VOLUME-7, ISSUE-2, FEBRUARY-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Anaesthesiology

A STUDY OF EFFECTS OF PREMDICATION WITH ORAL CLONIDINE ON HAEMODYNAEMIC CHANGES IN PATIENTS UNDERGOING LAPAROSCOPIC SURGERIES

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ABSTRACT

Objectives To assess the efficacy of oral clonidine 2-2.5mcg/kg as a premedication and its effect on haemodynamic changes associated with creation of pneumoperitoneum in laparoscopic surgery.Finally to evaluate and compare the side effects and complications in control and study group.

Methodology The patients were randomly allocated to two groups of 30 each study and control group.The study group received oral clonidine 2-2.5mcg with a sip of water 90 min prior to surgery.The control group received ora vit. c tablets as placebo with a sip of water 90 min prior to surgery. Systematic arterial pressure including the systolic diastolic and mean arterial pressure heart rate SpO_2 and $EtCO_2$ were timely recorded .

Results The results of the study indicate that premedication with oral clonidine (2-2.5mcg) in laparoscopic surgeries effectively counteracts the haemodnamic changes due to creation of pneumoperitoneum.The observations were discussed in terms of pulse rate , blood pressure SpO_2 ETCO2, post operative pain defined by VAS sedation score and side effects and it wasseen that Clonidine causes clinically significant reduction in pulse rate and blood pressure intraoperatively. Clonidine treated patients were sedated and comfortable postoperatively .The incidence of side effects was minimum in clonidine treated patients.

Conclusion. Premedication with oral clonidine (2-2.5mcg/kg) proved better than placebo in counteracting the haemodynaemic changes in laparoscpic surgeries.Clonidine causes clinically significant reduction in pulse rate and blood pressure intraoperatively. Clonidine treated patients were sedated and comfortable postoperatively .The incidence of side effects was minimum in clonidine treated patients.

KEYWORDS : SpO_2 (Saturation) and EtCO2(End tidal carbon dioxide) Laparoscopic cholecystectomy; Pneumoperitoneum, Haemodynamic response; Clonidine premedication.

INTRODUCTION

One of the greatest transformations within the history of surgery has been the paradigmatic shift away from open surgery and into the realm of operative laparoscopy, an approach that truly captured all that minimally invasive surgery was meant to mean.Laparoscopic surgery, also called minimally invasive surgery (MIS), bandaid surgery, keyhole surgery, or pinhole surgery is a modern surgical technique in which operations is the abdomen are performed through small incisions (usually 0.5-1.5cm) as compared to larger incisions needed in traditional surgical procedures.

Commonly done procedure are cholecystectomy, appendicectomy, varicocele repair, hernioplasty, adhesiolysis, diagnostic laparoscopy, thoracoscopy, myomectomies, endometriosis, infertility, tubal ligation etc. Benefits are reduced recovery time, rapid return to work , less post op ileus, reduced fasting and iv fluids , and improved cosmetic appearance.Because of these evident advantages laparoscopy have become popular worldwide and accepted by surgeons as well as by the patients.[1]

Laparoscopy (or peritoneoscopy) procedure allowing endoscopic access to the peritoneal cavity after insufflations of a gas to create space between the anterior abdominal wall & the viscera. The space is necessary for the safe manipulation of the instruments ad organs . The high solubility of CO_2 increases systematic absorption by the vasculature of the peritoneum this combined with smaller tidal volumes because of poor lung comlication , leads to increased arterial CO_2 levels which is known as hypercarbia if hypercarbia allowed to develop will stimulate the sympathetic nervous system and thus increase heart rate blood pressure and the risk of dysrhythmias these effects can prove especially challenging in patients with restrictive lung disease impaired cardiac function or intravascular volume depletion

Today as equipment and techniques improved and a greater number as well as more involved types of surgery are performed using laparoscopy . as a result of the frequency and complexity of much of this surgery it is imperative that the anaesthesiologist has the clear understanding of the procedure the physiologic changes and the potential complications. Major anaesthetic issues in laparoscopy are those related to creation of pneumoperitoneum and raised intra abdominal pressure and the attempts to find a suitable and safer agent and technique have been going on steadily. Clonidine which is an imidazoline compound and a selective alpha 2 adrenoceptor agonist is potent anti hypertensive drug and only recentrly it's anaesthtic properties in humans have been highlighted this drug is rapidly gaining popularity as it is effective in decreasing heart rate and arterial pressure. clonidine decreases the requirements for both IV and volatile anaesthetics numerous previous reports indicate that systematic as well as regional administration of clonidine has anaesthetic advantage which includes reduction of anaesthetic requirement improving haemodynamic stability and providing analgesia .Clonidine also alters esponse to ephedrine and atropine to clinical doses and attenuates the sympatho-adernal response to intubation .[2]

METHODOLOGY

Study population. The presen study was conducted in a prospective randomised fashion on 60 ASA grade I and II patients of age group 20-50 years in the department of anaesthesiology MGM medical college and MY hospital indore M.P. scheduled to undergone elective laparoscopic surgery.

Informed consent was obtained from all the patients followed by their preanaesthetic check up where detailed history was taken patients investigations were carried out.The patients were randomly allocated to two groups of 30 each study and control group.

- The study group received oral clonidine 2-2.5mcg with a sip of water 90 min prior to surgery.
- The control group received ora vit. c tablets as placebo with a sip of water 90 min prior to surgery.

Exclusion Criteria:-

1. patients with history of-myocardial infarction,chronic obstructive pulmonary disease diabetes mellitus ,asthma,valvular heart disease,congestive cardiac failure

2. Hypovolemic patients
3. Patients concomitantly talking clnidine beta blocker MAO inhibitors alpha methyl dopa benzodiazepine were also excluded

Baseline pulse rate respiratory rate systolic blood pressure diastolic blood pressure mean arterial pressure $EtCO_2$ SpO_2 and ECG were recorded before induction preloading done with ringer lactate 10ml/kg body weight.After pneumoperitoneum necessary changes in tidal volume respiratory rate were made to maintain normocapnia throughout the procedure any rise in mean arterial pressure more than 20% from the baseline was treated with propofol infusion 100-200mcg/kg/min.Systematic arterial pressure including the systolic diastolic and mean arterial pressure heart rate SpO_2 $EtCO_2$ and elecrocardiography (ECG) and ST segment analysis were recorded at the following points of time :-

1. Prior to induction
2. Befre pneumoperitoneum
3. 15 minutes after pneumoperitoneum
4. 30 minutes after pneumoperitoneum
5. 45 minutes after pneumoperitoneum
6. Ten minutes after release of co_2 and
7. Ten minutes afer extubation

In the early post operative period they were monitored for any evidence of complications or adverse events.Degree of sedation was closely monitored in patients of both the groups it was based on scoring system introduced by Chernik et al in 1990.

SEDATION SCORING

0 - wide awake
1 - sleeping comfortably but responding to verbal command
2 - deep sleep but arousable
3 - deep sleep not arousable

Intensity of pain assessed by using 10 point visual analogue scale (VAS) assessment of pain was done by patients themselves for this visual analogue scale (VAS) was used.The VAS was first described by Pilowsky aand bond MR in 1966 it is a 10 cm scale with 100 divisions drawn on white paper representing the continuum of pain. the top of scale at 100 represents maximum unbearable pain which the patient can imagine while the baseline 0 represents no pain.

LINEAR VISUAL ANALOGUE SCALE

VAS score rating -

- 0 - no pain
- 1-25 - mild pain (slightly uncomfortable)
- 26-50 - moderate pain (uncomfortable but can cope)
- 51-75 - severe pain (crying uncomfortable)
- 76-100 - very severe pain (unbearable)

The patient was asked to mark on the scale the degree of pain that he was having at that moment degree of analgesia was taken as distance between the mark and 100 and recorded as % of pain relief recording was done at 30 minute intervel till the patient had no relief.

Complications

Patients were closely observed postoperatively for 24 hrs to note the complications like nausea, vomiting, drowsiness, dryness of mouth , hypertension , bradycardia, shivering, itching, all relevant data were recorded in proforma prepared for the study and results thus obtained were subjected to statistical analysis. student test was used for parametric values while chi square test was used for non parametric values. p was computed and p value <0.005 was considered statistically significant . relevant literature was reviewed and discussed with findings of other workers.

OBSERVATION TABLES

The present study entitled "study of effect of premdication with oral clonidine (2-2.5 mcg) on haemodynamic changes in patients undergoing laparoscopic surgeries" was carried out in department of Anaesthesiology MGM medical college Indore (MP).The study was carried out of 60 patients of ASA grade I and II who underwent elective laparoscopic surgery.

TABLE -1 PREOPERATIVE ASSESSMENT

Parameters	Control Group	Study Group
ASA grade	Grade I -24, Grade II-6	Grade I-23, Grade II-7
Pulse rate	802+8.21	78.8+10.1
Systolic blood pressure	123+7.5	121.9+9.9
Diastolic blood pressure	75.6+8.5	78.5+6.3
Mean arterial pressure	90.4±7.3	86.7±9.02
SpO2	98.4±1.10	98.6±1.2

The difference in the base line data of each group was statistically insignificant (P>0.05)

TABLE -2 VARIATION OF PULSE RATE

Period of observation	Control group	Study Group
Prior to induction	81.6±10.0	83.4±9.8
After laryngoscopy and intubation	96.3±18.0	86.8±13.3
Before pneumoperitoneum	82.4±9.08	82.0±6.7
15 min. after pneumoperitoneum	93.4±12.8	84.09±9.07
30 min. after pneumoperitoneum	90.9±15.2	82.1±11.7
45 min. after pneumoperitoneum	91.02±16.7	81.3±10.8
10 min. after release of CO2	89.02±15.2	81.8±7.01
10 min. after extubation	86.5±10.9	80.6±7.5

The difference in pulse rates of both the groups were significant (P<0.05) except before induction and creation of pneumoperitoneum.

TABLE-3 VARIATION IN MEAN ARTERIAL PRESSURE

Peroid of observations	Control group	Study group
Prior to induction	94.7±10.4	91.2±11.07
After larygoscopy and intubation	111.0±18.2	100.8±12.8
Before pneumoperitoneum	97.5±15.1	92.4±17.01
15 min. after pneumoperitoneum	108.5±21.3	97.7±11.9
30 min. after pneumopertioneum	110.8±19.5	95.9±12.3
45 min. after pneumoperitoneum	109.9±17.02	96.0±14.6
10 min after release of CO2	98.9±15.6	93.9±12.8
10 min. after extubation	99.0±10.9	94.1±10.5

The difference in mean arterial pressure in two groups were statistically significant except prior to induction, before pneumoperitoneum and 10 min. after extubation. Variation from the base line value and the difference in Spo2 in both the groups during different time interval was statistically insignificant (P>0.05).

TABLE-4 SEDATION SCORE

Grade	Group I	Group II	Total
0	30(100%)	9(30.0%)	39
1	-	16(53.3%)	16
2	-	5(16.67%)	5
3	-	-	0
Total	30	30	60

In Group I all the patients were having sedation score of O.Better sedation score was obtained by addition of clonidine.

TABLE-5 MEAN VISUAL ANALOG SCALE (VAS) SCORE

Duration in hours	Control group	Study group
2 hours	15.83±5.58	1.2±0
4 hours	47.83±6.67	2.67±2.50
6 hours	73. ±7.83	7.167±8.97
8 hours	83.86±5.45	18.83±16.01

Mean VAS score was significantly lower in study group as compared to control group. The difference between the mean VAS score at different time, among both the groups, was statistically significant (p<0.001)

RESULTS The results of the study indicate that premedication with oral clonidine (2-2.5mcg) in laparoscopic surgeries effectively counteracts the haemodnamic changes due to creation of pneumoperitoneum.The observations were discussed in terms of pulse rate , bloo pressure SpO_2 ETCO2, post operative pain defined by VAS sedation score and side effects.

The difference in the base line data of each group was statistically insignificant (P>0.05The difference in pulse rates of both the groups were significant (P<0.05) except before induction and creation of pneumoperitoneum. The difference in mean arterial pressure in two groups were statistically significant except prior to induction, before pneumoperitoneum and 10 min. after extubation. Variation from the base line value and the difference in Spo2 in both the groups during different time interval was statistically insignificant (P>0.05). Mean VAS score was significantly lower in study group as compared to control group. The difference between the mean VAS score at different time, among both the groups, was statistically significant (p<0.001).

In Group I all the patients were having sedation score of O.Better sedation score was obtained by addition of clonidine. In study group hypotension and bradycardia is more as compared to control group.In study group 9 patients had dryness of mouth and none in control group.In both groups 2 patients had episodes of shivering post operatively.

STASTISTICAL ANALYSIS-
Data was analyzed using SPSS 20 statistical package. A descriptive analysis was done on all variables to obtain a frequency distribution. The mean + SD and ranges were calculated for quantitative variables. Continuous variables were compared by the Student t test. Proportions were analyzed with the chi-square test. A P value of 0.05 or less was considered statistically significant

DISCUSSION
Premedication is considered important in anesthesia . Premedication before anesthesia is considered as an important stage in the process of anesthesia. The goals are to produce anxiolysis, sedation, amnesia, analgesia, salivation reduction, vagolysis, sympathicolysis, to reduce gastric secretion and acidity and to prevent post-operative nausea and vomiting (PONV). Benzodiazepines are the most commonly used premedication agents in children. They produce anxiolysis, sedation, amnesia and reduce PONV. Despite their efficacy in the treatment of emergence agitation, midazolam premedication has not been reported to prevent it. Impaired post-operative cognitive function has been reported after midazolam premedication in children.The α2 adrenoceptor agonist (α2aa) clonidine has been shown to exhibit anesthetic, sedative, sympathicolytic and analgesic properties.Clonidine, an α2 adrenoceptor agonist, is gaining popularity among anesthesiologists. The goal of the present study was to perform a meta-analysis of studies comparing premedication with clonidine to a placebo.

The purpose of the study done by Wright PM et al was to evaluate oral clonidine in a dose of 0.3 mg as a routine premedicant. Sixty-nine normotensive female patients were studied in a randomized double-blind investigation in which clonidine was compared with an inert treatment. It was seen that Clonidine produced a significant reduction in anxiety (P < 0.05) and sedation and a reduction in the sleep dose of methohexitone (P < 0.05). Tachycardia in response to intubation was attenuated by clonidine (P < 0.05). However, the magnitude of the increase in arterial pressure after intubation was not affected. Intraoperative and postoperative hypotension were common after premedication with clonidine 0.3 mg and caution is urged in its use as a premedicant [1]

Dahmani S et.did a meta analysis of published studies and saw that premedication with clonidine is superior to benzodiazepines. . Almenrader N etal also studied premedication in children: a comparison of oral midazolam and oral clonidine. Benzodiazepines are the most commonly used premedication agents in children. They produce anxiolysis, sedation, amnesia and reduce PONV. Despite their efficacy in the treatment of emergence agitation, midazolam premedication has not been reported to prevent it. Impaired post-operative cognitive function has been reported after midazolam premedication in children.The α2 adrenoceptor agonist (α2aa) clonidine has been shown to exhibit anesthetic, sedative, sympathicolytic and analgesic properties.Clonidine, an α2 adrenoceptor agonist, is gaining popularity among anesthesiologists.Both studies were similar and their results were in support with our study results .[2,3]

Clonidine, an alpha 2-adrenoceptor agonist, has been shown to be effective as a preanesthetic medication in adults. The current study by Mikawa K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H. shows efficacy of oral clonidine premedication in children.In this prospective, randomized, double-blind, controlled clinical trial, 105 children, aged 4-12 yr, undergoing elective ophthalmologic surgery received 0.4 mg/kg diazepam, 2 micrograms/kg clonidine, or 4 micrograms/kg clonidine orally. Clonidine produced significant sedation, and the effect was dose related. Clonidine, 4 micrograms/kg, provided better quality of separation and acceptance of mask than the two other regimens. This dose of clonidine attenuated the increases in blood pressure and heart rate after tracheal intubation. No clinically significant perioperative hypotension or bradycardia was observed. These data indicate that, even in pediatric surgery, the combination of 4 micrograms/kg and 0.03 mg/kg oral clonidine is an effective premedication. However, the safety and optimal dose of clonidine in this setting remain to be determined.[4]

Taittonen MT studied effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state .Both drugs are potent anti hypertensive and only recentrly their anaesthtic properties in humans have been highlighted. These drugs are rapidly gaining popularity as they are effective in decreasing heart rate and arterial pressure. Clonidine decreases the requirements for both IV and volatile anaesthetics numerous previous reports indicate that systematic as well as regional administration of clonidine has anaesthetic advantage which includes reduction of anaesthetic requirement improving haemodynamic stability and providing analgesia.[5]

Kumar A, Bose S et al in a randomized double-blind study,saw the effects of clonidine premedication as a sedative, anxiolytic, analgesic and oculohypotensive agent .They studied in 100 elderly patients (62 to 65 ± 10 years, ASA grade I–II) undergoing elective intraocular surgery under local anaesthesia.The control group (Group A, n = 50) received oral diazepam 0.15 mg/kg 120 min before surgery and Group B (n = 50) received oral clonidine 300 μg 120 min before surgery. Two hours after the premedication, there was significantly more sedation (P<0.05) and less subjective anxiety (P<0.05) in the clonidine group than in the control group. There was a significant fall in intraocular pressure (IOP) from 20 ± 0.5 to 13 ± 0.5 mmHg (P<0.05) and significant reduction in systolic and diastolic blood pressure (BP) and heart rate (HR) (P<0.05) in the clonidine group as compared to the control group. Perioperatively, significantly more supplementation with i.v. diazepam was given in the control group than in the clonidine group (P<0.01). The incidence of intra-operative hypertension (P<0.01) and tachycardia (P<0.05) was significantly greater in the control group than in the clonidine group. A significantly larger number of patients in the clonidine group scored a Post-Anaesthesia Recovery (PAR) score of 10 as compared to the control group (P<0.01). There was no statistical difference in the postoperative Visual Analogue Scale (VAS) scores for pain, number of analgesic requests and emesis.

Hence premedication with oral clonidine in these elderly patients undergoing elective intraocular surgery produced intraoperative sedation, reduction in anxiety and decrease in intraocular pressure. Postoperative recovery was improved in the clonidine group.**[6]**

Pouttu J et al studied oral premedication with clonidine and its effects on stress responses during general anaesthesia. The effect of clonidine (4.5 μg kg^{-1}) on haemodynamics and hormonal stress responses was evaluated in 21 female patients undergoing breast surgery. The standardized general anaesthesia included diazepam as premedicant, thiopentone, enflurane, N_2O, fentanyl and vecuronium. Venous plasma concentrations of noradrenaline, adrenaline, growth hormone, vasopressin, and Cortisol were assayed at various times before, during and after surgery. Clonidine attenuated the sympathoadrenal response; arterial blood pressure and heart rate increases in association with intubation were lower in clonidine-premedicated patients. Noradrenaline levels were lower throughout and 3 h after surgery in the clonidine group ($P<0.05$). Adrenaline levels were lower in this group 2 min after intubation ($P<0.05$). Growth hormone, vasopressin and Cortisol plasma levels were increased at the end of and after surgery, with no differences between the groups. In spite of the effect on sympathoadrenal response, clonidine did not have any significant additive anxiolytic effect. Statistically significant differences were not found as to need for postoperative analgesics.[7]

Sung CS et al studied effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic surgeries .They concluded that premedication with clonidine, in comparison with midazolam, exhibited a superior effect on sedation at induction, decreased the incidence of emergence agitation and produced a more effective early post-operative analgesia. Compared with diazepam, clonidine was superior in preventing post-operative nausea and vomiting (PONV). Premedication with clonidine is superior to midazolam in producing sedation, decreasing post-operative pain and emergence agitation. However, the superiority of clonidine for PONV prevention remains unclear while other factors such as nausea prevention might interfere with this result.[8]

Das M, Ray M et al did their study on haemodynamic changes during laparoscopic cholccystectomy and saw the effect of clonidine premedication. Clonidine has been shown to reduce perioperative haemodynamic instability. The aim of the study was to investigate the clinical efficiency of oral clonidine premedication in prevention of haemodynamic response associated with pneumoperitoneum. Sixty adult patients of ASA physical status I& II, scheduled for elective laparoscopic cholecystectomy were recruited for a prospective randomized, double-blinded comparative study. They were randomly allocated to one of the two groups to receive either oral clonidine 150 gg (Group C) or ranitidine 150 mg (Group P .Significant rise in heart rate was observed following pneumoperitoneum in Group P as compared to Group C. Similarly, rise in systolic arterial pressure, diastolic arterial pressure and mean arterial pressure was more in Group P following pneumoperitoneum. Nitroglycerine drip was started in 33.3% patients in Group P to control intraoperative hypertension. Incidence of postoperative nausea-vomiting and shivering was also less in Group C.To conclude, clonidine premedication provides perioperative haemodynamic stability, hence it can be recommended as a routine premedication for laparoscopic procedure.[9]

Singh S, Arora K. Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Gupta K, Sharma D, Gupta PK. Oral premedication with pregabalin or clonidine for hemodynamic stability during laryngoscopy and laparoscopic cholecystectomy: A comparative evaluation.[10,11]

Malek J et al did study on adverse hemodynamic changes during laparoscopic cholecystectomy and their possible suppression with clonidine premedication. They also did a comparison with intravenous and intramuscular premedication. Aho M, Lehtinen AM et al studied effects of intramuscular clonidine on hemodynamic and plasma beta-endorphin responses to gynecologic laparoscopy. Both study findings are in conjunction with our study .[12,13]

CONCLUSION: On the basis of present study following conclusions were drawn:

- Premedication with oral clonidine (2-2.5mcg/kg) proved better than placebo in counteracting the haemodynaemic changes in laparoscpic surgeries.
- Clonidine causes clinically significant reduction in pulse rate and blood pressure intraoperatively.
- Clonidine treated patients were sedated and comfortable postoperatively .
- The incidence of side effects was minimum in clonidine treated patients.

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