Original Research Article

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Effect of Oral Clonidine Premedication on Perioperative Haemodynamic Response and Post Operative Analgesic Requirements for Patients Undergoing Laparoscopic Surgeries

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Abstract

Background: The first focus on haemodynamic response to laryngoscopy and tracheal intubation was done in 1950 by Burstein. King et al in (1951) described the abnormal circulatory reaction to laryngoscopy. Its association with a rise in blood pressure, tachycardia and increased level of catecholamines was highlighted by Prys-Roberts in (1971) and by Siedlecki in 1975. Recognizing the hazardous effect of such reflex reactions, many techniques were studied and clinically tried to obtund these reactions. At the same time, The first publication on diagnostic laparoscopy by Raoul Palmer appeared in the early 1950s, followed by the publication of Frangenheim and Semm. Hans Lindermann and Kurt Semmpractised CO_2 hysteroscopy during the mid-1970s. However this procedure is not risk free, In fact it produces significant changes in haemodynamically compromised patients.The hallmark of laparoscopy is creation of carbon dioxide pneumoperitonium and change in the patients position from trendelenburg to reverse trendelenburg. It also results in stress hormone responses (cortisol, epinephrine and non–epinephrine) especially when CO_2 pneumoperitonium is used concomitantly. Laryngoscopy with or without tracheal intubation amounts to a highly noxious stimulus to the homeostasis of the patient.

Aims: Designed to assess the effect of oral Clonidine premedication on hemodynamic response to endotracheal intubation and to compare intra-operative haemodynamic parameters, pain and sedation scores, time of first post-operative analgesia and dverse effects

Material and Method: Total 60 patients ASA grade I and II in the age group 20 to 55 years were included in this study and they were randomly divided into two groups:

Group 1 (n=30), patient received oral clonidine 150 mcg orally 90 min before induction

Group 2 (n=30), patients received oral vitamin C 100 mg orally 90 min before induction

All patients were posted for elective surgeries and were randomly selected.

Conclusion: The basal and perioperative arterial blood pressure and heart rate after giving premedication was lower in clonidine group as compared to placebo group. Time for 1st post-operative analgesia requirement in clonidine group was significantly prolonged in comparison with the ranitidine group.

Keywords: Clonidine; Laparoscopic Surgeries; Hemodynamic Response and Analgesia.

Introduction

Reid and Bruce in 1940, Burstein in 1950 and King, Harris in 1951described the haemodynamic response to laryngoscopy and intubation of the trachea [1]. It is characterized by hypertension, tachycardia and increased concentration of circulating catecholamines (Prys-Roberts 1971) [2]. Though transitory, they may be deleterious to the patient because of the increased cardiac work involved. They may also be associated with arrhythmias.

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Oral Clonidine, an alpha-2 agonist, which acts on the central nervous system to reduce the sympathetic outflow, has been used in this study in a dose of 150mcg to assess its usefulness in attenuating the haemodynamic response [3]. After oral intake, onset of action starts within 30-60 minutes and peak plasma concentration is reached within 90 minutes which is comparable to intravenous clonidine. Keeping in mind the cost-effectiveness and the ease of administration, oral clonidine has been used in this study. Premedication with clonidine blunts the stress response to tracheal intubation, surgical stimuli and the narcotic and anaesthetic doses are also reduced. In addition clonidine increases cardiac baroreceptor reflex sensitivity to increase in systolic blood pressure, and thus stabilizes blood pressure [4,5].

Accordingly, this study was designed to evaluate the effects of oral clonidine premedication on heamodynamic response and modulation of post-operative pain in patients undergoing laparoscopic surgeries.

Aims and Objectives

This prospective randomized, single blind, comparative study was conducted on adult patients undergoing laparoscopic surgeries with the following objectives;

- Designed to assess the effect of oral Clonidine premedication on hemodynamic response to endotracheal intubation
- To compare intra-operative haemodynamic parameters.
- To compare pain and sedation scores
- To compare time of first post-operative analgesia
- To compare both adverse effect

Material and Methods

Preanaesthetic evaluation was done a day before the proposed surgery. Relevant history was taken, physical examination carried out and cardiovascular and respiratory systems were assessed for any abnormalities. Basic routine investigations were carried out in all cases. Other investigations like blood urea, serum creatinine and chest X ray were done whenever necessary.

Patients of ASA grade I and grade II, of either sex, older than 20years but younger than 55years and scheduled for laparoscopic surgeries were included in study.

Patients not fulfilling eligibility criteria such as lack of patient consent, drug dependence, history of bronchial asthma, allergy to clonidine, hypertensive and diabetic patients, patients with severe coronary insufficiency, recent myocardial infarction, concomitant use of monoamine oxidase inhibitors, tricyclic antidepressants, or opioids and regnant patients were excluded from this study.

Study Method

All patients were advised to take tablet Alprazolam 0.5 mg before bedtime and be nil orally after 10p.m. on the preoperative day. After arrival in the pre-op room vitals were checked,peripheral venous access and standard monitoring were secured and inj. ondansetron 4mg/iv and ranitidine 50mg/iv, oral clonidine given 150mcg/90 min prior to surgery. After shifting the patient to operation theatre, base line pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, ECG, SpO_2 and intraoperatively end tidal carbon dioxide ($ETCO_2$) were recorded.

Patients were premedicated with intravenous injection glycopyrolate 0.2mg, and inj Midazolam-1mg, and sedated with pentazocine 0.6mg/kg IV, on operating table 5 min before induction of anaesthesia. Induction of anaesthesia was carried out with inj. propofol 2mg/kg with 2% lidocaine and muscle relaxant vecuronium 0.1 mg/kg given IV. After intubating the patient, maintained with propofol 100mcg/kg/min, isoflurane, N_2O/40% O_2 mixture. Controlled mechanical ventilation was applied to maintain endtidal CO_2 between 30-40 mmHg. The mean arterial blood pressure was maintained (MAP) was maintained at 20% above or below the pre – operative value by adjusting the rate of propofol.

Haemodynamics was recorded, prior to induction, 1 min after endotracheal intubation, 5 min after endotracheal intubation and every 30mins intraoperatively. At the end of surgery, patient was given neostigmine 0.05 mg/kg and glycopyrrolate 0.01mg/kg intravenously to reverse the neuromuscular blockade. The patient was extubated after a satisfactory reversal and throat suction and transferred to recovery room. Intraoperatively, all patients were infused with Ringer lactate and Dextrose normal saline in a dose of 6 ml/kg/hour in the first 30-minute and 4 ml/kg/hour subsequently till the end of surgery. Patients were followed up postoperatively at hourly intervals till 9 hours after administration of clonidine, keeping in mind the elimination half time of clonidine and VAS, sedation score and adverse events was recorded at 30min, 60min, 90min, and 120min postoperatively.

Rescue analgesia was given with Inj.Diclofenac sodium 75mg/iv over 30 min 12hrly. The following parameters were observed and noted :

1. Vital signs including pulse, systolic Blood pressure, diastolic blood pressure, SpO_2, respiratory rate, were monitored at
   1. base line
   2. pre induction
   3. 1 min after intubation
   4. 5min after intubation
   5. Start of pneumoperitoneum
   6. 30 min after intubation
   7. 15min after Release
   8. After extubation
2. Emergence times from the discontinuation of anesthesia to the removal of endotracheal tube were noted.
3. Side effects like hypotension, bradycardia, sedation, post-operative nausea and vomiting, cough shivering etc.
4. Times to requirement of first analgesic were noted. Rescue analgesia as given in the form of inj diclofenac sodium 75 mg iv.
5. Pain intensity was assessed using a 10 cm visual analog scale (VAS) 0-no pain 10-intolerable pain.

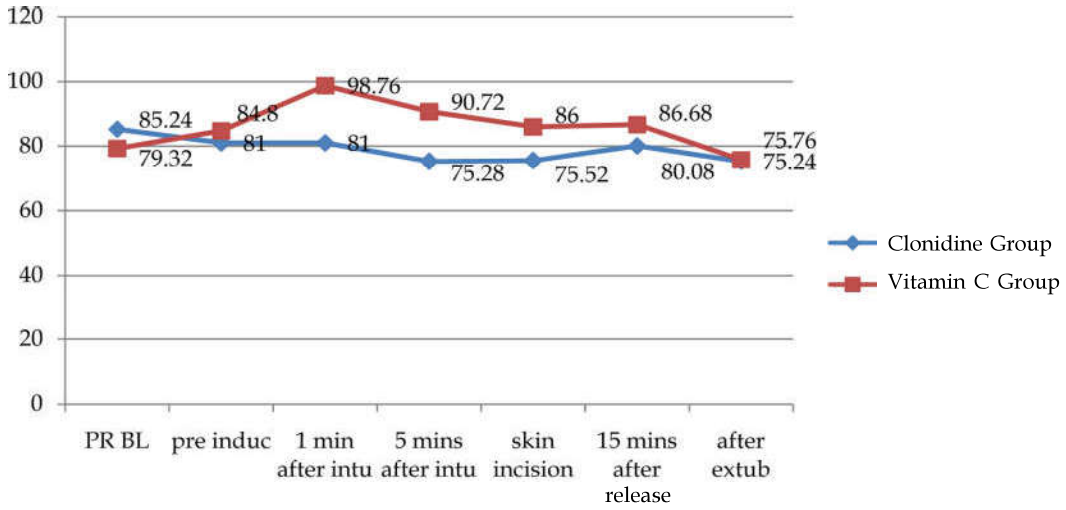
The degree of sedation was graded as

0 point - patient awake and talkative

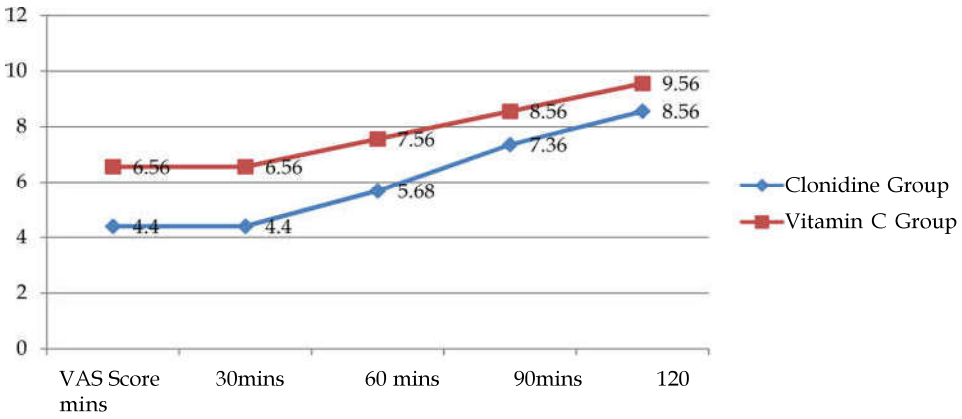
1 point - patient awake but uncommunicative

2 point – patient drowsy, quiet and easily arousable

3 point – patient asleep.



Graph 1: Mean Pulse rate for Clonidine group is significantly lower than for Vitamin C group at 1 mins, 5 mins after intubation, skin incision and 15 mins after release. (P value <0.05/0.01). However there is no significant difference in Mean Pulse Rate between Clonidine Group and Vitamin C group, pre induction and after extubation. (P value >0.05)

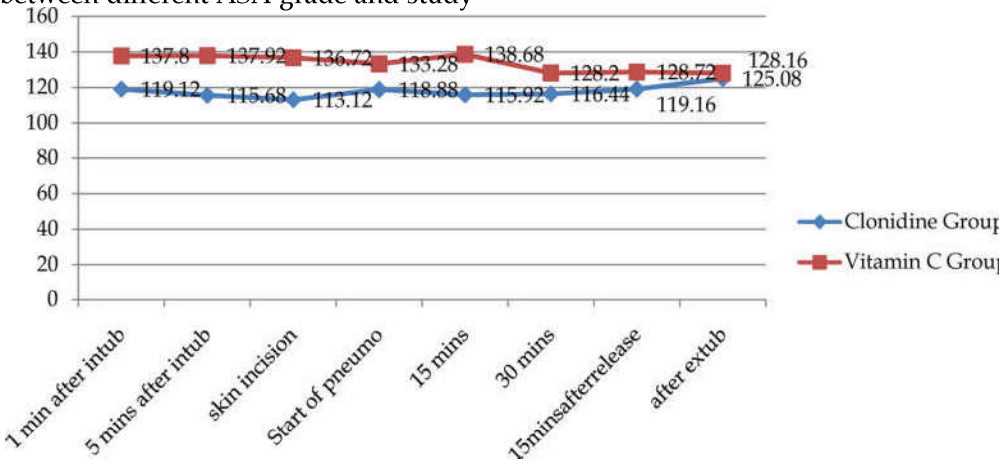


Graph 2: Mean VAS-Score for Clonidine group is significantly lower than for Vitamin C group at baseline, 30 mins, 60 mins, 90 mins and 120 mins

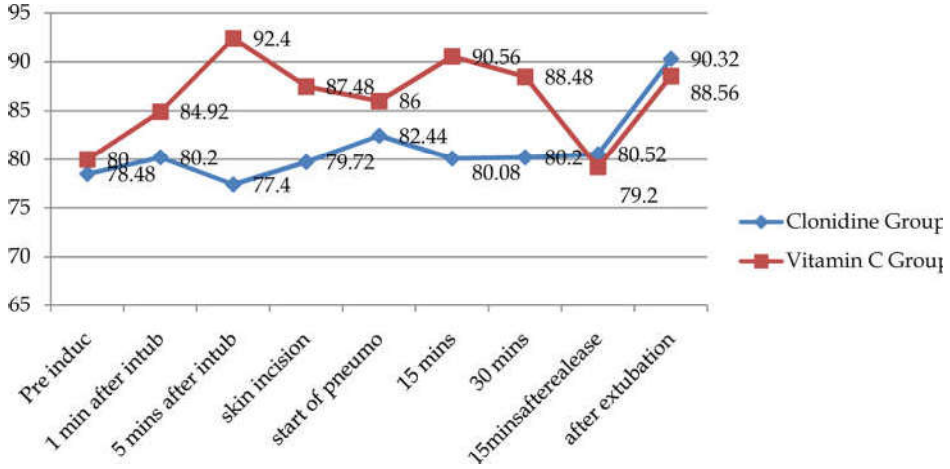
Results

There was no statistically significant difference between different age, weight and gender of study population. There was no statistically significant difference between different ASA grade and study population. The mean hemoglobin was higher in clonidine group as compared to vitamin C group though statistically not significant.

Respiratory Rate between Clonidine group and Vitamin C group are not significantly different across all observations. (P value >0.05)



Graph 3: Mean Systolic Blood Pressure for Clonidine group is significantly lower than for Vitamin C group at 1 mins, 5 mins after intubation, skin incision, start of pneumo peritoneum, 15 mins and 30 mins (P value <0.01). However there is no siginificant difference in Mean Systolic Blood Pressure between Clonidine Group and Vitamin C group after extubation. (P value >0.05)



Graph 4: Mean Diastolic Blood Pressure for Clonidine group is significantly lower than for Vitamin C group at 1 mins, 5 mins after intubation, skin incision, start of pneumo peritoneum, 15 mins and 30 mins (P value <0.05/ 0.01). However there is no significant difference in Mean Diastolic Blood Pressure between Clonidine Group and Vitamin C group pre induction, 15 mins after release and after extubation (P value >0.05)

Table 1: Trend of VAS over a period of time amongst different study group

	Group	Mean	Std. Deviation	Std. Error Mean	T value	P value
VAS-score (baseline)	Clonidine Group	4.40	0.500	0.100	-15.173	<0.01 (Highly Significant)
	Vitamin C Group	6.56	0.507	0.101		
30 min	Clonidine Group	4.40	0.500	0.100	-15.173	<0.01 (Highly Significant)
	Vitamin C Group	6.56	0.507	0.101		
60 min	Clonidine Group	5.68	0.476	0.095	-13.512	<0.01 (Highly Significant)
	Vitamin C Group	7.56	0.507	0.101		
90 min	Clonidine Group	7.36	0.490	0.098	-8.514	<0.01 (Highly Significant)
	Vitamin C Group	8.56	0.507	0.101		
120 min	Clonidine Group	8.56	0.507	0.101	-6.973	<0.01 (Highly Significant)
	Vitamin C Group	9.56	0.507	0.101		

Table 2: Emergence time in minutes amongst different study group

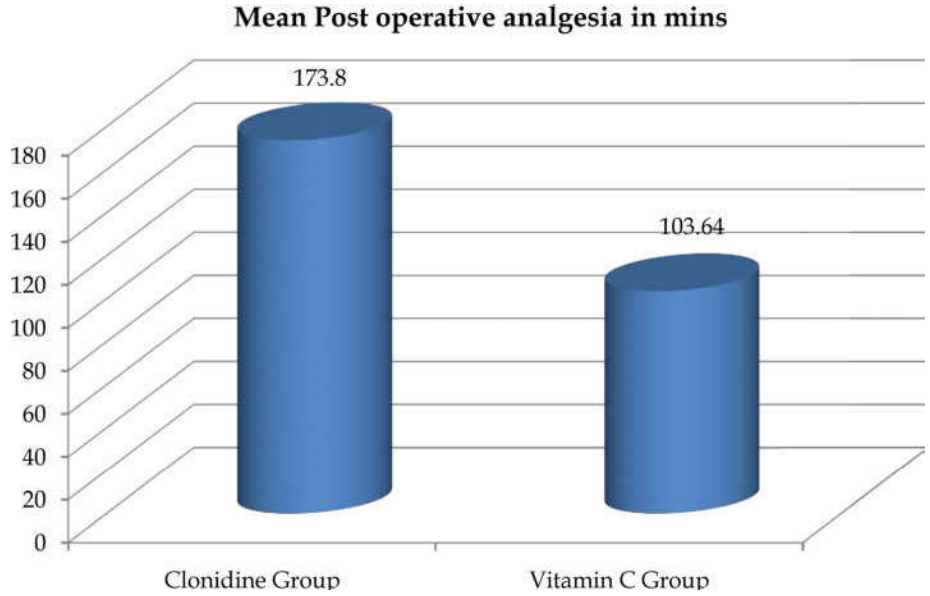
	Group	Mean	Std. Deviation	Std. Error Mean	T value	P value
Emergence time (min)	Clonidine Group	4.40	0.645	0.129	0.864	> 0.05 (Not Significant)
	Vitamin C Group	4.24	0.663	0.133		

Independent sample t test applied. T value is 0.864, P value >0.05

Table 3: Post-operative analgesia in minutes amongst different study group

	Group	Mean	Std. Deviation	Std. Error Mean	T value	P value
1st post op analgesia (min.)	Clonidine Group	173.80	17.443	3.489	15.815	< 0.01 (Highly Significant)
	Vitamin C Group	103.64	13.702	2.740		

Independent sample t test applied. T value is 15.815, P value <0.01.



Graph 5: Post-operative analgesia was significantly higher in clonidine group as compared to vitamin C group

As seen in the Table 1, SpO_2 readings between Clonidine group and Vitamin C group are not significantly different across all observations (P value >0.05).

As seen in the Table 2, Emergence time was higher in clonidine group as compared to vitamin C group though statistically not significant $ETCO_2$ readings between Clonidine group and Vitamin C group are not significantly different across all observations. (P value >0.05), except at 1 min after intubation.

Discussion

Laparoscopic surgeries have revolutionized the world of surgeries. But it also results in stress hormone responses (cortisol, epinephrine and nor epinephrine) due to pneumoperitonium and changes in position from trendelenburg to reverse trendelenburg. Clonidine is an alpha -2 adrenoceptor agonist. It shows central sympatholytic effect. Clonidine has been shown to reduce perioperative hemodynamic instability, and augments the effectsof anaesthesia.

Pneumoperitonium during laparoscopic surgery produces significant haemodynamic changes, which can be detrimental especially in elderly and haemodynamically compromised patients. Various techniques and pharmacological agents have been used to counteract these detrimental effects of pneumoperitonium.

During laparoscopic surgery procedural changesin the patient's position and surgical stress, especially following pneumoperitonium cause labile haemodynamics. The choice of anesthetic technique for upper abdominal laparoscopic surgery is mostly limited to general anesthesia with muscle paralysis, tracheal intubation and IPPV.

This study was carried out in 25 ASA grade I and II patients, to evaluate the effect of clonidine premedication on haemodynamic response and the post-operative pain associated with laparoscopic surgeries. Clonidine is rapidly and completely absorbed after oral administration and reaches peak plasma concentrations within 60-90min.

In my study tablet clonidine was given 90min before scheduled laparoscopic surgeries Clonidine, an imidazoline derivative is a selective alpha 2 adrenergic agonist. It is a potent anti-hypertensive drug. It produce dose related fall in the heart rate and blood pressure associated with decreased systemic venous resistance and cardiac output. Clonidine was administered 150MCG orally 90min before surgery in our study.

Dose of clonidine varied from 2 to 5 mcg/kg in different studies, higher dose of clonidine that is 5mcg/kg is usually required for potentiation of postoperative analgesia by intra thecal morphine. A small oral dose of clonidine decreased the incidence of perioperative myocardial ischemic episodes without affecting haemodynamic stability.

Aho et al used 3mcg /kg and 4.5mcg/kgclonidine for suppression of haemodynamicresponse to pneumoperitonium.rise in blood pressure and heart rate was less in both the groups but 4.5mcg/kg clonidine produced greater fall in the mean arterial pressure before induction [6].

Joris et al used very high dose of clonidine, 8mcg / kg for reducing the level of catecholamine and vasopressin following pneumoperitonium [7].

Malek et. al. used 150mcg of clonidine as i.v infusion and intramuscularly while Sung et al used 150mcg of oral clonidine as premedication for maintenance of haemodynamic stability during pneumoperitonium [8].

In my study, tablet clonidine 150mcg orally was given 90min. before scheduled surgery. Hypertension and tachycardia were noticeable during the application of CO_2 pneumoperitonium in the placebo group. Clonidine premedication effectively blunted the cardiovascular response to surgical stress, especially pneumoperitonium. Compared with the base line values there was significantly less increase in heart rate and SBP, DBP in the clonidine group compared to the placebo group.

Following pneumoperitonium with CO_2, patients were hyperventilated to maintain normocapnia. Every effort was made to maintain intra-abdominal pressure. Haemodynamic changes associated with pneumoperitonium were first recognized in 1947.

Diamant et al reported 35% decrease in cardiac output In a dogwith raised intraabdominal pressure of 40mmHg [9].

Ishizaki et. al. tried to evaluate the safe intra-abdominal pressure during laparoscopic surgery. They observed significant fall in cardiac output at 16 mm of Hg of intra-abdominal pressure. Haemodynamic alterations were not observed at 12 mm of Hg of intra-abdominalpressure. Based on all these observations the current recommendation is to monitor intra-abdominal pressure and to keep it as low as possible [10].

Cunningham et. al. [11] and Dorsaty et. al. (12) assessed the ejection fraction of left ventricle by trans esophageal echocardiography during pneumo-peritonium. No significant change in ejection fraction was reported up to 15mmHg of intra-abdominal pressure. Considering all these facts intra-abdominal pressure was kept below 14 mmHg.

Despite of maintaining normocapnia and keeping intra-abdominal pressure below 14mmHg significant rise in heart rate, SBP, DBP was noticed in placebo group. Rise in SBP, DBP was statistically significant. Slight fall in SBP, DBP, was noticed following premedication with clonidine. Following intubation and pneumoperitonium, increase in arterial pressure was noticed but it never crossed the base line value. Hence clonidine premedication was able to achieve haemodynamic stability during pneumoperitonium.

Similar findings were reported by Aho et. al., joris et. al., Malek et. al., Sung et. al., Yu et. al. and laisalmi et. al. [6-8,13-15]. Aho et. al. observed that 4.5mcg/kg of clonidine significantly decreased the mean arterial pressure before induction of anesthesia, so they recommended 3mcg/kg of clonidine for perioperative haemodynamic stability [6].

Joris et. al. used higher dose of clonidine for reduction of catecholamine and vasopressin associated with pneumoperitonium. Clonidine significantly reduced the concentration of catecholamine but not vasopressin and cortisol concentration [7].

Similarly Sung et. al. observed haemodynamic stability during pneumoperitonium with 150mcg clonidine. Requirement of sevoflurane was also less in clonidine group [13].

Finally Yu et. al. recommended the routine use of clonidine premedication in laparoscopic patients [14].

The adverse effects in the post op period were less in the patients who had clonidine premedication in comparison to the placebo group. Side effects were observed less in clonidine group with nausea occurring in only 10% cases as compared to placebo

group 13.3% though not significant (p>0.05). No case of Shivering and vomiting was found in clonidine group [15]. This finding corroborates with the findings of Nicholaou et. al., where they concluded that the clonidine inhibits cold thermoregulatory response due to an effect on central integration control and output from the thermoregulatory centers.

Thus he opined that clonidine can be used as an effective agent for inhibition of perioperative shivering which can adversely increase metabolic rate and cardiac work and may also disrupt surgical repair or result in wound dehiscence [16].

Clonidine increases gastrointestinal motility by decreasing sympathetic outflow and increasing parasympathetic outflow from central nervous system.Although many workers have reported the antiemetic property of clonidine, the mechanism by which it acts warrants further investigation.

In our study time of requirement for 1st dose of analgesic was prolonged in patients of clonidine in comparison with the placebo group. Most of the patients in the clonidine group required only 1 dose of during the post-operative 24hrs period while most patients in the placebo group required 2 or more than 2 doses of paracetamol 1gm i.v.

Similarly more patients in the clonidine group required no diclofenac sodium or only one dose of diclofenac sodium during the post-operative period of 24hrs, while 2 or more than 2 doses were requiredin most of the placebo group patients. The median time for 1stpost-operative analgesia in clonidine group is 172.5min. In ranitidine group is 101.5. Time for 1stpost-operative analgesia requirement in clonidine group was significantly prolonged in comparison with the ranitidine group with p value <0.05.

Conclusion

After discussing and reasoning the observations and results, study can be summarized as follows

- The basal and perioperative arterial blood pressure and heart rate after giving premedication was lower in clonidine group as compared to placebo group.
- Time for 1stpost-operative analgesia requirement in clonidine group was significantly prolonged in comparison with the ranitidine group.

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