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RESEARCH ARTICLE

PERIOPERATIVE HAEMODYNAMIC RESPONSE OF ORAL CLONIDINE PREMEDICATION IN GYNAE LAPROSCOPIC SURGERIES.

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Abstract

Introduction:-

Laproscopic surgery also called minimally invasive surgery (MIS), bandaid surgery, or keyhole surgery, is a modern surgical technique in which operations in the abdomen are performed through small incisions (usually 0.5–1.5 cm) as opposed to the larger incisions needed in laparotomy. Keyhole surgery makes use of images displayed on TV monitors to magnify the surgical elements.

In 1902,Georg Kelling, of Dresden, Germany, performed the first laparoscopic procedure in dogs and in 1910, Hans Christian Jacobaeus, of Sweden, reported the first laparoscopic operation in humans.[1]

In 1972, Clarke invented, published, patented, presented, and recorded on film laparoscopic surgery, with instruments marketed by the Ven Instrument Company of,Buffalo,NewYork,USA.[2]

In 1975, Tarasconi, Department of Ob-Gyn of the University of Passo Fundo Medical School (Brazil), started with organ resection laparoscopy(Salpingectomy), first reported November 1976 and later published in The Journal of Reproductive Medicine in 1981. This laparoscopic surgical procedure was the first laparoscopic organ resection reported in medical literature.(3)

Laparoscopic cholecystectomy was introduced by Phillipe Mouret in 1987. [4]

The hallmark of laparoscopy is creation of carbon dioxide (CO_2) pneumoperitoneum and change in the patients position from Trendelenberg to reverse Trendelenberg. It also results in stress hormone responses (cortisol, epinephrine and nor-epinephrine) especially when CO_2 pneumoperitoneum is used concomitantly.[5]

Various hemodynamic changes occure during pneumoperitonium created during laproscopy . Pneumoperitonium affects several homeostatic systems leading to alteration in acid base balance ,cardio vascular ,pulmonary physiology and stress response . The extent of cardiovascular changes associated with pneumoperitonium include an

increase in mean arterial pressure ,decrease in cardic output and increase in systemic vascular resistance which in turn compromise tissue perfusion.

Clonidine:
has been investigated and prescribed first as an antihypertensive drug in the 1950s. It has found new uses later, including treatment of some types of neuropathic pain, opioid detoxification, sleep hyperhidrosis, and as veterinary anaesthetic drug. Clonidine is used to treat anxiety and panic disorder. It is also FDA approved to treat ADHD in an extended release form. Clonidine treats high blood pressure by stimulating α_2 -receptors in the brain which decreases cardiac output and peripheral vascular resistance, lowering blood pressure. It has specificity towards the presynaptic α_2-receptors in the vasomotor center in the brainstem. This binding decreases presynaptic calcium levels, thus inhibiting the release of norepinephrine (NE). The net effect is a decrease in sympathetic tone.

Clonidine is a centrally-acting α-adrenergic receptor agonist with more affinity for α2 than α1. It selectively stimulates receptors in the brain that monitors catecholamine levels in the blood. These receptors close a negative feedback loop that begins with descending sympathetic nerves from the brain that controls the production of catecholamines (epinephrine, also known as adrenaline, and norepinephrine also known as noradrenaline) in the adrenal medulla. By fooling the brain into believing that catecholamine levels are higher than they really are, clonidine causes the brain to reduce its signals to the adrenal medulla, which in turn lowers catecholamine production and blood levels. The result is a lowered heart rate and blood pressure,with side effects of dry mouth and fatigue. If clonidine is suddenly withdrawn , causes rebound hypertension.

In addition, clonidine increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure and thus stablises, blood pressure. [6]

Clonidine modulates the hemodynamic changes induced by pneumoperitoneum by inhibiting the release of catecholamines and vasopression(7)

Materials and methodology:-

Study designs and methods:-

- After approval of the hospital ethics committee on 3rd Feb. 2014 this study was initiated. Written informed consent from patients obtained.
- The study was a prospective randomized placebo-controlled trial in sixty patients undergoing laparoscopic hysterectomy under general anaesthesia.

- Inclusion criteria:-
  (a) Patients posted for elective laparoscopic hysterectomy.
  (b) Aged between 18 and 60 years
  (c) Belonging to ASA grade I or II.
  (d) Body weight 40 to 80 kg

- Exclusion criteria:-
  (a) Patients belonging to ASA grade III and above
  (b) Patients with history of asthma, increased intracranial pressure, congestive heart failure, valvular heart disease, Coronary Artery Disease, on concomitant Monoaminase Oxidase inhibitors, with history of bleeding and coagulation disorders.
  (c) Unwillingness of patients.
  (d) Known hypersensitivity to any drugs being used (clonidine , vitamin B complex)
  (e) Contraindication to laparoscopic surgery.

Material required:-

1. Tab Clonidine

2. Tab Vitamin B-complex (Placebo)

Methodology:-

- After institutional and ethical committee approval and written informed consent, we investigated 60 patients (ASA I or II) undergoing elective laparoscopic hysterectomies, under general anaesthesia.
- The study was undertaken over the period of two years.
- The patients were evaluated preoperatively and explained the nature of study.
- Each patient was randomly assigned to one of two groups – group A and group B. Thirty patients of group A received Tab Clonidine 3μg.kg^{-1} orally 60-90 minutes before surgery while thirty patients of group B received Tab vitamin B-complex (Placebo) orally 60-90 minutes before surgery.
- Anaesthesia Technique On arrival in the operating room, baseline heart rate and non invasive blood pressure were taken. Monitors were applied (ECG, non-invasive blood pressure, pulse oximetry and capnography) I.V. line was secured and Inj. Ringer's Lactate was started. Inj. Glycopyrrolate 0.004mg.kgi.v, Inj. Ondansetron 0.1 mg/kg i.v, given. Patients were preoxygenated with 100% O_2 for 3 minutes. Induction was accomplished by Inj. Thiopentone sodium 5-7mg.kg i.v followed by Inj. Succinylcholine 2 mg.kg and patient was intubated with appropriate no. of endotracheal tube. Following induction of anaesthesia, a urinary catheter and nasogastric tube was placed. Anaesthesia was maintained with 50% O_2 and N_2O mixture along with 0.4%-0.6% Isoflurane and Inj. Atracurium bromide . Controlled ventilation was done with circle system having soda lime canister. Intraoperative monitoring included heart rate, non-invasive blood pressure, ECG, pulse oximetry and capnography. After creation of pneumoperitoneum patient was hyperventilated to maintain normocapnia. Mean intraabdominal pressure was kept at 13+/-1 mmHg in both the groups.

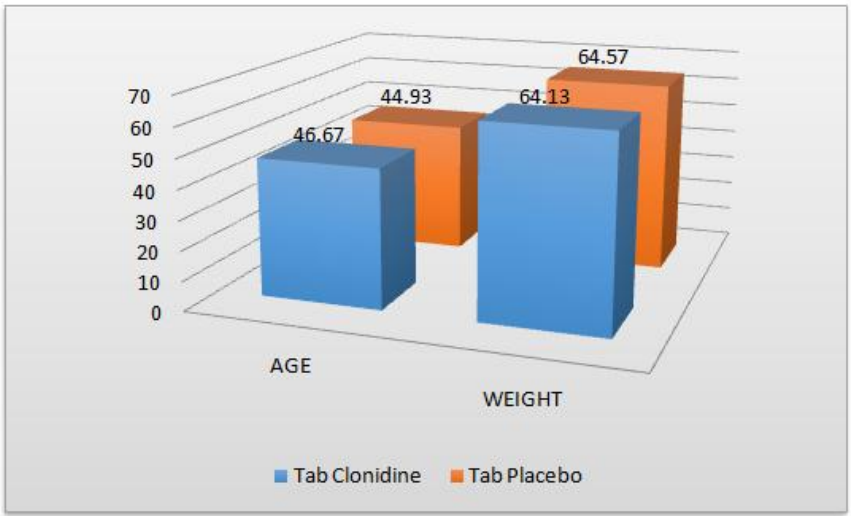
- Heart Rate, Systolic, Diastolic and Mean Arterial Pressures were measured at following points of time:
  (a) Prior to induction
  (b) 15 min after intubation
  (c) At skin incision
  (d) 15 min after CO_2 pneumoperitoneum
  (e) 30 min after CO_2 pneumoperitoneum
  (f) 10 min after release of CO_2 pneumoperitoneum
- In cases of acute and severe hemodynamic fluctuations the following remedial interventions were undertaken: For bradycardia (heart rate < 50 beats/min) Inj Atropine 0.6 mg IV. Significant hypotension (MAP < 60 mmHg) was treated with Inj ephedrine and intravenous crystalloids. Hypertension (MAP > 110 mmHg) was managed by increasing concentration of inhalational agents or IV beta adrenoceptor blockers (Inj Esmolol /Metoprolol) or Inj NTG IV.
- Patients in whom surgery could not be completed laparoscopically and open hysterectomy done have been excluded from the study.
- Patients were observed in post operative care unit for hemodynamics and for side effects like nausea, vomiting, and reduced urine output for 6 hrs.

Observation & results:-

The study consisted of 60 patients posted for elective laparoscopic hysterectomy. Group A i.e. Tab. Clonidine Group and Group B i.e., Tab Placebo group with 30 patients in each group. The patients were selected by randomized computer assisted tables. It included 60 females patients.

Table No. 1 Age& Weight distribution:-

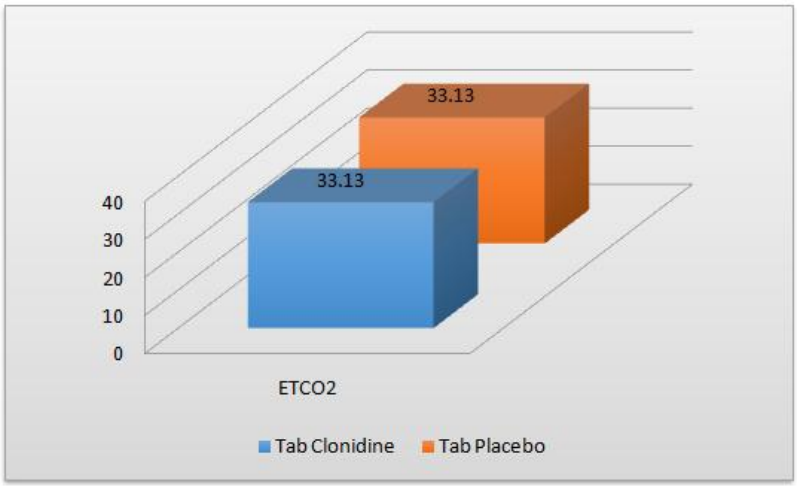
	GROUP	N	Mean	Std. Deviation	P value
AGE	Group A -Tab Clonidine	30	46.67	5.616	0.178
	Group B -Tab Placebo	30	44.93	4.127	Not Significant
WEIGHT	Group A -Tab Clonidine	30	64.13	5.829	0.781
	Group B -Tab Placebo	30	64.57	6.163	Not Significant



The mean ETCO2 in both Group Aand Group B was 33.13 mmHg with a standard deviation of 1.224 mmHg (p=1.000).Table 5 shows these findings. The both groups were comparable in this regard and the hemodynamic variations intraoperatively were not secondary to raised ETCO2 values.

Table No. 2 $ETCO_2$ Distribution:-

	GROUP	N	Mean	Std. Deviation	P value
$ETCO_2$	Group A -Tab Clonidine	30	33.13	1.224	1.000
	Group B -Tab Placebo	30	33.13	1.224	Not Significant



Heart rate:-

The heart rates between the two groups intraoperatively were compared by unpaired t-test at specific time intervals during the surgery. The heart rate prior to induction and 15 min after intubation was comparable in both the groups. Group A and Group B were observed to have p value not significant prior to intubation (p=0.023) and 15 min after intubation (p=0.185).Almost all readings except for the readings prior to intubation (p=0.023) and 15 min after intubation (p=0.185), in which heart rate of Group B was found to be significantly higher than Group A.

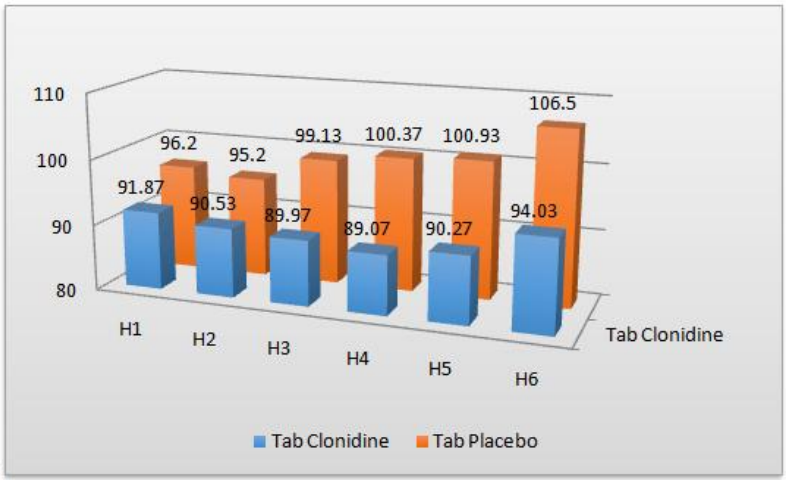
The maximum heart rate observed in Tab Clonidine group (Group A) was 102 bpm, whereas minimum heart rate observed was 85 bpm. In Tab Placebo (Group B) the maximum heart rate observed was 129 bpm whereas the minimum heart rate observed was 75 bpm. The maximum mean heart rate in Group A of 94.03+/-2.942 bpm was found at 15 min after release of CO_2 pneumoperitoneum, whereas maximum mean heart rate in Group B of 106.50+/-9.254 bpm was found at 15 min after release of CO_2 pneumoperitoneum.Per operatively, heart rate was lower in the group A as compared to the group B. The above observations were statically significant (p<0.005).

Table No. 3 HEART RATE:-

	GROUP	N	Mean	Std. Deviation	P value
H1	Tab Clonidine	30	91.87	3.866	0.023 Not Significant
	Tab Placebo	30	96.20	9.397	
H2	Tab Clonidine	30	90.53	3.309	0.185 Not Significant
	Tab Placebo	30	95.20	18.744	
H3	Tab Clonidine	30	89.97	3.275	0.0001 Significant
	Tab Placebo	30	99.13	7.619	
H4	Tab Clonidine	30	89.07	3.258	0.0001 Significant
	Tab Placebo	30	100.37	9.357	
H5	Tab Clonidine	30	90.27	2.741	0.0001 Significant
	Tab Placebo	30	100.93	9.798	
H6	Tab Clonidine	30	94.03	2.942	0.0001 Significant
	Tab Placebo	30	106.50	9.254	

Abbreviations used in table:-

Heart Rate	Time
H1	Prior to induction
H2	15 min after intubation
H3	At skin incision
H4	15 min after CO_2 pneumoperitoneum
H5	30 min after CO_2 pneumoperitoneum
H6	15 min after release of CO_2pneumoperitoneum



1. DG

Systolic blood pressure:-

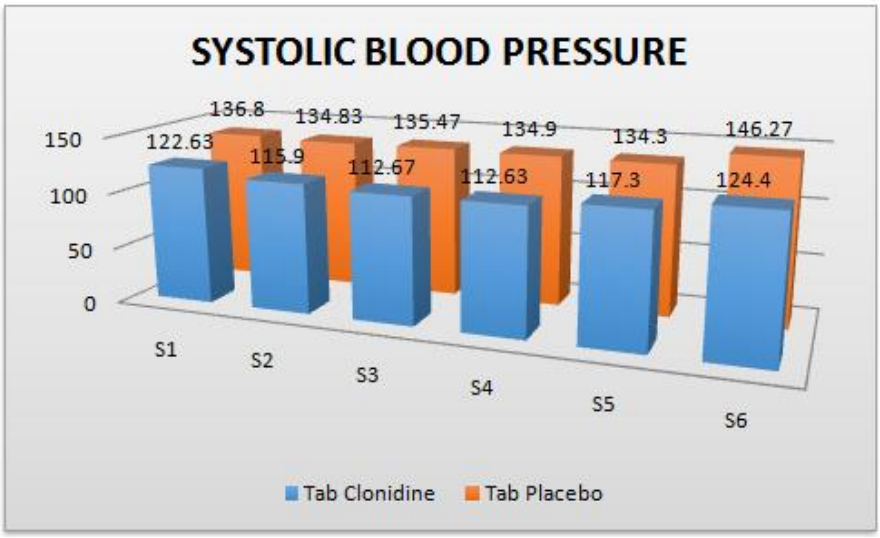
The intraoperative Systolic blood pressures (SBP) were compared between the two groups as below by unpaired t-test. The maximum SBP in Group A was 136 mmHg prior to induction. The minimum SBP in Group A was 100 mmHg. The maximum SBP in Group B was 172 mmHg and the minimum SBP in Group B was 109 mmHg. The maximum mean SBP of 124.40+/-5.769mmHgin Group A was found at 15 min after release of CO_2 pneumoperitoneum whereas maximum mean SBP in Group B of 146.27+/-14.147mmHg was found at 15 min after release of CO_2pneumoperitoneum. Per operatively, SBP was lower in the group A as compared to the group B. The above observations were statically significant ($p<0.005$).

Table No. 4 Systolic BP:-

	GROUP	N	Mean	Std. Deviation	P value
S1	Tab Clonidine	30	122.63	7.015	0.0001 Significant
	Tab Placebo	30	136.80	11.961	
S2	Tab Clonidine	30	115.90	5.359	0.0001 Significant
	Tab placebo	30	134.83	12.709	
S3	Tab Clonidine	30	112.67	5.797	0.0001 Significant
	Tab Placebo	30	135.47	13.685	
S4	Tab Clonidine	30	112.63	5.869	0.0001 Significant
	Tab Placebo	30	134.90	11.883	
S5	Tab Clonidine	30	117.30	5.879	0.0001 Significant
	Tab Placebo	30	134.30	10.803	
S6	Tab Clonidine	30	124.40	5.769	0.0001 Significant
	Tab Placebo	30	146.27	14.147	

Abbreviations used in table:

Systolic BP	Time
S1	Prior to induction
S2	15 min after intubation
S3	At skin incision
S4	15 min after CO_2 pneumoperitoneum
S5	30 min after CO_2 pneumoperitoneum
S6	15 min after release of CO_2pneumoperitoneum



Diastolic blood pressure:-

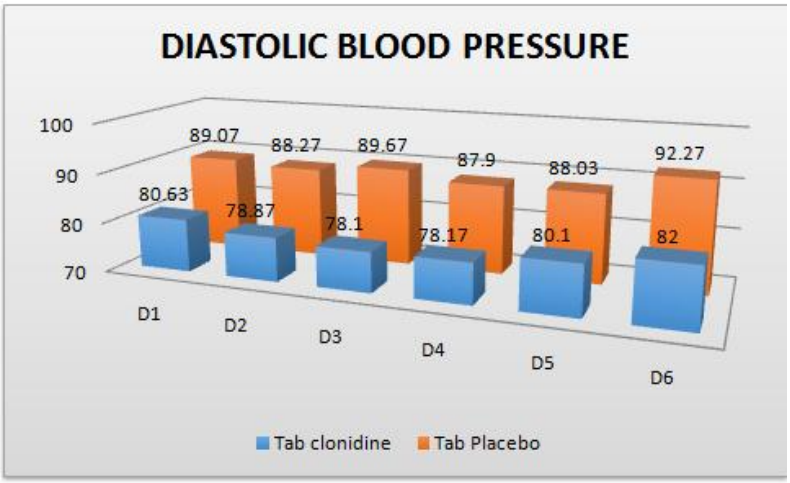
The intraoperative diastolic blood pressures (DBP) were compared between the two groups as below by unpaired t-test. The maximum DBP in Group A was 91 mmHg 30 min after CO_2 pneumoperitoneum. The minimum DBP in Group A was 71 mmHg. The maximum DBP in Group B was 109 mmHg 15 min after CO_2 pneumoperitoneum and the minimum DBP in Group B was 74 mmHg15 min after intubation. The maximum mean DBP of 82.00+/-3.332mmHgin Group A was found at 15 min after release of CO_2 pneumoperitoneum whereas maximum mean DBP in Group B of 92.27+/-7.041mmHg was found at 15 min after release of CO_2 pneumoperitoneum. Per operatively, DBP was lower in the group A as compared to the group B. The above observations were statically significant ($p<0.005$).

Table No.5 Diastolic BP:-

	GROUP	N	Mean	Std. Deviation	P value
D1	Tab Clonidine	30	80.63	3.489	0.0001 Significant
	Tab Placebo	30	89.07	6.617	
D2	Tab Clonidine	30	78.57	2.979	0.0001 Significant
	Tab Placebo	30	88.27	7.561	
D3	Tab Clonidine	30	78.10	3.055	0.0001 Significant
	Tab Placebo	30	89.67	6.718	
D4	Tab Clonidine	30	78.17	3.130	0.0001 Significant
	Tab Placebo	30	87.90	7.503	
D5	Tab Clonidine	30	80.10	4.513	0.0001 Significant
	Tab Placebo	30	88.03	5.780	
D6	Tab Clonidine	30	82.00	3.332	0.0001 Significant
	Tab Placebo	30	92.27	7.041	

Abbreviations used in table:-

Diastolic BP	Time
D1	Prior to induction
D2	15 min after intubation
D3	At skin incision
D4	15 min after CO_2 pneumoperitoneum
D5	30 min after CO_2 pneumoperitoneum
D6	15 min after release of CO_2pneumoperitoneum



Mean arterial pressure:-

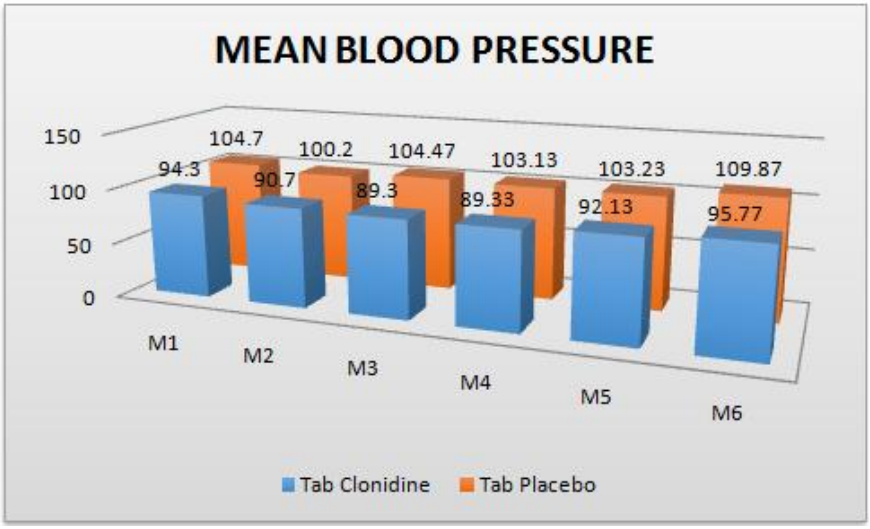
The intraoperative Mean arterial pressures (MAP) were compared between the two groups as below by unpaired t-test. The maximum MAP in Group A was 103 mmHg 30 min after CO_2 pneumoperitoneum. The minimum MAP in Group A was 81 mmHg. The maximum MAP in Group B was 124 mmHg 15 min after intubation and the minimum MAP in Group B was 85 mmHg15 min after intubation. The maximum mean MAP of 95.77+/-3.598 mmHg in Group A was found at 15 min after release of CO_2pneumoperitoneum whereas maximum mean MAP in Group B of 109.87+/-8.661mmHg was found at 15 min after release of CO_2 pneumoperitoneum. Per operatively, MAP was lower in the group A as compared to the group B. The above observations were statically significant ($p<0.005$) except mean blood pressure 15 min after intubation.

Table No. 6 Mean Arterial Pressure:-

	GROUP	N	Mean	Std. Deviation	P value
M1	Tab Clonidine	30	94.30	4.145	0.0001 Significant
	Tab Placebo	30	104.70	8.112	
M2	Tab Clonidine	30	90.70	3.405	0.010 Not Significant
	Tab Placebo	30	100.20	19.099	
M3	Tab Clonidine	30	89.30	3.554	0.0001 Significant
	Tab Placebo	30	104.47	8.407	
M4	Tab Clonidine	30	89.33	3.262	0.0001 Significant
	Tab Placebo	30	103.13	8.237	
M5	Tab Clonidine	30	92.13	4.629	0.0001 Significant
	Tab Placebo	30	103.23	7.011	
M6	Tab Clonidine	30	95.77	3.598	0.0001 Significant
	Tab Placebo	30	109.87	8.661	

Abbreviations used in table:-

MEAN BP	Time
M1	Prior to induction
M2	15 min after intubation
M3	At skin incision
M4	15 min after CO_2 pneumoperitoneum
M5	30 min after CO_2 pneumoperitoneum
M6	15 min after release of CO_2pneumoperitoneum

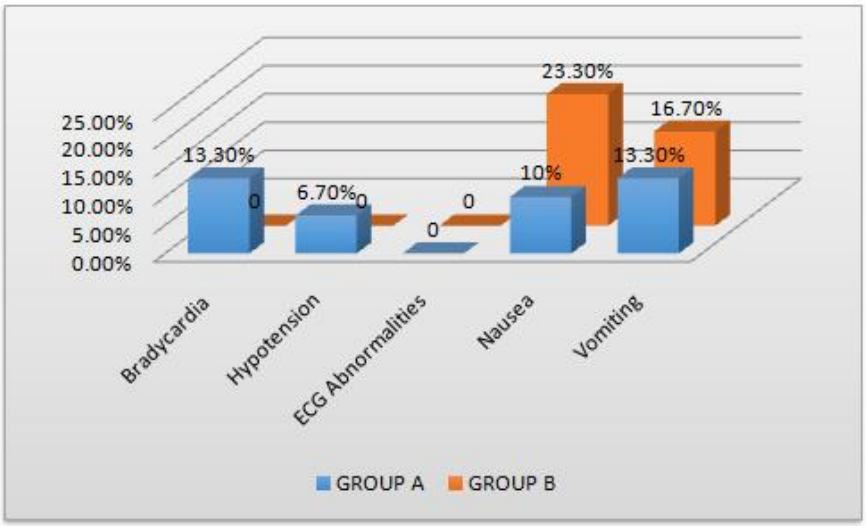


Side effects:-

The side effects were studied for the intraoperative period and nausea vomiting was studied 6 hrs post operatively. 4 patients (13.3%) in Group A had persistent bradycardia without hypotension, which was treated with Inj. Atropine 0.6 mg I.V. bolus whereas no patient in group B had bradycardia. 2 patients (6.7%) in Group A had significant Hypotension i.e. fall in MAP by > 20 % of the baseline which was treated by fluid boluses. No patient in the study had any ECG abnormalities intraoperatively. Only one patient (3.3%) in Group A had reduced Urine output <0.5 ml/kg /hr.3 (10%) Vs 7 (23.3%) patients in Group A and Group B respectively had Nausea. 4 (13.3%) Vs 5 (16.7%) patients in Group A and Group B respectively had vomiting which needed treatment by Inj. Ondansatron 0.08 mg/kg.

Table no. 7 Complications:-

SIDE EFFECTS	Group A	Group B	Comments
Bradycardia	4(13.3%)	0 (0%)	Treated with Inj. Atropine 0.6 mg I.V. bolus
Hypotension	2(6.7%)	0 (0%)	Treated by fluid boluses
ECG Abnormalities	0 (0%)	0 (0%)	
Nausea	3 (10%)	7 (23.3%)	Treated by Inj. Ondansatron 0.08 mg/kg.
Vomiting	4 (13.3%)	5 (16.7%)	Treated by Inj. Ondansatron 0.08 mg/kg.



Discussion:-

In recent years, laparoscopic surgery has become a common clinical practice. These laparoscopic procedures may involve changes in patient position and require a longer period of intra-abdominal carbon dioxide insufflations. An appraisal of the potential problems is essential for optimal anesthetic care of patients undergoing laparoscopic surgery.

The Role of premedication, in ancient time, was to prevent the side effects of many anaesthetic agents eg. anticholinergic agent was given to prevent salivation and bradycardia produce by ether and cyclopropane. But with development of newer anaesthetic with minimal side effects, the role of premedication has changed and now the goal of modern anaesthesia practice is to decrease anxiety and to provide better haemodynamic stability perioperatively[61].

In our study we had used clonidine as premedication because it is sedative, anxiolytic and sympatholytic property provides stable haemodynamic stability and prevent symatho–somatic response to surgery in peri-operative period [62]. Clonidine premedication effectively blunted the cardiovascular response to surgical stress, especially pneumoperitonium[62].

"The choice of anaesthetic technique for upper abdominal laparoscopic surgery is mostly limited to general anaesthesia with muscle paralysis, tracheal intubation and intermittent positive pressure ventilation (IPPV).Tracheal intubation and IPPV ensure airway protection and control of pulmonary ventilation to maintain normocarbia. Isoflurane is the preferred volatile anesthetic agent, as it has less arrhythmogenic and myocardial depressant effects.[63]We had also used Isoflurane as volatile anaesthetic agents in our study.

Clonidine an imidazole derivative is a selective α 2adrenergic agonist[15]and centrally acting potent antihypertensive drug. It decreases the heart rate and blood pressure associated with decreased cardiac output and SVR. Profound hypertension and tachycardia occurs during application of CO2 pneumoperitoneum. Pneumoperitoneum along with head down position lead to significant hemodynamic changes i.e. increase in MAP and SVR and decrease in cardiac output[64]. The decline in cardiac output and venous return can be attenuated by increasing circulating volume before pneumoperitoneum. However increase in MAP and SVR can be attenuated with clonidine.[64]

Our study was conducted in 60 adult patients divided in two groups of 30 each belonging to ASA physical status I and II. We had used Tab. Clonidine as oral premedication to evaluate it's hemodynamic response in laproscopic Hysterectomy. As Clonidineis rapidly and completely absorbed after oral administration and reaches peak plasma concentrations within 60-90min[15]. Similarly **Hayashi Y and Maze M.** has used oral clonidine 90 min before anaesthesia in their study and they found that it is effective orally and completely gets absorbed and its peak effect occurs within 1-3 hours of administration.[65]

In our study, Tab. Clonidine 3 $\mu g.kg^{-1}$was given 60-90 min before scheduled laparoscopy. Similarly **Masayoshi Uchida et al** in 2004 used 3 μg.kg-1 and observed responses to hypercapnia in the clonidinepropofol subgroup were significantly attenuated.[150] Higher doses (5 μg.kg-1) were used by **Ghingone et al** for reduction of hemodynamic response to endotracheal intubation[66]**. Yu et. al. and Sung C S et. al.** used 150μg orally as a premedication for maintenance of hemodynamic stability during pneumoperitoneum.[16,67] Following carbon dioxide pneumoperitoneum IAP was kept below 13 mmHg. Patients were hyperventilated to maintain normocapnia. The pulse rates, Systolic, Diastolic and Mean arterial pressures were noted at specific duration. We used clonidine at 3μg.kg because at this dose there is less chances of hypotension and bradycardia.

The demographic profile of the patients were comparable which provided an unbiased platform for statistical analysis. Various demographic variables such as age, weight were comparable in both groups and was found out to be statistically non-significant($p>0.05$). Weight in placebo group was 64.57±6.163 and in clonidine group it was 64.13±5.829 ($p>0.05$), which was also statistically insignificant.

The heart rates between the two groups intraoperatively were compared by unpaired t-test at specific time intervals during the surgery. The heart rate prior to induction and 15 min after intubation was comparable in both the groups. Study group (Group A) and control group (Group B) were observed to have p value not significant prior to intubation ($p=0.023$) and 15 min after intubation ($p=0.185$).Almost all readings except for the readings prior to intubation ($p=0.023$) and 15 min after intubation ($p=0.185$), in which heart rate of Group B was found to be significantly higher than Group A. Our study conceded with study done by **Sung et al, Yu et al, and Joris et al** had similar observations in their studies with clonidine.[16,67,39]

The maximum heart rate observed in (Clonidine) study group (Group A) was 102 bpm, whereas minimum heart rate observed was 85 bpm. In Control group (Group B) the maximum heart rate observed was 129 bpm whereas the minimum heart rate observed was 75 bpm. The maximum mean heart rate in Group A of 94.03+/-2.942 bpm was found at 15 min after release of CO_2 pneumoperitoneum, whereas maximum mean heart rate in Group B of 106.50+/-9.254 bpm was found at 15 min after release of CO_2 pneumoperitoneum.Per operatively, heart rate was lower in the group A as compared to the group B. The above observations were statically significant ($p<0.005$).In spite of maintaining normo capniaand IAP <14 mm Hg, significant rise in the heart rate were observed in the group B. It was observed that Heart rate increased in response to pneumoperitoneum in the control group and remained elevated throughout the surgery. In the clonidine group A heart rate remained closed to the baselinevalues[68].

The intraoperative Systolic blood pressures (DBP) were compared between the two groups as below by unpaired t-test. The maximum SBP in Group A was 136 mmHg prior to induction. The minimum SBP in Group A was 100 mmHg. The maximum SBP in Group B was 172 mmHg and the minimum SBP in Group B was 109 mmHg. The maximum mean SBP of 124.40+/-5.769mmHg in Group A was found at 15 min after release of CO_2

pneumoperitoneum whereas maximum mean SBP in Group B of 146.27+/-14.147mmHg was found at 15 min after release of CO_2 pneumoperitoneum. Per operatively, SBP was lower in the group A as compared to the group B.The above observations were statically significant ($p<0.005$)[69].

The intraoperative Diastolic blood pressures (SBP) were compared between the two groups as below by unpaired t-test. The maximum DBP in Group A was 91 mmHg 30 min after CO_2 pneumoperitoneum. The minimum DBP in Group A was 71 mmHg. The maximum DBP in Group B was 109 mmHg 15 min after CO_2 pneumoperitoneum and the minimum DBP in Group B was 74 mmHg15 min after intubation. The maximum mean DBP of 82.00+/-3.332mmHgin Group A was found at 15 min after release of CO_2 pneumoperitoneum whereas maximum mean DBP in Group B of 92.27+/-7.041mmHg was found at 15 min after release of CO_2 pneumoperitoneum. Per operatively, DBP was lower in the group A as compared to the group B. The above observations were statically significant ($p<0.005$)[70].

The intraoperative Mean blood pressures (MBP) were compared between the two groups as below by unpaired t-test. The maximum MBP in Group A was 103 mmHg 30 min after CO_2 pneumoperitoneum. The minimum MBP in Group A was 81 mmHg. The maximum MBP in Group B was 124 mmHg 15 min after intubation and the minimum MBP in Group B was 85 mmHg15 min after intubation. The maximum mean MBP of 95.77+/-3.598mmHg in Group A was found at 15 min after release of CO_2pneumoperitoneum whereas maximum mean MBP in Group B of 109.87+/-8.661mmHg was found at 15 min after release of CO_2pneumoperitoneum. Per operatively, MBP was lower in the group A as compared to the group B. The above observations were statically significant ($p<0.005$).[71]

All the patient were studied for any complication intraoperatively & post operatively for 6 hour. 4 patients (13.3%) in Group A had persistent bradycardia without hypotension, which was treated with Inj. Atropine 0.6 mg I.V. bolus whereas no patient in group B had bradycardia. 2 patients (6.7%) in Group A had significant Hypotension i.e. fall in MAP by > 20 % of the baseline which was treated by fluid boluses. No patient in the study had any ECG abnormalities intraoperatively.3 (10%) Vs 7 (23.3%) patients in Group A and Group B respectively had Nausea. 4 (13.3%) Vs 5 (16.7%) patients in Group A and Group B respectively had vomiting which needed treatment by Inj. Ondansatron 0.08 mg/kg i.v. We observed that Patients in group A suffered less from nausea and vomiting. Our study was in accordance with T**. Asai et al**[69] who also found that Clonidine decreases incidence of vomiting by inhibiting contraction at stomach and pylorus. **Shivinder Singh and Kapil Arora et al**, [66]found that incidence of nausea and vomiting was less in the Clonidine group compared to the control group (28% vs 52%) though not significant (P> 0.05). Bradycardia and hypotension were found only in the Clonidine group and was also statistically insignificant. **Aho et al,**[46] used Clonidine for prevention of hemodynamic responses associated with laparoscopic surgery. **Yu et al,**[67] used 150µg of oral Clonidine as premedication for maintenance of hemodynamic stability during pneumoperitoneum and recommended its routine use as premedication in laparoscopic surgeries. The intraoperative stress response like tachycardia ,hypertension and increase in SVR was reduced by preoperative administration of alpha2 agonists as premedication. Thus it appears that Clonidine is an appropriate premedication in laparoscopic hysterectomy to fulfill the anaesthetic aims of reducing stress response with minor treatable adverse effects.

Conclusion:-

In conclusion, Premedication with single oral dose of clonidine 3mcg/kg given 60-90 min before can attenuate the hemodynamic responses in laparoscopic hysterectomy has been found to be relatively safe as well as effective method to provide stable haemodynamics and protection against stress response caused by pneumoperitoneum. Clonidine also affords an added advantage of reduction in postoperative complications such as nausea & vomiting. However, this drug should be evaluated further in elderly patients or patients having pre-existing cardiac risk factors undergoing laparoscopic surgeries to prove its safety and efficacy. Thus it appears that clonidine is an appropriate premedication in laparoscopic hysterectomy to fulfill the anaesthetic aims of reducing stress response and subsequent adverse effects.

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