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Attenuation of Cardiovascular Responses to Pneumoperitoneum and Reduction of Perioperative Haemodynamic Instability during Laparoscopic Surgery with Oral Clonidine Premedication.

Dr Subhashree Sahu[1], Dr Monalee Baviskar[2], Dr Shilpi Yadav[3], Dr Archana Har[4], Dr Madishatty Uday Kumar[5]

[1]*Junior Resident, Department of Anaesthesiology, MGM Medical College and Hospital, Kamothe*
[2]*Assistant Professor, Department of Anaesthesiology, MGM Medical College and Hospital, Kamothe*
[3]*Associate Professor, Department of Anaesthesiology, MGM Medical College and Hospital, Kamothe, Corresponding Author*
[4]*Professor, Department of Anaesthesiology, MGM Medical College and Hospital, Kamothe*
[5]*Junior Resident, Department of Anaesthesiology, MGM Medical College and Hospital, Kamothe*

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ABSTRACT

BACKGROUND: The cardiovascular changes associated with laparoscopy (during pneumoperitoneum -carbon dioxide gas insufflation) are an increase in systemic vascular resistance, mean arterial pressure, pulmonary vascular resistance, myocardial filling pressures accompanied by a fall in the cardiac index and tissue perfusion. These changes are not only related to the mechanical factors as they outlast the end of pneumoperitoneum. The neurohumoral factors like catecholamines, prostaglandins, the rennin aldosterone angiotensin system (RAAS), vasopressin are potential mediators.

METHODS AND MATERIALS: Our randomized double blind prospective placebo controlled study is to be carried out in 60 adult patients in the age group of 18-75 years who belonged to ASA class I and II scheduled for elective laparoscopic surgeries of duration >1 hour. They were assigned to two groups to receive either Clonidine 3ug/kg (Group C) and placebo-VIT C (Group P) orally with sips of water 90 min before estimated time of induction of anaesthesia. Same anaesthesia technique was used in both the groups. Intra abdominal pressure was kept between 12-14 mm Hg and End tidal CO2 between 30-35mmHg throughout the surgical procedure and airway pressure kept within normal limits. MAP was not allowed to increase more than 30% of baseline value. Isoflurane concentration were adopted to maintain haemodynamic stability.

RESULTS: The perioperative Heart Rate which was variable at each time interval was slower in the clonidine group in comparison with the placebo group.

The clonidine group had statistically significant low systolic and diastolic and mean blood pressure during pre induction, post intubation, pneumoperitoneum, post extubation and immediate postoperative period in PACU (post anaesthesia care unit) compared to the non-clonidine group.

The Isoflurane concentration required for maintaining acceptable perioperative hemodynamic stability was reduced in patients of the clonidine group.

During the intra-operative period (pneumoperitoneum) more patients in the placebo group suffered from hypertension which could not be managed with alteration of Isoflurane concentration alone and needed some antihypertensive treatment for intervention.

In immediate postoperative period, intensity of pain was less (as assessed by the time of first analgesic requirement by patient according to demand - which was prolonged) in patients of clonidine group in comparison with the placebo group.

CONCLUSION: Premedication with low dose oral clonidine 3 ug/kg in patients undergoing laparoscopic surgery provides stable perioperative hemodynamics as revealed by less acute cardiovascular events that needed rescue drugs thus giving protection against stress response triggered by pneumoperitoneum. It also affords sparing effect on Isoflurane and good postoperative analgesia and lessens the severity of hemodynamic changes and complications during post-operative period.

Thus, low dose clonidine (3 ug/kg) can be reasonably recommended as a premedicant for all laparoscopic procedures.

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KEYWORDS: Laparoscopic surgery, pneumoperitoneum, Intra abdominal pressure, Clonidine, Intra operative stress response, Post operative pain

I. INTRODUCTION

Laparoscopy has revolutionized surgeries and has become popular in the recent years. It has become the gold standard in any surgeries as it offers multiple benefits than conventional (open) surgery and has been promoted as a gentle surgery[1]. But it presents several challenges for the anaesthesiologist. Compared to open procedures, laparoscopy is characterized by better maintenance of homeostasis[2].

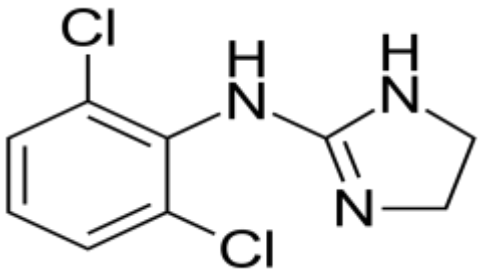
The cardiovascular changes associated with laparoscopy (during pneumoperitoneum-carbon dioxide gas insufflation) are an increase in systemic vascular resistance, mean arterial pressure, pulmonary vascular resistance, myocardial filling pressures accompanied by a fall in the cardiac index and tissue perfusion.

These changes are not only related to the mechanical factors as they outlast the end of pneumoperitoneum. The neurohumoral factors like catecholamines, prostaglandins, the rennin aldosterone angiotensin system (RAAS), vasopressin are potential mediators.

Clonidine a centrally acting alpha$_2$ adrenenergic agonist is an antihypertensive medication and also has properties which are potentially beneficial for anaesthesia. It has been recently used for anaesthesia preedication, providing sedative, anxiolytic and analgesic effect and can reduce requirements of anaesthetics and analgesics.

It inhibits release of catecholamines and vasopressin which mediate the increase in systemic vascular resistance observed during pneumoperitoneum and thus modulates the hemodynamic changes induced by pneumoperitoneum. Hence clonidine premedication may prevent perioperative myocardial ischaemia patients at risk, related to inereased orygen consumption induced by increased c workload by improving myocardial oxygen balance.

PHARMACOLOGY OF CLONIDINE-(C9-H9-C12-N3)



MECHANISM OF ACTION AND EFFECTS:

It is a synthetic centrally acting imidazoline derivative with predominantly alpha-2 adrenergic agonist activity. The overall effect is to decrease sympathetic activity, enhance parasympathetic tone and reduce circulatory catecholamines. Alpha 2 adrenergic agonists produce clinical effects when binded to the alpha-2 adrenergic receptors which are distributed widely in the body.

There are 3 subtypes of alpha-2 adrenergic receptors, alpha-2a, alpha-2b and alpha-2c, each of which may be uniquely responsible for some of the effects of alpha-2 adrenergic agonists.

A high density of alpha-2 adrenergic receptors has also been demonstrated in the vagus nerve, intermediolateral cell column and the substantia gelatinosa. The dorsal horn of the spinal cord contains alpha-2a adrenoreceptors while the primary sensory neurons contain both alpha-2a and alpha-2c subtypes of adrenoreceptors.

The ability of clonidine to modify the function of K+ channels in the CNS (cell membranes become hyperpolaroid) may be the mechanism for profound decreases in anaesthetic requirements produced by clonidine and other even more selective alpha2 adrenergic agonist such as dexmedetomidine.

PHARMACOKINETICS:

Clonidine can be administered by the enteric (oral and rectal), Neuraxial (epidural and subarachnoid), intravenous, intra-articular and transdermal routes.
Oral clonidine is readily absorbed, has a 30-60 min onset of action and lasts for 6- 12 hours.
It reaches peak plasma concentration in 60-90 min.
It has an elimination t1/2 of 8-12 hours

II. MATERIAL AND METHODS

Our randomized double blind prospective placebo controlled study was carried out in 60 adult patients scheduled for elective laparoscopic surgeries of duration > 1 hour.

The study was approved by the institutional Ethical committee and written valid

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informed consent was obtained from all the patients before being included in the study.

The study was conducted on 60 adult patients in the age group of 18-75 years and who belonged to ASA class I and II.

Patients with known allergy to Clonidine and NSAIDS, Patients taking clonidine, methyl-dopa, b-blocking drugs, mono-amine oxidase inhibitors were excluded.

Detailed pre anaesthetic evaluation was carried out with history, general examination and systemic examination including airway assessment. Vital parameters including pulse rate, respiratory rate, blood pressure, oxygen saturation was noted.

They were randomly assigned to two groups to receive either clonidine 3 ug /kg (group C) and placebo-vitamin C (group P) orally with sips of water 90 min before estimated time of induction of anaesthesia.

(GROUP C) with Tablet Vit C (ascorbic acid) as placebo (GROUP P) with sips of water confirming that the heart rate >45 min and systolic blood pressure > 100 mmHg (baseline reading).

PREMEDICATION

Premedication Given to all patients in each group with IV Midazolam 0.03 mg /kg, IV Fentanyl 2 mcg /kg, IV Ondansetron 0.05 - 0.15 mg/kg, IV Glycopyrolate 0.004 mg/kg if required(HR<45).

INDUCTION

In both groups, adequate preoxygenation was achieved by giving 100% oxygen for 3 min
Induced was done with IV Pentothal sodium 5-7 mg/kg was given slowly and incremental doses of 25 mg. Endotracheal intubation was facilitated by IV succinylcholine 1.5 mg/kg. Direct laryngoscopy was done and an appropriate sized cuffed endotracheal tube was passed beyond the vocal cords. Air entry was checked by auscultation of chest and after confirming equal air entry, the cuff was inflated with air till there was no paratracheal leak palpated on either side of trachea.

MAINTENANCE

Maintenance with oxygen-nitrous oxide mixture (50:50) with adequate isoflurane. To facilitate IPPV neuromuscular blockade was achieved with Vecuronium bromide 0.08 mg/kg was given as a loading dose and 1/5 of the loading dose was repeated as and when neuromuscular blockade with the previous dose starts wearing off.

Adequate depth of anaesthesia and optimum hemodynamic and surgical conditions were maintained with 02 + N20 (50:50) + Isoflurane.

Intraabdominal pressure (IAP) was kept between 12-15 mmg throughout the surgical procedure.
After pneumoperitoneum necessary changes in ventilator settings (Tidal volume-decreased,
Respiratory frequency-increased, PEEP was added-5 cm H2O) were made to maintain normocapnia. Air entry was again checked after 10 min to confirm bilateral equality and adequacy at bases.
The tidal volume (Vt) and the ventilatory frequency (RR) was adjusted and intermittent positive pressure ventilation (IPPV) was continued by mechanical ventilator to maintain End Tidal CO2 between 30-35 mmHg and Peak Airway Pressures kept within normal limits between 18-22 cm of H2O.

RESCUE DRUGS USED WERE:

- MAP >110 OR 30% ABOVE BASELINE - Esmolol (500microgram/kg bolus -followed by 50 microgram/kg iv infusion), NTG-nitroglycerine (1-2.5 mg/kg iv infusion),
- MAP <60 OR 30% BELOW BASELINE - Ephedrine 3-6 mg IV bolus doses.
- HR <40 - Glycopyrrolate(0.2 mg) or atropine(0.5 mg)

After release of pneumoperitoneum and once the closure (peritoneal and abdominal wall) was started, the ventilator settings and patient position again changed to normal.

POST OPERATIVE PAIN RELIEF:
Was provided with 0.25% preservative and dextrose free Bupivacaine at port and drainage site as local infiltration (2cc at each port) just before closure of incision.

REVERSAL

At the end of surgery when spontaneous breathing pattern was established, neuromuscular blockade was reversed with IV neostigmine 0.05 mg/kg and IV glycopyrrolate 0.008 mg/kg. Patients were extubated after doing an oral suction and return of oropharyngeal reflexes and shifted to recovery.

IN THE RECOVERY ROOM (POST ANAESTHESIA CARE UNIT)
MODIFIED RAMSAY SEDATION SCALE:
1. Agitated, restless, irritable, anxious
2. Calm, tranquil, co-operative, oriented
3. Responds to oral commands.
4. Responds to light, glabellar tap, loud noise
5. Sluggish response to light, glabellar tap, loud noise.
6. No response

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Heart Rate, Blood pressure, SpO2, End tidal CO2, End tidal Isoflurane, Dial concentration of Isoflurane vaporizer and Intraabdominal pressure were recorded at the following points of time:

- Prior to administration of clonidine (Baseline Reading)
- On arrival in operation (preinduction)
- Post intubation
- Before pneumoperitoneum
- After pneumoperitoneum
- After release of pneumoperitoneum
- After extubation
- Post op in recovery room for 2 hours

III. OBSERVATION AND RESULTS

The heart rate and blood pressure were noted before giving the medication (clonidine or placebo) and was recorded as baseline reading.

The heart rate and blood pressure were monitored preinduction, postintubation, just before creation of pneumoperitoneum (insufflation of CO2 gas) , during pneumoperitoneum, after release of pneumoperitoneum (exsufflation), postextubation and 2 hrs postoperatively and compared with baseline value.

Following CO2 insufflation, normocapnia (End Tidal CO2 in a range of 35-40 mmHg) was maintained. Mean intraabdominal pressure was kept constant between 12-14 mmHg.

The anaesthetic management in our study was to maintain the perioperative hemodynamic parameters (HR and MAP) within 30% of the baseline values.

The mean heart rate (HR) and mean arterial pressure (MAP) in both the groups was compared. The End Tidal-Isoflurane was recorded in both the groups and was compared. The side effects in both groups C and P were noted and compared during intraoperative and postoperative period.

The perioperative HR which was variable at each time interval was slower in the Clonidine group in comparison with the placebo group. The clonidine group had statistically significant low systolic and diastolic and mean blood pressure pre induction, post intubation, during pneumoperitoneum, post extubation and during their immediate postoperative period in PACU (post anaesthesia care unit) compared to the non-clonidine group.

None of the patients showed any evidence of ischaemia or arrhythmia intraoperatively. On the contrary there were episodes of bradycardia that needed acute drug intervention in some patients of clonidine group. 2 patients had to be given IV glycopyrrolate 0.2 mg.

Adverse events during postoperative period were nausea, vomiting, shivering and restlessness. These were less in group C in comparison with placebo premedication.

Both groups had mild somnolence, which was comparable.

No side effects other than bradycardia was observed in clonidine group, but no treatment was required as no patient had HR less than <45/min.
Intensity of pain was less (as assessed by the time of first analgesic requirement in immediate postoperative period was prolonged) in patients of clonidine group in comparison with the placebo group.

IV. STATISTICAL ANALYSIS

Chi square test and Mann-Whitney Test was applied for analysis of quantitative data and following were considered -
P Value:
>0.05 - not significant
<0.05 - significant
<0.01 - very significant
<0.001 - highly significant
Z score: of 1.96 would indicate that the locations of the distributions are different at p = 0.05.

Table No.1

Variables	Group							
	Clondine				Control			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
ASA	1.27	0.45	1.00	1.00	1.27	0.45	1.00	1.00
Dose of Clonidine-3mcg/kg	154.07	39.90	152.00	91.25	158.10	26.11	154.50	41.25
Duration of surgery	2.00	0.41	2.13	0.86	2.13	0.34	2.18	0.33

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Variables	Group				Mann-Whitney Test applied		
	Clondine		Control				
	Mean Rank	Sum of Ranks	Mean Rank	Sum of Ranks	Z- value	p- value	Difference is-
ASA	30.50	915.00	30.50	915.00	0.000	1.000	Not significant
Dose of Clonidine-3mcg/kg	29.65	889.50	31.35	940.50	-0.378	0.706	Not significant
Duration of surgery	27.73	832.00	33.27	998.00	-1.233	0.217	Not significant

Table No.2
COMPARISON OF HEART RATE AT VARIOUS TIME INTERVALS BETWEEN CLONIDINE AND CONTROL GROUPS

Heart rate at-	GROUP							
	CLONIDINE				CONTROL			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Baseline	77.97	7.22	77.50	10.00	76.47	7.31	77.00	11.50
Pre induction	72.77	8.10	72.00	12.00	78.13	7.09	77.50	10.25
Post intubation	80.50	8.69	81.50	11.50	91.33	7.14	89.50	6.75
Pre insufflations	71.20	8.28	72.50	11.75	75.30	6.60	74.50	11.25
Post insufflation- 15 min	69.87	8.23	69.50	11.00	77.80	6.99	77.00	12.25
Post insufflations-30 min	67.87	7.63	68.00	11.50	77.37	6.49	77.00	9.75
Post insufflations-45 min	67.60	7.94	68.00	9.00	77.70	646	78.00	10.50
Post insufflations-60 min	66.28	7.66	66.00	6.50	78.59	6.51	78.00	11.00
Post insufflation-75 min	65.20	8.17	66.00	8.00	79.24	7.53	79.00	14.00
Post insufflations-90 min	64.35	9.12	65.00	12.25	79.46	6.61	79.50	10.50
Post insufflation-105 min	62.65	8.17	65.00	13.50	78.50	5.71	79.50	7.25
Post insufflation-120 min	64.20	9.57	65.00	13.50	78.44	6.06	79.00	10.00
Exsufflation	67.27	7.73	67.00	8.00	73.13	5.78	72.00	8.00
Post-extubation	79.93	6.67	80.00	10.75	92.00	4.09	91.50	6.00
Post –op-30 min	71.77	5.84	70.00	6.00	78.50	6.83	78.50	14.25
Post-op-60 min	69.87	6.10	70.00	6.25	80.33	5.74	81.00	10.00
Post-op-90 min	68.13	6.77	68.00	5.00	78.03	4.58	78.50	4.75
Post-op-120 min	68.53	4.61	68.00	5.00	75.53	3.80	75.00	6.00

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Heart rate at-	GROUP				Mann-Whitney Test applied		
	CLONIDINE		CONTROL				
	Mean Rank	Sum of Ranks	Mean Rank	Sum of Ranks	Z-value	p-value	Difference is-
Baseline	32.02	960.50	28.98	869.50	-0.675	0.500	Not significant
Pre-induction	24.60	738.00	36.40	1092.00	-2.622	0.009	Significant
Post-intubation	20.18	605.50	40.82	1224.50	-4.582	4.61E-06	Significant
Pre-insufflation	26.57	797.00	34.43	1033.00	-1.748	0.081	Not significant
Post-insufflation-15 min	22.23	667.00	38.77	1163.00	-3.674	0.0002	Significant
Post-insufflation-30 min	20.55	616.50	40.45	1213.50	-4.421	9.82 E-06	Significant
Post-insufflation-45 min	20.22	606.50	40.78	1223.50	-4.568	4.93 E-06	Significant
Post-insufflation-60 min	18.12	525.50	40.88	1185.50	-5.137	2.80 E-07	Significant
Post-insufflation-75 min	15.56	389.00	37.79	1096.00	-5.187	2.14 E-07	Significant
Post-insufflation-90 min	12.93	258.50	32.77	917.50	-4.845	1.27 E-06	Significant
Post-insufflation-105 min	9.88	168.00	25.67	462.00	-4.562	5.07 E-06	Significant
Post-insufflation-120 min	6.50	65.00	13.89	125.00	-2.860	0.0042	Significant
Exsufflation	22.60	678.00	38.40	1152.00	-3.509	0.0004	Significant
Post-extubation	17.02	510.50	43.98	1319.50	-5.988	2.12 E-09	Significant
Post-op-30 min	21.97	659.00	39.03	1171.00	-3.800	0.0001	Significant
Post-op-60 min	18.63	559.00	42.37	1271.00	-5.273	1.35 E-07	Significant
Post-op-90 min	18.42	552.50	42.58	1277.50	-5.379	7.49 E-08	Significant
Post-op-120 min	18.88	566.50	42.12	1263.50	-5.171	2.33 E-07	Significant

Table No.3
COMPARISON OF MEAN ARTERIAL PRESSURE AT VARIOUS TIME INTERVALS BETWEEN CLONIDINE AND CONTROL GROUPS

Mean arterial pressure at-	GROUP							
	CLONIDINE				CONTROL			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Baseline	94.64	7.32	95.33	13.33	94.00	6.06	93.67	9.25
Pre induction	90.16	6.57	90.33	11.50	94.68	7.71	92.83	9.33
Post intubation	91.94	7.24	93.33	13.33	111.19	7.84	108.00	11.50
Pre insufflations	84.70	6.08	84.33	10.33	91.28	4.53	91.17	6.50

Post insufflation- 15 min	96.60	5.90	96.50	9.25	113.11	8.35	111.83	7.33
Post insufflations-30 min	92.62	5.87	91.50	8.75	114.61	11.16	111.67	10.08
Post insufflations-45 min	90.07	6.25	89.50	8.83	110.74	9.51	108.50	8.75
Post insufflations-60 min	88.20	4.11	88.50	6.25	111.80	10.69	107.00	11.00
Post insufflation-75 min	85.48	3.95	85.33	5.17	108.79	7.81	107.33	7.17
Post insufflations-90 min	86.46	4.88	85.00	7.67	108.50	7.56	106.50	6.83
Post insufflation-105 min	87.61	5.41	86.67	11.50	108.49	8.42	105.67	11.33
Post insufflation-120 min	86.15	4.10	86.67	6.83	107.85	9.51	103.67	19.67
Exsufflation	84.64	6.18	82.83	6.25	97.36	5.49	97.33	5.92
Post-extubation	95.71	4.43	95.00	6.17	112.08	7.25	111.00	6.25
Post –op-30 min	89.78	5.20	91.17	7.33	98.03	5.15	97.00	9.33
Post-op-60 min	87.11	4.16	87.00	6.33	99.18	5.03	100.33	9.50
Post-op-90 min	85.09	5.16	84.67	7.17	96.33	3.86	95.67	6.33
Post-op-120 min	85.30	4.70	83.33	8.33	93.36	4.12	92.33	4.83

Heart rate at-	GROUP				Mann-Whitney Test applied		
	CLONIDINE		CONTROL				
	Mean Rank	Sum of Ranks	Mean Rank	Sum of Ranks	Z-value	p-value	Difference is-
Baseline	31.87	956.00	29.13	874.00	-0.607	0.544	Not significant
Pre-induction	25.67	770.00	35.33	1060.00	-2.146	0.032	Significant
Post-intubation	15.73	472.00	45.27	1358.00	-6.551	5.71E-11	Significant
Pre-insufflation	21.55	646.50	39.45	1183.50	-3.972	7.12E-05	Significant
Post-insufflation-15 min	16.40	492.00	44.60	1338.00	-6.256	3.95E-10	Significant
Post-insufflation-30 min	15.80	474.00	45.20	1356.00	-6.521	6.99E-11	Significant
Post-insufflation-45 min	15.80	474.00	45.20	1356.00	-6.522	6.95E-11	Significant
Post-insufflation-60 min	14.50	406.00	43.00	1247.00	-6.483	9.01E-11	Significant
Post-insufflation-75	13.00	325.00	40.00	1160.00	-6.291	3.16E-10	Significant

min							
Post-insufflation-90 min	10.05	191.00	33.46	937.00	-5.747	9.09E-09	Significant
Post-insufflation-105 min	9.29	158.00	26.74	508.00	-4.961	7.02E-07	Significant
Post-insufflation-120 min	5.00	45.00	14.00	126.00	-3.578	0.0003	Significant
Exsufflation	17.98	539.50	43.02	1290.50	-5.555	2.78E-08	Significant
Post-extubation	16.12	483.50	44.88	1346.50	-6.382	1.74E-10	Significant
Post-op-30 min	19.72	591.50	41.28	1238.50	-4.788	1.68E-06	Significant
Post-op-60 min	16.42	492.50	44.58	1337.50	-6.253	4.02E-10	Significant
Post-op-90 min	16.63	499.00	44.37	1331.00	-6.156	7.45E-10	Significant
Post-op-120 min	18.75	562.50	42.25	1267.50	-5.219	1.80E-07	Significant

Table No 4

Variables	GROUP							
	CLONIDINE				CONTROL			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
SEDATION SCORE- 1 HOUR POST OP	1.43	0.50	3.00	1.00	1.57	0.57	3.50	1.00
TIME OF FIRST ANALGESIA REQUIREMENT (OPIOIDS/NSAIDS)	2.34	0.54	2.28	0.66	1.11	0.77	1.00	1.71

Variables	Group				Mann-Whitney Test applied		
	CLONIDINE		CONTROL				
	Mean rank	Sum of Ranks	Mean rank	Sum of Ranks	Z-value	p-value	Difference is
SEDATION SCORE- 1 HOUR POST OP	24.13	724.00	36.87	904.00	-2.971	0.003	Significant
TIME OF FIRST ANALGESIA REQUIREMENT (OPIOIDS/NSAIDS)	45.50	1365.00	15.50	465.00	-6.660	2.73E-11	Significant

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V. DISCUSSION

Pneumoperitoneum during laparoscopic surgery, especially carbon dioxide gas insufflation, produces significant hemodynamic changes in healthy patients. Hypertension and tachycardia accompanied by increased sympathetic nervous system activity may lead to an imbalance between myocardial oxygen demand and supply. The cardiovascular changes associated with laparoscopy is an increase in systemic vascular resistance (SVR), mean blood pressure(MAP) and myocardial filling pressures, accompanied by a fall in the cardiac index (CI). Heart rate does not change or increases only slightly.[6]

The increase in SVR is not only related to mechanical factors but also neurohumoral factors as it outlasts the end of pneumoperitoneum. The neurohumoral factors like catecholamines (norepinephrine and epinephrine), prostaglandins, the renin angiotensin system especially vasopressin are potential mediators. These surges are reasonably expected to cause an increase in systemic vascular resistance and mean arterial pressure. These changes can be detrimental especially in elderly patients.

Clonidine premedication has been proved to prevent perioperative myocardial ischemia by improving myocardial oxygen balance.[8]

It causes a reduction of tonic sympathetic outflow (documented to decrease plasma catecholamine levels) and prevents activation of RAAS (renin angiotensin aldosterone system) seen as decreased plasma renin activity. Oral clonidine premedication decreases the release of pro-inflammatory cytokines interleukin (IL)-6, IL-1b and tumour necrosis factor and stress hormones cortisol and adrenocorticotropic hormone (ACTH).

The drug has been recently used for anaesthetic premedication, providing sedative, anxiolytic and analgesic effects that reduce the requirement for IV and volatile anaesthetics and narcotics.

Clonidine smoothed the changes in arterial pressure, HR, SVR and cardiac output during laparoscopic surgery (as seen in many studies), which are caused by CO2 PP. These benefits are mediated by a reduction of neurohumoral secretion secondary to stress induced sympatho-adrenal hyperactivation.

Clonidine premedication prevents sympathetic hyperactivity but does not suppress hypothalamo pituatary adrenocortical responses in patients undergoing laparoscopy.

Clonidine effects are not only limited to the pre and intra-operative period but also extend to postoperative period. The only limitation is that it cannot be applied to patients presenting for emergency surgery.

Joris et al used very high dose of clonidine - 8 mcg/kg for reducing the level of catecho lamine and vasopressin following PNO. Malek et al used 150 mcg/kg of clonidine as IV infusion and intramuscularly while Sung et al and Yu et al used 150 ug/kg of oral clonidine as premedication for maintenance of hemodynamic stability during PNO.

MEAN HEMODYNAMIC VALUES WERE AS FOLLOWS-

Thus clonidine premedication was able to effectively blunt the cardiovascular response to surgical stress especially pneumoperitoneum and achieve hemodynamic stability. Similar findings were reported by Aho et al ,Joris et al, Malek et al, Sung et al, Yu et al and Laisalmi et al.

			CLONIDINE	CONTROL GROUP
PRE INDUCTION	HR 72.77+/-8.1 MAP 90.16+/-6.57			78.13+/-7.09 94.68+/-7.71
POST INTUBATION	HR 80.50+/-8.69 MAP 91.94+/-7.24			91.33+/-7.14 111.19+/-7.84
POST INSUFFLATION	HR	30 MIN 60 MIN 90 MIN	67.87+/-7.63 66.28+/-7.66 64.35+/-9.12	77.37+/-6.49 78.59+/-6.51 79.46+/-6.61
	MAP	30 MIN 60 MIN 90 MIN	92.62+/-5.87 88.20+/-4.11 86.46+/-4.88	114.61+/11.16 111.80+/10.69 108.50+/-7.56
POST EXTUBATION	HR 79.93+/-6.67 MAP			92.00+/-4.09 112.08+/-7.25

	95.71+/-4.43		
POST OPERATIVE	HR	30 MIN	7 1.77+/-5.84 78.50+/-6.83
		60 MIN	69.87+/-6.10 80.33+/-5.74
	MAP	30 MIN	89.78+/-5.20 99.18+/-5.03
		60 MIN	87.11+/-4.16 96.33+/-3.86

Thus clonidine premedication was able to effectively blunt the cardio vascular response to surgical stress especially pneumoperitoneum and achieve hemodynamic stability. Similar findings were reported by Aho et al. Joris et al, Malek et al. Sung et al. Yu et al and Laisalmi et al.

In our study the depth of anaesthesia was viewed by the reflection of cardiovascular variables (HR, MAP) at an inspired isoflurane concentration greater than 0.6-0,8%. Electroencephalography was not applied to monitor the neurophysiologically defined depth of anaesthesia.

Entholzner et al showed that premedication with clonidine would result in a synergistic effect on the central nervous system which was well correlative with the neurophysiologically defined depth of anaesthesia. As clonidine would blunt the sympathetic outflow, evaluation of anaesthetic depth solely based o the cardiovascular response to surgical stress could be unreliable and unrealistic and patients premedicated with clonidine would likely be subjected to inadequate anaesthesia. However the fact that none of our patients in the clonidine group had intraoperative awareness or recall of introperative events might suggest that the depth of anaesthesia in these patients was sufficient or acceptable.

Anxiolysis in the clonidine group was better than in the placebo group. Patients of clonidine group were much calmer than patients of the control group. These findings were also reported by Beer et al.

No patients with Clonidine premedication suffered from respiratory depression in our study, which coincided with Sung cs et al, Jarvis et all and Prause et al.

The number of analgesics required in the placebo group was also higher than in the clonidine group. Only 4 patients of the clonidine group had to be given tramadol within 2 hours postop as an additional analgesic in contrast to 22 patients in the non-clonidine group who received the same This postoperative anaigesic effect of clonidine in our study was in agreement with reports by Mikawa et al, Samso et al, Segal et al and Behamou et al. Despite the fact that clonidine was not a pure analgesic and 150 ug oral Clonidine premedication without another postoperative supplement could not completely relieve postoperative pain, clonidine premedication provided additional postoperative analgesia. The decrease in patient demand analgesia could also improve post-operative care.

Thus clonidine, an alpha agonist, has been shown to decrease peripheral sympathetic outflow without increasing the baroreceptor reflex and decreases the anaesthetic requirement.

Thus it appears to be an appropriate drug for premedication in laparoscopic surgery to fulfill the anaesthetic aims of reducing stress response and subsequent adverse events.

VI. CONCLUSION

Premedication with oral low dose clonidine provides stable perioperative hemodynamics as revealed by less acute cardiovascular events that needed rescue drugs and protection against stress response triggered by pneumoperitoneum in patients undergoing laparoscopic surgery.

Thus low dose oral clonidine 3mcg/kg can be reasonably recommended as a routine premedication for all laparoscopic procedures.

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