogenecity and myocardial depression with halothaneand coronary steal with isoflurane68,69.

Opiods like fentanyl suppresses the haemodynamic response by increasing the depthofanesthesiaanddecreasingthesym pathetic activity.Opioidsarefoundtobe effective in blunting pressor responses to pneumoperitoneum but they caused chest wall rigidity, respiratory depression and prolong the recovery time.70,71,72,73

When the sympathetic nervous system is activated, as during exercise or stress, stimulationofβreceptorsintheheartproduces positivechronotropic,inotropic,and dromotropic effects; these responsesare blunted by β-adrenergicreceptor antagonists. On short-term administration of beta blocker such as propranolol decreases cardiac output; and increases the peripheral resistance as a result of blockade of vascular beta2 receptors and compensatory reflexes, such as increased sympathetic nervous system activity, leading to activation of vascular alpha receptors. DrugslikeLabetalol,Carvedilol,andBucindolol which havegotbothbeta2 and alpha1 blocking property maintain the cardiac output with a greater fall in peripheral resistance74.

Labetalol is an adrenergic receptor blocking agent with mild alpha1- and predominant beta-adrenergic receptor blocking actions (alpha:beta blockade ratio of 1:7forIVand1:3fororal administration).TheonsetofactionofIVlabetalolis5min.

andpeakeffectisseenat5-15minutes.Administrationoflabetalollo werssystemic blood pressure by decreasing systemic vascular resistance (alpha1 blockade).

Blockade of alpha 1 adrenergic receptors inhibits vasoconstriction induced by endogenous catecholamines; vasodilation may occur in both arteriolar resistance vesselsandveins.Inadditiont oproducingvasodilationbyalpha1blockade,labetalol may cause vasodilation that is mediated by beta2 adrenergic agonistic activity37.

Labetalol attenuates the reflex tachycardia triggered by fall in blood pressure by simultaneousbeta1blockade.Sincecate cholamineshavepositivechronotropicand inotropic actions, beta receptor blockade produces a decrease in heart rate and myocardial contractility. Cardiac output however remains unchanged.

It is possible that existing depressant effects of the Anaesthetic drugs could accentuate the blood pressure lowering properties of labetalol. Presynaptic alpha2 receptors are spared by labetalol such that released norepinephrine can continue to inhibit further release of catecholamines via negative feedback mechanismresulting fromstimulation of alpha2 receptors. Labetalol has shown a better safety profile and haemodynamic stability. These properties suggest that it would be the ideal agent to attenuate the cardiovascular changes occurring on pneumoperitoneum inlaproscopicsurgeries. Inviewoftheseadvantages oflabetalol thepresentstudywas carried out to evaluate its efficacy in blunting the pressor response to pneumoperitoneum in laparoscopic surgeries

SUMMARY

A prospective randomized observational study was conducted on 81 patients undergoing elective laparoscopic surgery after the approval from the Ethical committee. All the patients were informed about the study and informed consent was taken.

All the patients were premedicated; monitors attached and general anaesthesia was given. All patients were induced as per the proceedure explained earlier. Baseline haemodynamic parameters like pulse rate, systolic and diastolic blood pressure, mean arterial blood pressure, SPO2 and ETCO2 were recorded 5minutes prior to pneumoperitoneum. Later haemodynamic parameters were monitored every 5, 10, 15, 30, 45, 60, 75, 90 minutes and 30min post desufflation. Then the change in the haemodynamic parameters from baseline, at various interval and post-desufflation were observed and statistically analysed using pair t test.

Various complications were also recorded In this study significant changes were observed in the parameters like heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure. No significant changes were observed in the parameters like SPO2 and ETCO2.

Intraoperative complications like bradycardia and hypotension were observed in some patients which were managed effectively with inj atropine and iv crystalloids. Postoperative complications like nausea, vomiting, and shivering were observed in some patients which were managed effectively with injondansetron, blankets and warm fluids .

CONCLUSION

Though laparoscopic surgery is considered a gentle surgery the procedure is indeed not risk free, because of “Pneumoperitoneum” required, which has significant hemodynamic effect.

In our study 81 patients under ASA 1&2 undergoing laparoscopic cholecystectomy were studied. We studied the effect of Labetalol which is an alpha and beta blocker on the haemodynamic changes to CO2 insufflation and desufflation and its complications 2hrs in the postoperative period.

This Study shows that the hemodynamic changes varied from baseline, but the change remained insignificant in case

of end tidal carbon dioxide and arterial oxygen saturation, but the heart rate, systolic, diastolic and mean arterial blood pressures were significantly increased. The pressor response to pnemoperitoneum is mainly due to sympathetic stimulation, which can be overcome by using various methods like IV drugs like β blockers, dexmeditomidine, clonidine, magnesium sulfate, epidural analgesia and decrease in flow rate of carbon dioxide insufflation.

It is therefore very important to attenuate the pressor response to pneumoperiotoneum in Laproscopic surgeries.

Labetalol is able to blunt both hypertension and tachycardia produced as a result of CO2 insufflation in the abdominal cavity during laproscopy by blocking both alpha and beta adrenergic receptors. Thus we conclude that Labetalol IV (0.5 mg/kg) is effective in attenuating the pressor response to pneumoperitoneum in laproscopic surgeries.

References

1. Cho, E. J., & Min, T. K. (2005). Cardiac arrest after gas insufflation for laparoscopic surgery: Two case reports. Korean Journal of Anesthesiology, 49(5), 712–715.
2. Myles, P. S. (1991). Bradyarrhythmias and laparoscopy: A prospective study of heart rate changes with laparoscopy. Australian and New Zealand Journal of Obstetrics and Gynaecology, 31(2), 171–173.
3. Iwasaka, H., Miyakawa, H., Yamamoto, H., Kitano, S., Taniguchi, K., Honda, N., & Noguchi, T. (1996). Respiratory mechanics and arterial blood gases during and after laparoscopic cholecystectomy. Canadian Journal of Anaesthesia, 43(2), 129–133.
4. Rauh, R., Hemmerling, T. M., Rist, M., & Jacobi, K. E. (2001). Influence of pneumoperitoneum and patient positioning on respiratory system compliance. Journal of Clinical Anesthesia, 13(5), 361–365.
5. Kelling, G. (1902). Über Oesophagoskopie, Gastroskopie und Cölioskopie. Münchener Medizinische Wochenschrift, 49, 21–24.
6. Ruddock, J. C. (1934). Peritoneoscopy. Western Journal of Surgery, Obstetrics and Gynecology, 42, 392–405.
7. Power, F. H., & Barnes, A. C. (1941). Sterilization by means of peritoneoscopic fulguration: A preliminary report. American Journal of Obstetrics and Gynecology, 41(6), 1038–1043.
8. Safran, D. B., & Orlando, R., 3rd. (1994). Physiologic effects of pneumoperitoneum. The American Journal of Surgery, 167(2), 281–286.
9. Miller, R. D. (Ed.). (1986). Anesthesia (2nd ed., Vols. 1–3). Churchill Livingstone.
10. Zargar, J. A., Zargar, I. A., & Mehraj-ud-Din. (2002). Effect of metoprolol and esmolol on rate pressure product and ECG changes during laryngoscopy and tracheal intubation in controlled hypertensive patients. Indian Journal of Anaesthesia, 46(5), 365–368.
11. Magnusson, J., Werner, O., Carlsson, C., Norden, N., & Pettersson, K. I. (1983). Metoprolol, fentanyl and stress response to microlaryngoscopy: Effect on arterial pressure, heart rate and plasma concentration of catecholamines, ACTH and cortisol. British Journal of Anaesthesia, 55(5), 405–408.
12. Kim, H. Y., Chung, C. W., Lee, H. Y., & Yim, C. H. (1994). The effect of labetalol on the hemodynamic response to endotracheal intubation. Korean Journal of Anesthesiology, 27(11), 1611–1619.
13. Ramanathan, J., Sibai, B. M., Mabie, W. C., Chauhan, D., & Ruiz, A. G. (1988). The use of labetalol for attenuation of the hypertensive response to endotracheal intubation in preeclampsia. American Journal of Obstetrics and Gynecology, 159(3), 650–654.
14. Vecchio, R., MacFadyen, B. V., & Palazzo, F. (2000). History of laparoscopic surgery. Panminerva Medica, 42(1), 87–90.
15. Sharma, K. C., Kabinoff, G., Ducheine, Y., Tierney, J., & Yadegar, J. (1997). Laparoscopic surgery and its potential for medical complications. Heart & Lung: The Journal of Acute and Critical Care, 26(1), 52–64.
16. Reza, M. M., Blasco, J. A., Andradas, E., Cantero, R., & Mayol, J. (2006). Systematic review of laparoscopic versus open surgery for colorectal cancer. British Journal of Surgery, 93(8), 921–928.
17. Cuschieri, A. (2005). Laparoscopic surgery: Current status, issues and future developments. The Surgeon, 3(3), 125–130, 132–135, 137–138.
18. Menes, T., & Spivak, H. (2000). Laparoscopy: Searching for the proper insufflation gas. Surgical Endoscopy, 14(11), 1050–1056.
19. Graff, T. D., Arbegast, N. R., Phillips, O. C., Harris, L. C., & Parks, C. E. (1959). Gas embolism: A comparative study of air and carbon dioxide as embolic agents in the systemic venous system. American Journal of Obstetrics and Gynecology, 78(2), 259–263.
20. Magno, R., Medegard, A., Bengtsson, R., & Kjellmer, I. (1979). Acid-base balance during laparoscopy. Acta Obstetricia et Gynecologica Scandinavica, 58(1), 81–85.
21. Brodsky, J. B., Lemmens, H. J., Collins, J. S., & Morton, J. M. (2005). Nitrous oxide and laparoscopic bariatric surgery. Obesity Surgery, 15(4), 494–496.
22. Neuhaus, S. J., Gupta, A., & Watson, D. I. (2001). Helium and other alternative insufflation gases for laparoscopy. Surgical Endoscopy, 15(6), 553–560.
23. Brackman, M. R., Finelli, F. C., Light, T. D., Koch, T. A., & Althaus, S. J. (2003). Helium pneumoperitoneum ameliorates hypercarbia and acidosis associated with carbon dioxide insufflation during laparoscopic gastric bypass in pigs. Obesity Surgery, 13(5), 768–771.
24. de Waal, E. E., & Kalkman, C. J. (2003). Haemodynamic changes during low-pressure carbon dioxide pneumoperitoneum in young children. Paediatric Anaesthesia, 13(1), 18–25.
25. Gutt, C. N., Oniu, T., Mehrabi, A., Schemmer, P., Kashfi, A., Kraus, T., & Büchler, M. W. (2004). Circulatory and respiratory complications of carbon dioxide insufflation. Digestive Surgery, 21(2), 95–105.
26. Hazebroek, E. J., Haitsma, J. J., Lachmann, B., & Bonjer, H. J. (2002). Impact of carbon dioxide and helium insufflation on cardiorespiratory function during prolonged pneumoperitoneum in an experimental rat model. Surgical Endoscopy, 16(7), 1073–1078.