ORIGINAL ARTICLE

EFFECT OF PREOPERATIVE INTRAVENOUS CLONIDINE ON HEMODYNAMIC RESPONSE DURING LAPAROSCOPIC SURGERIES

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BACKGROUND AND OBJECTIVES: Laparoscopy is a minimally invasive procedure used as a diagnostic and therapeutic tool for abdominal and pelvic pathologies. Laparoscopy offers many benefits compared to open surgeries, but it leads to increase in stress hormones, increased peripheral vascular resistance and decreased cardiac output causing hemodynamic fluctuation. In addition, ventilatory changes and increases in partial pressure of carbon dioxide also occur during laparoscopic surgeries due to pneumoperitoneum. To overcome these hemodynamic effects of insufflation various methods have been used like combined epidural with general anesthesia, propofol infusion, high dose of opioids, beta blockers, nicardipine, oral clonidine etc. In this study, we used intravenous clonidine as premedication to suppress these changes. **METHODS:** After obtaining ethical committee clearance and informed consent from patient, we enrolled 60 adult patients, aged between 20-60 years, of ASA grade 1 and 2 posted for laparoscopic intra-abdominal surgeries. The patients were divided into 2 groups of 30 each randomly, viz: **Group C Study group**: Injection clonidine, 2mcg/kg, as premedication was given intravenously, 15 min prior to induction of anesthesia. **Group N Control group:** received injection normal saline, 5cc, intravenously. For both the groups same type of anesthesia and analgesia was given. Heart rate, blood pressure, mean arterial pressure were recorded in both groups. Sedation, incidence of post-operative nausea vomiting after extubation were also observed. Statistical analysis was done using student T test and P value obtained. **RESULTS:** In the present study, decreases in heart rate, systolic, diastolic and mean arterial blood pressures were noticed in the clonidine group. Inspite of maintaining normocapnia and keeping intra-abdominal pressure below 14mmm of Hg significant rises in heart rate, systolic, diastolic and mean arterial blood pressures were noticed in the control group. **CONCLUSION:** From this study, we conclude that intravenous clonidine 2mcg/kg, given 15 min prior to induction provides stable hemodynamics and protection against stress response to intubation and carbon dioxide insufflation in patients undergoing laparoscopic surgeries. Clonidine provides the added advantages of reduction in postoperative complications of nausea, vomiting and shivering.
KEYWORDS: ANETHESIA, LAPAROSCOPY, CLONIDINE, HEMODYNAMIC.

INTRODUCTION: Laparoscopy is a minimally invasive procedure used as a diagnostic and therapeutic tool for abdominal and pelvic pathologies. There are a number of advantages to the patient with laparoscopic surgery over the conventional laparotomy technique. These include shorter hospital stay, rapid return to normal activities, less pain and smaller incisions.[1]

During laparoscopic procedures, abdominal organs are visualized by intra-abdominal insufflation of carbon dioxide. The use of pneumoperitoneum in combination with positional changes may cause significant hemodynamic and respiratory changes.[2] These changes are considered to be

ORIGINAL ARTICLE

mediated by mechanical and neurohumoral factors. Catecholamine, renin angiotensin system and vasopressin are released during pneumoperitoneum.[2]

To overcome these hemodynamic effects of insufflation various methods have been used like combined epidural with general anesthesia, propofol infusion, high dose of opioids, beta blockers, nicardipine, oral clonidine etc.

In this study, we used intravenous clonidine as premedication to suppress these changes. Clonidine is an alpha 2 adrenergic agonist known to cause suppression of outflow of sympathetic nervous system.[3-5]

In addition, clonidine attenuates the stress response to intubation.[2, 5-7] It is also beneficial in preventing postoperative nausea and vomiting (PONV) and shivering[8] in the postoperative period.

MATERIALS AND METHODS: The present study is a randomized controlled trial. After obtaining ethical committee clearance and informed consent from patient, we enrolled 60 adult patients, aged between 20-60 years, of ASA grade 1 and 2 posted for laparoscopic intra-abdominal surgeries. The patients were divided into 2 groups of 30 each randomly, viz:

Group C Study group: Injection clonidine, 2mcg/kg, as premedication was given intravenously, 15 min prior to induction of anesthesia.

Group N: Control group- received injection normal saline, 5cc, intravenously.

For both the groups same type of anesthesia and analgesia was followed.

EXCLUSION CRITERIA:
1. Patients with ASA 3 or 4 grade.
2. Patients less than 20 years and more than 60 years of age.
3. Pregnant and nursing women.
4. Patients on beta blockers.

BEFORE SURGERY: Standard anesthetic technique was followed in both the groups.

Premedication: Inj. Clonidine 2mcg/kg, slow intravenous, given 15min prior to induction in Group C.

DURING SURGERY:

Preinduction:
- Intravenous Ondansetron 4mg
- Intravenous Fentanyl 2mcg/kg
- Intravenous Midazolam 0.03mg/kg

General anesthesia was given with:

Induction: With injection Propofol 2mg/kg.

Intubation: Under effect of injection Rocuronium 1mg/kg

Maintenance: O_2 + Air + Isoflurane + Rocuronium intermittent bolus muscle relaxant.

Intraoperative Monitoring:

Pulse rate, Blood pressure, SpO_2, $ETCO_2$ were monitored intraoperatively.

ORIGINAL ARTICLE

Reversal:

After surgery patients were reversed with injection Neostigmine, 0.04mg/kg with injection Glycopyrrolate, 0.01mg/kg body weight intravenous, slowly.

OBSERVATION AND RESULTS: Observation and results were obtained from the two groups by statistical analysis with paired and unpaired T tests and calculating the p value.

$p > 0.05$ was considered as not significant.

$p < 0.05$ was considered as significant

$p < 0.01$ was considered as highly significant.

Parameter	Study drug (n=30)			
	Mean±SD	Min	Max	Median
Age	36.9 ± 11.9	21.0	58.0	34.5
Weight	52.7 ± 6.7	43.0	70.0	51.5
Sex	**N**	**%**	-	-
Male	08	26.66	-	-
Female	22	73.33	-	-
Table 1: Demographic Data of the Patients- Study Group				

The mean age in study group was 36.9±11.9 years and mean weight was 52.7±6.7 kg. There were 8 males and 22 females in the study group.

Parameter	Control drug (n=30)			
	Mean±SD	Min	Max	Median
Age	35.6 ± 12.5	21.0	60.0	30.5
Weight	55.17 ± 9.6	42.0	78.0	54.5
Sex	**N**	**%**	-	-
Male	10	66.66	-	-
Female	20	33.33	-	-
Table 2: Demographic Data of the Patients- Control Group				

The mean age in control group was 35.6±12.5 years and mean weight was 55.17±9.6 kg. There were 10 male and 20 female in the control group.

ORIGINAL ARTICLE

HR	Study drug (n=30)			Control drug (n=30)		
	Mean ±SD	% change from Baseline	p value	Mean ±SD	% change from Baseline	p value
Pre-Op	88.2±14.6	0.0		87.8±7.2	0.0	-
Before induction	89.0±14.5	0.9	0.539	81.9±7.4	5.0	< 0.001
After intubation	91.4±10.7	3.5	0.158	96.9±6.7	19.7	< 0.001
CO_2 insufflation	89.4±13.1	1.4	0.525	89.4±7.5	13.0	< 0.001
5 min after insufflations	88.2±14.2	0.0	0.988	90.3±8.4	13.9	< 0.001
15 min after insufflations	88.7±10.5	0.5	0.819	89.9±8.0	13.4	< 0.001
30 min after insufflations	87.9±11.2	-0.3	0.912	88.1±8.4	11.7	< 0.001
60 min after insufflations	87.3±12.0	-1.0	0.712	90.5±8.6	14.0	< 0.001
90 min after insufflations	89.3±13.3	1.2	0.667	89.1±8.8	12.7	< 0.001
120 min after insufflations	89.1±10.8	1.0	0.723	89.1±9.3	12.6	< 0.001
After CO_2 desufflation	90.5±11.1	2.6	0.339	90.9±9.4	14.4	< 0.001
Table 3: Change in Heart Rate in Study and Control Groups						

Statistical analysis with paired t test was done. There was no significant percentage change in heart rate from the baseline (p>0.05) throughout the procedure in the study group.

In the control group, the percentage increase in the heart rate from the baseline was maximum after intubation (19.7%) and it was highly significant (p<0.01). The percentage change in the heart rate remained elevated from the baseline throughout the procedure and was highly significant (p<0.01).

Systolic Blood Pressure	Study drug (n=30)	Control drug (n=30)	p value	Significance
	Mean±SD	Mean±SD		
Pre-Op	124.1 ± 11.7	119.5 ± 9.1	0.097	NS
Preinduction	120.5 ± 14.5	118.2 ± 7.6	0.438	NS
After intubation	122.5 ±16.2	135.0 ± 12.1	0.001	HS
CO_2 insufflation	116.2 ± 13.2	132.2 ± 11.1	0.001	HS
5 min after insufflation	117.2 ± 14.5	132.5 ± 9.2	0.001	HS
15 min after insufflation	113.6 ± 11.9	136.5 ± 10.1	0.001	HS
30 min after insufflation	112.5 ± 10.3	130.7 ± 6.5	0.001	HS
60 min after insufflation	112.1 ± 12.2	130.2 ± 6.6	0.001	HS
90 min after insufflation	112.8 ± 13.2	130.1 ± 6.1	0.001	HS
120 min after insufflation	113.2 ± 12.8	129.7 ± 5.7	0.001	HS
After desufflation	115.0 ± 12.2	126.1 ± 9.0	0.001	HS
Table 4: Comparison of Systolic Blood Pressures in Patients of Study and Control Groups				

NS-Not significant, HS-Highly significant

Statistical analysis with unpaired t test was done. Results showed that in the preoperative and preinduction periods there was no statistically significant (p>0.05) difference in systolic blood pressures in the two groups. After intubation, carbon dioxide insufflation, at 5 min, 15 min, 30 min, 60 min, 90 min, 120 min and after carbon dioxide desufflation, the statistical difference in two groups

ORIGINAL ARTICLE

was highly significant (p<0.01) with a significant increase in the mean systolic blood pressures in the control group.

Diastolic Blood Pressure	Study drug (n=30)	Control drug (n=30)	P value	Significance
	Mean±SD	Mean±SD		
Pre-Op	82.7 ± 8.8	80.4 ± 6.2	0.2407	NS
Preinduction	79.3 ± 11.1	82.3 ± 7.6	0.2321	NS
After intubation	82.1 ± 10.9	88.9 ± 9.3	0.0111	HS
CO_2 insufflation	78.4 ± 9.1	87.4 ± 6.5	0.0001	HS
5 min after insufflation	80.9 ± 11.4	89.3 ± 7.4	0.0013	HS
15 min after insufflation	77.5 ± 8.8	87.9 ± 4.5	0.0001	HS
30 min after insufflation	77.6 ± 6.5	89.5 ± 3.5	0.0001	HS
60 min after insufflation	77.4 ± 8.6	92.1 ± 5.0	0.0001	HS
90 min after insufflation	77.3 ±9.0	90.7 ± 6.4	0.0001	HS
120 min after insufflation	79.2 ± 9.1	89.3 ± 5.0	0.0001	HS
After desufflation	79.2 ± 9.8	86.2 ± 7.8	0.0034	HS
Table 5: Comparison of Diastolic Blood Pressure in Patients of Study and Control Groups				

NS-Not significant, HS-Highly significant

Statistical analysis with unpaired t test was done. Results showed that in the preoperative and preinduction periods, there was no statistically significant difference (p>0.05) in the diastolic blood pressure in the two groups. After intubation, carbon dioxide insufflation, 5 min, 15 min, 30 min, 60 min, 90 min, 120 min and after carbon dioxide desufflation, the statistical difference in the two groups was highly significant (p<0.01) with a significant increase in the mean diastolic blood pressure in the control group.

Mean	Study drug (n=30)	Control drug (n=30)	P value	Significance
	Mean±SD	Mean±SD		
Pre-Op	96.8 ±9.8	94.1 ± 6.1	0.2034	NS
Preinduction	94.4 ± 11.5	93.6 ± 6.6	0.7324	NS
After intubation	96.0 ± 13.1	104.1 ± 8.2	0.0059	HS
CO_2 insufflation	90.4 ± 9.9	102.4 ± 7.6	0.0001	HS
5 min after insufflation	93.1 ±13.4	103.5 ± 7.5	0.0005	HS
15 min after insufflation	89.7 ± 9.5	103.7 ± 4.7	0.0001	HS
30 min after insufflation	89.7 ± 7.4	102.7 ± 3.8	0.0001	HS
60 min after insufflation	89.0 ± 9.3	104.7 ± 5.0	0.0001	HS
90 min after insufflation	89.1 ± 9.9	103.1 ± 5.2	0.0001	HS
120 min after insufflation	90.6 ± 10.1	102.3 ± 4.8	0.0001	HS
After CO_2 desufflation	91.0 ± 10.0	99.3 ± 7.8	0.0007	HS
Table 6: Comparison of Mean Blood Pressures in Patients of Study and Control Groups				

NS-Not significant, HS-Highly significant

ORIGINAL ARTICLE

Statistical analysis with unpaired t-test was done. Results showed that in preoperative and preinduction periods, there was no statistically significant (p>0.05) difference in the mean blood pressures in the two groups. After intubation, carbon dioxide insufflation, 5 min, 15 min, 30 min, 60 min, 90 min, 120 min and after carbon dioxide desufflation, the statistical difference in the two groups was highly significant (p<0.01), with a significant increase in the mean blood pressure in the control group.

Side Effects	Study drug (n=30)	Control drug (n=30)	P value
Urinary retention	1(3.33%)	0	1
Sedation (Ramsay score 2-3)	6(20%)	0	0.0237
Shivering	2(6.66%)	9(30%)	0.0419
PONV	1(3.33%)	6(20%)	0.1028
Table 7: Side Effects			

The table shows side effects in both study and control groups. 20% of the patients in the study group were well sedated with significant p value (0.0237). A high incidence of shivering (30%) with significant p value of (0.0419) and PONV (20%) was seen in the control group.

DISCUSSION: Laparoscopic surgery has a long and colorful history since its origin in 1901 by Kelling.[9] Laparoscopic cholecystectomy was first performed by Philip Mouret in 1987.[10]

Laparoscopy offers many benefits compared to open surgeries, but it leads to increase in stress hormone responses (cortisol, epinephrine and norepinephrine), increased peripheral vascular resistance and decreased cardiac output causing hemodynamic fluctuation. In addition, ventilatory changes and increases in partial pressure of carbon dioxide also occur during laparoscopic surgeries due to pneumoperitoneum.[2] All these changes have been studied by various authors over the last decade.

Mealy K, Gallagher H et al (1992)[11] studied the physiologic and metabolic responses to open and laparoscopic cholecystectomy. Deterioration in perioperative respiratory function was significantly less for laparoscopic surgery. Arterial blood gas determinations indicated a greater perioperative decrease in arterial pH. Hormonal profile changes demonstrated an increase in urinary vanillylmandelic acid in the laparoscopic cholecystectomy group; no differences were detected in urinary cortisol, metanephrine or nitrogen excretion. Acute phase response was greatest in patients undergoing open cholecystectomy as determined by erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. These data indicate improved respiratory and subjective response and diminished acute phase response associated with laparoscopic surgery. Catabolic hormone release may, however, be increased.

Westerband A, Van De Water J, et al (1992)[12] studied the cardiovascular changes in laparoscopic cholecystectomy in 16 patients and concluded that a decrease of 30% in the cardiac index (CI) and 5% in the heart rate (HR), along with an increase of 15% in mean arterial pressure (MAP) and 79% in the calculated total peripheral resistance index occurred. This elevation in after load can lead to an increase in myocardial oxygen demand and potential risk of myocardial ischemia or cardiac failure in susceptible individuals.

ORIGINAL ARTICLE

Cunningham AJ et al (1993)[13] measured cardiovascular changes associated with the reverse Trendelenburg position during laparoscopic cholecystectomy using transoesophageal echocardiography. End tidal carbon dioxide (EtCO$_2$) values increased after insufflation of carbon dioxide with values significantly higher after lateral tilt positioning. Creation of pneumoperitoneum was associated with an increase in left ventricular end systolic wall stress concomitant with increases in peak airway pressure and mean arterial pressure. In addition, the left ventricular end diastolic area decreased after reverse Trendelenburg positioning. Left ventricular ejection fraction was maintained throughout the study.

Wakizaka Y et al (1994)[14] studied the effects of carbon dioxide insufflation during laparoscopic cholecystectomy on the arterial blood gases and pH. They observed that insufflation of carbon dioxide causes large change in PaCO$_2$ and pH in patients who had a history of major cardiac or respiratory disease. They also showed that low insufflation pressures and short duration of surgery is beneficial for the maintenance of a normal physiological state.

In recent years, laparoscopic surgery has become a common clinical practice. Pneumoperitoneum required for laparoscopic surgery produces significant hemodynamic changes, which can be detrimental especially in elderly and hemodynamically compromised patients.[15] Various techniques and pharmacological agents have been used to counteract the hemodynamic effects of pneumoperitoneum.

We evaluated the efficacy of intravenous clonidine in maintaining the hemodynamic stability during laparoscopic surgery.

Clonidine is a centrally acting alpha 2 agonist initially used as an antihypertensive drug. It is a highly lipid soluble drug and easily crosses blood brain barrier. It causes a reduction of tonic sympathetic outflow and decrease in blood pressure and heart rate. It attenuates hypertension, tachycardia and norepinephrine release in response to stress induced by anesthetic and surgical procedures.[3]

The present study was conducted in 60 adult patients. They were divided into 2 groups, study and control, with 30 patients in each, belonging to ASA grade 1 & 2. The study group received injection clonidine 2mcg/kg intravenously, 15 minutes prior to induction and the control group received normal saline. Intraoperative monitoring of heart rate, blood pressure and EtCO$_2$ was done. In the post-operative period, we observed patients for occurrence of complications like excess sedation, nausea, vomiting and shivering.

In the present study, the mean heart rate was 88.2±14.6 bpm in the preoperative period in the study group. In the control group it was 87.8±14.6bpm. There was 3.5% increase in heart rate after intubation, in the study group whereas, in the control group it increased by 19.7%, which is highly significant (P<0.01). This change in heart rate remained increased throughout the procedure in control group while it remained close to baseline in study group (Table-3). Our findings are similar to study conducted by, Mirinmoy Das, Manjushree Ray, Gauri Mukherjee.[6] In their study they have shown, that there was significant rise in heart rate in control group while heart rate remained towards baseline in the clonidine group.

In the present study, there was no statistically significant difference in systolic blood pressure in the two groups (p>0.05) during preoperative and preinduction periods. The statistical difference in the two groups was highly significant after intubation, carbon dioxide insufflation, 5 min, 15 min, 30 min, 60 min, 90 min, 120 min after insufflation and after desufflation (p<0.01) with significant

ORIGINAL ARTICLE

increase in mean systolic blood pressure in the control group. The mean systolic blood pressure in preoperative period was 124±11.7mm of Hg in the study group and 119.5±9.1mm of Hg in the control group. In the study group, the mean systolic blood pressure remained less than the baseline throughout the study. There was 1.3% fall in mean systolic blood pressure from baseline after intubation. In control group, the mean systolic blood pressure remained elevated from the baseline throughout the study. There was 11.5% increase in the mean systolic blood pressure from the baseline after intubation (Table-4).

In the present study, there was no statistically significant difference in the diastolic blood pressure in the two groups during preoperative and preinduction periods (p>0.05). The statistical difference in two groups was highly significant after intubation, carbon dioxide insufflation, 5 min, 15 min, 30 min, 60 min, 90 min, 120 min and after desufflation (p<0.01) with significant increase in diastolic blood pressure in control group. The mean diastolic blood pressure in pre-operative period was 82.7±8.8 mm of Hg in the study group and 80.4±6.2 mm of Hg in the control group. In the study group, there was 0.7% fall in the mean diastolic blood pressure from the baseline after intubation. The mean diastolic blood pressure remained less than the preoperative period throughout the procedure, whereas in the control group there was 9.6% increase in mean diastolic blood pressure from the baseline after intubation. The mean diastolic blood pressure remained elevated from the baseline throughout the procedure (Table-5).

In the present study, there was no statistically significant difference in the mean arterial blood pressure in the two groups during preoperative and preinduction periods (p>0.05). The statistical difference in two groups was highly significant after intubation, carbon dioxide insufflation, 5 min, 15 min, 30 min, 60 min, 90 min, 120 min and after desufflation (p<0.01) with significant increase in mean arterial blood pressure in control group. The mean arterial blood pressure in pre-operative period was 96.8±9.8 mm of Hg in the study group and 94.1±6.1 mm of Hg in the control group. In the study group, there was 0.8% fall in the mean arterial blood pressure from the baseline after intubation. The mean arterial blood pressure remained less than the baseline throughout the study, whereas in control group, there was 9.6% increase in the mean arterial blood pressure from the baseline after intubation. The mean arterial blood pressure remained elevated from the baseline throughout the study (Table-6).

Sunita Goel, Manju Sinha[3], in their study have shown that there was a significant fall in the systolic, diastolic and mean arterial blood pressures in the clonidine group while there was a significant increase in the control group with significant inter group comparison.

In a similar study by Mirinmoy Das, Manjushree Ray, Gauri Mukherjee [6], a significant increase in systolic, diastolic and mean blood pressure in the control group throughout the intraoperative period from the baseline was seen. In the clonidine group they found that the patients remained hemodynamically stable.

In the present study, decreases in heart rate, systolic, diastolic and mean arterial blood pressures were noticed in the clonidine group. Inspite of maintaining normocapnia and keeping intra-abdominal pressure below 14mmm of Hg significant rises in heart rate, systolic, diastolic and mean arterial blood pressures were noticed in the control group. This suggests that clonidine premedication provides perioperative hemodynamic stability.

In the postoperative period, we observed patients for the occurrence of complications like excessive sedation, nausea, vomiting and shivering.

ORIGINAL ARTICLE

We evaluated sedation with the Ramsay sedation score and found that the sedation score was higher in the study group compared to the control group. 20% patients in the study group had a sedation score between 2 and 3 as compared to a sedation score of 1 to 2 in the control group. This showed that patients in the study group were more comfortable and pain free as compared to the control group (Table 7).

Sunita Goel, Manju Sinha[3] concluded that the sedation, analgesic sparing and anxiolytic effects of clonidine offer a distinct advantage.

In the present study, we found that the incidence of shivering in the study group was 6.6%, while in the control group it was 30% (Table 7). This shows that clonidine has additional advantage of preventing shivering in the postoperative period. Similar findings were reported by Mrinmoy Das, Manjushree Ray, Gauri Mukherjee in their study.

PONV is a distressing phenomenon occurring often after laparoscopic surgery. In our study, about 20% of patients complained of postoperative nausea and vomiting in the control group as compared to 3.33% in the study group (Table7).

Javaherfroosh F, M.Raza Pipelzadeh, Namazi M (2009)[16] in their study showed that clonidine reduces postoperative nausea and vomiting following laparoscopic gynecological surgery.

CONCLUSION:

From our study, we derive the following conclusion:

- Preoperative medication with intravenous clonidine provides haemodynamic stability during laparoscopic surgery.
- Clonidine premedication blunts the pressor response to laryngoscopy

In addition to the above it was also observed that,

- Clonidine premedication has good sedative properties and analgesic sparing effect.
- Postoperative nausea and vomiting is reduced in clonidine premedicated patients.
- Clonidine prevents shivering in the postoperative period.

Thus, we conclude that intravenous clonidine premedication provides stable hemodynamics in laparoscopic surgeries.

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ORIGINAL ARTICLE

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