Original Research Article

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Effect of Premedication with Intravenous Clonidine in Modulating the Haemodyanamic Responses during Laparoscopic Surgeries

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Abstract

Context: Pneumoperitoneum during laparoscopic surgeries leads to adverse effects on cardiovascular physiology which in turn compromises tissue perfusion.

Aims: To study the effect of premedication with intravenous clonidine in modulating the haemodyanamic responses during laparoscopic surgeries.

Settings and Design: Prospective randomised double blinded study.

Methods and Material: The study was conducted in a group of sixty patients undergoing laparoscopic surgeries who were randomly allocated into two groups each having thirty patients namely group green who received 2µg/kg of intravenous clonidine in 100 ml normal saline 15 minutes prior toinduction and group red who received 100 ml of plain saline 15 minutes prior to induction. Haemodyanamic parameters during induction, intubation, pneumoperitoneum and extubation were monitored. The postoperative pain scores and time to first analgesic request were documented.

Statistical Analysis used: Student's t test was used for the haemodyanamic parameters. Chi square test was used for non parametric values and corresponding p was computed. P value of <0.05 was considered statistically significant.

Results: There was a 20 to 27% increase in heart rate in group red during haemoperitoneum whereas the increase in group green (clonidine group) was 16%. The mean systolic BP varied from 134±17.75 to 95.23± 9.93 in green group whereas in red group it varied from 144±14.57 to 129.93±13.44. Postoperative visual analogue score was 3.36 in group green as compared to 7.36±1.54 in red group.

Conclusions: Patients receiving intravenous clonidine as premedication showed stable haemodyanamics and better analgesia and sedation as compared to those who didn't receive clonidine.

Keywords: Laparoscopy; Haemodyanamics; Pneumoperitoneum; Clonidine; Analgesia.

Introduction

The creation of capnoperitoneum during laparoscopic surgeries leads to adverse cardiovascular effects such as an increase in mean arterial pressure, decrease in cardiac output and increase in systemic vascular resistance which in turn compromise tissue perfusion [1,2]. Clonidine is a cost effective centrally acting alpha2 selective partial adrenergic agonist; alpha2:alpha1 selectivity ratio being 220:1. It inhibits the release of catecholamines and vasopressin [3]. The primary outcome of this study was to study the haemodynamics after premedication with intravenous clonidine in patients undergoing laparoscopic surgeries. The secondary outcome was to study the other actions of clonidine i.e pain and sedation scores and time to analgesic request.

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Materials and Methods

After approval from the hospital ethics and research committee, a prospective randomised double blinded comparative study was conducted on 60 adult patients undergoing laparoscopic surgeries for a period of nine months. The criteria for enrolling the patients in the study were as follows:

Inclusion Criteria

Patients undergoing laparoscopic surgeries under general anaesthesia, age between twenty and sixty years, ASA grade 1 and 2, elective surgeries with a duration of approximately two to three hours.

Exclusion Criteria

Ischaemic heart disease, aortic stenosis, left ventricular failure, atrioventricular block, patients on beta blockers, MAO inhibitors and benzodiazepines, laparoscopic surgeries that got converted to open surgeries.

After preoperative assessment patients fulfilling the study criteria were selected and preoperative orders to be nil orally for six hours before surgery was given. Patients were randomly assigned to one of the two groups (green or red) each having having thirty patients according to a random table created by a personal computer. Two batches of similar looking one ml ampoules which were colour coded as green and red were secured from pharmacy. The green ampoules contained 150µg/ml of clonidine and red ampoules contained saline. The content of the colour coded ampoules was known only to the pharmacist. The patients in group green were given 2µg/kg of clonidine in 100ml saline 15 mintes before induction and the patients in group red were given 100 ml of saline 15 minutes before induction. On the day of the surgery intravenous access was secured and after checking the anaesthesia machine and equipments and noting the name, age, weight and sex, the patient was shifted to the operation theatre. Monitors were connected and baseline parameters namely pulse oximeter, non invasive blood pressure and ECG were recorded. Premedication with the study drug was administered as an infusion at a dose of 2µg/kg in 100ml saline over 15minutes prior to induction. Intravenous glycopyrrolate 0.2 mg and i.v fentanyl 1.5µg/ml was given to all patients. Patient was induced with 2mg/kg of intravenous propofol and endotracheal intubation facilitated with atracurium (0.5mg/kg). Patient was maintained on isoflurane 1%, oxygen and nitrous oxide (total flow 3L/min) and relaxation was maintained with i.v atracurium. The minute ventilation was controlled and adjusted to end tidal carbondioxide between 32-45 mm of Hg. The intraabdominal pressure (IAP) was maintained at less than 14 mm of Hg. Bradycardia, defined as heart rate less than 20% of baseline or absolute heart rate less than 50 per minute whichever is less was treated with 20µg/kg of atropine. Hypotension, defined as BP less than 25% of baseline or systolic BP less than 90 mm of Hg was treated with 5-10 mg bolus ephedrine IV. Intr operatively the haemodyanamics were monitored as:

- Baseline
- 5 minutes after premedication
- 15 mintes after premedication (T0)
- Immediately after intubation (T1)
- 3 minutes after intubation (T2)
- Before pneumoperitoneum (PNO) (T3)
- 15 minutes after PNO (T4)
- 30 minutes after PNO (T5)
- 10 minutes after release of PNO (T6)
- 10 minutes after extubation (T7)

In addition the $ETCO_2$ and SpO_2 was monitored. Towards the end of the surgery, all patients were given ondansetron 0.15mg/kg and were reversed with iv neostigmine 5µ/kg and glycopyrrolate 10µg/kg. After extubation the patients were shifted to PACU and vitals monitored for 60 minutes. The Ramsay sedation score was assessed postoperatively after shifting to PACU.

Degree of sedation (Ramsay scale)

1. Awake and agitated
2. Awake and comfortable
3. Asleep but arousable
4. Asleep but sluggish response
5. No response to call or touch

Ten point visual analogue scale (VAS) was noted at the end of 60 minutes postoperatively before shifting the patient to the ward. The time to first analgesic request; TAR (period elapsed between the end of surgery to the time when the first analgesic was administered at patient's request) was noted. The results obtained in the study were recorded in a tabulated proforma. Descriptive and inferential statistical analysis were used in the study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on cateogorical

measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made .Student T test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between 2 groups. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant Figures

+ suggestive significance (P value: 0.05<P<0.10)

*Moderately significant (P value: 0.01<P≤ 0.05)

*** Strongly significant (P≤0.01)

Sample size estimation

Proportion known population

$n = [(z^2 * p * q) + ME^2] / [ME^2 + z^2 * p * q / N]$

Proportion unknown population:

$n = [(z^2 * p * q) + ME^2] / (ME^2)$

ME: is the margin of error, measure of precision.

and Z is 1.96 as critical value at 95%CI

N: population size

n: Sample size

σ: Standard deviation

Z: Critical value based on Normal distribution at 95% Confidence Interval

Standard deviation: $SD = \sqrt{\frac{\sum (x - \bar{x})^2}{n-1}}$

Statistical Software

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Results

The patients were randomised into the intravenous clonidine group/test group (green) group and intravenous saline/control (red) group. The two groups were comparable in respect to age [Table 1], sex [Table 2], weight [Table 3], duration [Table 4] and ASA physical status.

The mean heart rate varied from 88.07±17.30 to 73.5±18.14 in clonidine group.it varied from 132±18.3 to 89.3±14.40 in control group. The heart rate after 15 minutes of infusion (T0) of clonidine was significantly lower when compared to that in control group (p<0.05). Immediately after intubation (T1) and 3 minutes after intubation (T2), the increase in heart rate, to the respective baseline, was 8.3% and 10.3% respectively in the control group whereas in clonidine group the increase was only by 6% and 10% respectively. Before pneumoperitoneum (T3) the heart rates had a statistically significant difference in both the the groups (p<0.01). After 15 minutes (T4) and 30 minutes (T5) of pneumoperi-toneum there was a significant difference in heart rates between the two groups (<0.001). There was a 20 to 27% increase in heart rates between in the control group during pneumoperitoneum whereas the increase in clonidine group was 16% and 10%. At all points the heart rates in clonidine group in comparison to control group was lower which was statistically significant [Figure 1]. The mean systolic BP varied from 134.67±17.75 to 95.23±9.93 in clonidine group whereas in control group it varied from 144±14.57 to 129.93±13.44. Although there was no significant difference in systolic BP between both groups after 5 minutes of infusion, systolic BP after 15 minutes (T0) of clonidine was significantly lower when compared to control group (p<0.01). After intubation the systolic BP (T1) decreased in clonidine group by 20% and increased in the control group by 3% when compared to the respective baseline values, which was statistically significant. Before pneumoperitoneum (T3), 15 minutes and 30 minutes after pneumoperitoneum the

Table 1: Age distribution of patients studied

Age in years	Test group		Control group	
	No	%	No	%
21-30	3	10.0	4	13.3
31-40	7	23.3	6	20.0
41-50	11	36.7	13	43.3
51-60	8	26.7	5	16.7
>60	1	3.3	2	6.7
Total	30	100.0	30	100.0
Mean ± SD		45.50±11.25		44.77±11.38

Samples are age matched with p=0.803

Table 2: Gender distribution of patients studied

Gender	Test group		Control group	
	No	%	No	%
Male	7	23.3	15	50.0
Female	23	76.7	15	50.0
Total	30	100.0	30	100.0

Samples are gender matched with p=0.060

Table 3: Comparison of weight (kg) in two groups of patients studied

Weight (kg)	Test group		Control group	
	No	%	No	%
<50	7	23.3	4	13.3
51-60	12	40.0	10	33.3
61-70	5	16.7	12	40.0
>70	6	20.0	4	13.3
Total	30	100.0	30	100.0
Mean ± SD	58.43±13.26		62.60±8.66	

Mean weight is statistically similar with P = 0.155

Table 4: Comparison of Duration (hrs) of surgery in two groups of patients studied

Duration (hrs)of surgery	Test group		Control group	
	No	%	No	%
1-2 hours	1	3.3	4	13.3
2-4 hours	28	93.3	25	83.3
>4 hours	1	3.3	1	3.3
Total	30	100.0	30	100.0
Mean ± SD	3.16±0.55		3.03±0.76	

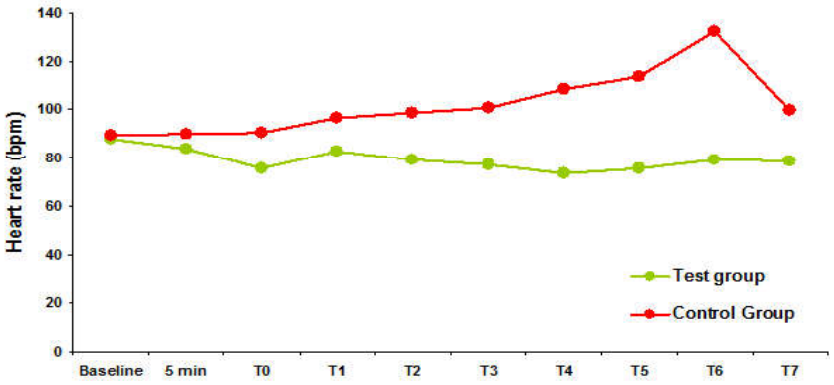

Fig. 1: Comparison of heart rate (bpm) in two groups of patients studied

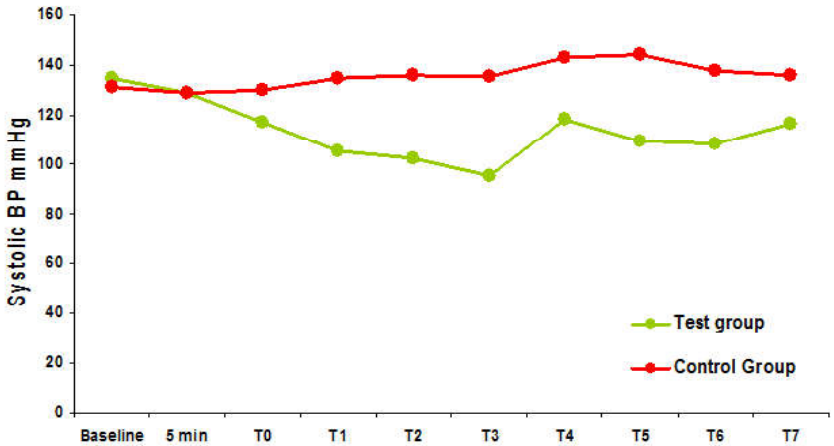

Fig. 2: Comparison of Systolic BP mmHg in two groups of patients studied

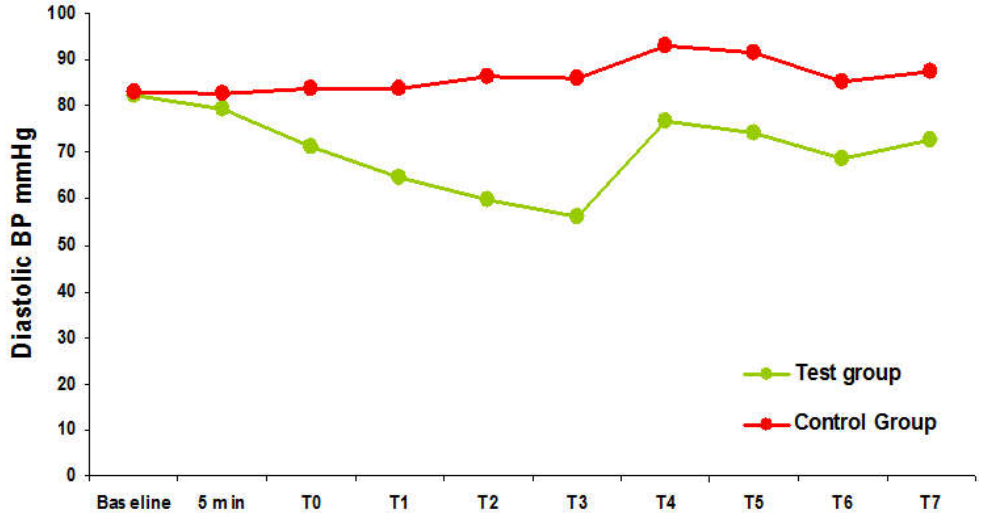

Fig. 3:

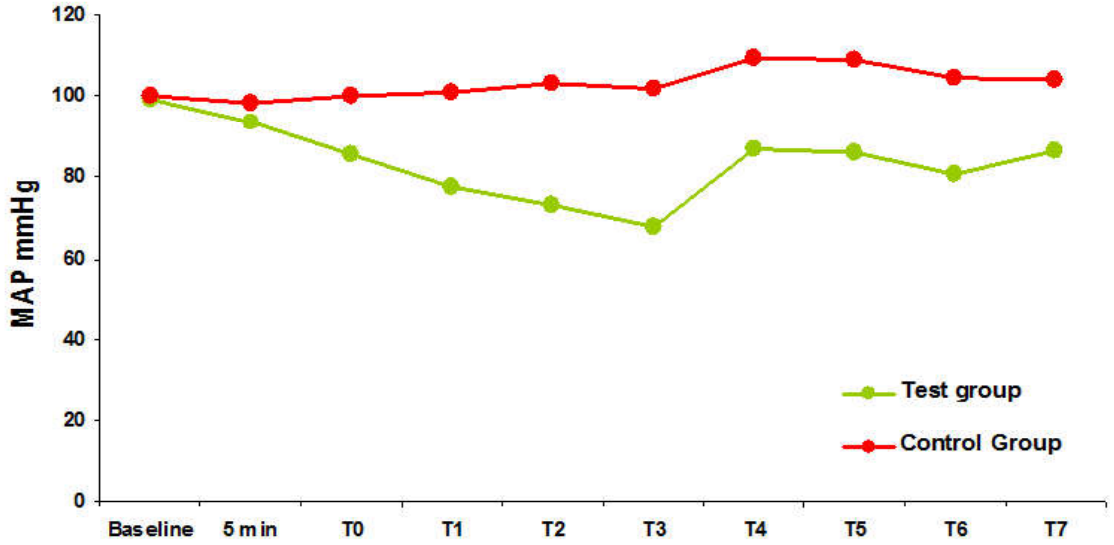

Fig. 4:

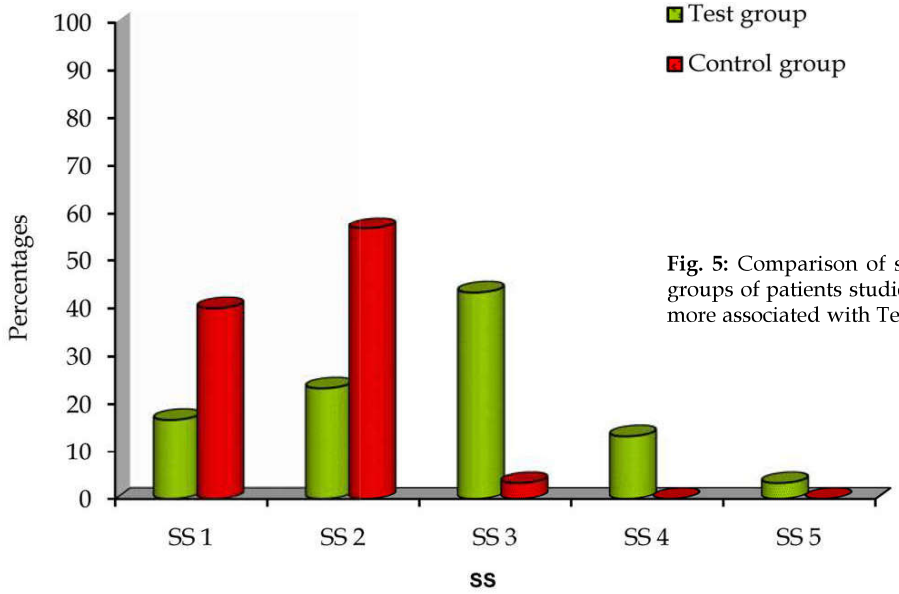

Fig. 5: Comparison of sedation scale (SS) in two groups of patients studied SS score is significantly more associated with Test group with P = <0.001**

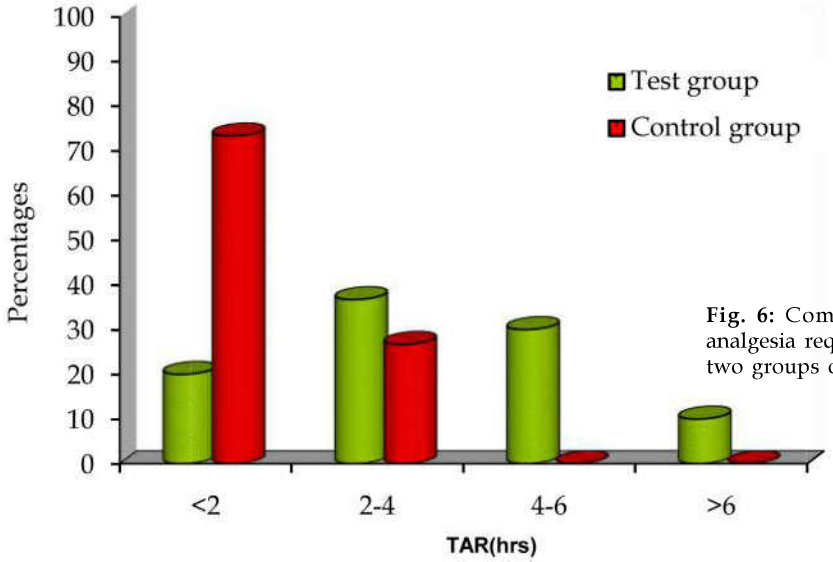

Fig. 6: Comparison of time to analgesia request (TAR) in hrs in two groups of patients studied

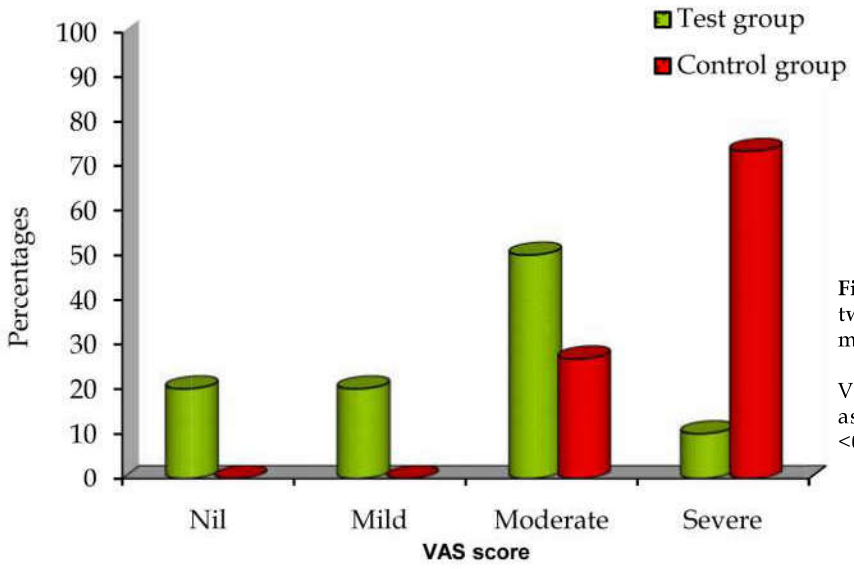

Fig. 7: Comparison of VAS score in two groups of patients studied at 60 minutes post operatively

VAS score is significantly less associated with Test group P = <0.001**

systolic pressures were significantly lower in clonidine group than control group . In the clonidine group there was a decrease of 12.45% and 18.8% after 15 minutes and 30 minutes of pneumoperitoneum respectively. In the control group there was increase in systolic BP after 15 and 30 minutes of pneumoperitoneum by 9-10%. At all points of time the systolic BP in clonidine group compared to the control group was lower which was statistically significant (p<0.001)[Figure 2]. Although 5 minutes after infusion of the drug there was no statistically significant difference in diastolic BP in both groups, post intubation and immediately thereafter at all points of time the diastolic BP was significantly lower in clonidine group than the control goup (p<0.001) [Figure 3]. Since mean arterial pressure is derived from systolic and diastolic pressures, it followed the same trends. It was seen to be significantly lower in clonidine group as compared to the control group [Figure 4]. Patients in clonidine group were significantly more sedated when compared to the patients in control group [Figure 5]. Mean TAR (hours) is significantly more in test group with P=<0.001** [Figure 6]. VAS score is significantly less associated with test group P=<0.001** [Figure 7].

Discussion

Laparoscopic surgeries have the advantage of reduced postoperative pain due to smaller incisions and less haemorrhage and shorter recovery times and significant cost savings. They involve the creation of carbondioxide pneumoperitoneum which causes

increases in intraabdominal pressure(IAP). IAPs higher than 10 mm of Hg induces significant alterations in haemodyanamics. Dexter et al [1] randomised patients to insufflation pressures of either 7 or 15 mm of Hg during laparoscopic cholecystectomy. Heart rate and mean arterial pressure in both groups increased but stroke volume and cardiac output were significantly more depressed in the high pressure group. In a study by Mc Laughlin et. al. [2] intraabdominal pressures of 15 mmof Hg caused a 30% decrease in cardiac output (CO) and stroke volume (SV) and a 60% increase in mean arterial pressure (MAP) from preinsufflation levels, and these changes were determined to be statistically significant. Considering all these facts the IAP was kept below 14 mm of Hg in the present study. The alpha 2 adrenergic agonists like clonidine have a central sympatholytic action. They improve haemodyanamic stability during surgery and are known to reduce the anaesthetic and opiod consumption by causing sedation, anxiolysis and analgesia. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and a decrease in systolic blood pressure, heart rate and cardiac output [3]. The ability of clonidine to modify the potassium channels in the CNS and thereby hyperpolarize the cell membranes may be the the mechanism for profound decrease in anaesthetic requirements produced by clonidine [4]. Studies using oral clonidine administered 60 to 90 minutes before induction of anaesthesia have shown good results in minimising the haemodyanamic changes during laparoscopic surgery [5].

Although the bioavailability of clonidine is 90% after oral administration , it requires 2 to 4 hours to reach its peak effect [6], necessitating its ingestion at least 2 hours prior to induction to achieve the desired clinical effect. Intravenous clonidine has its onset of action within 15 minutes. Therefore its administration 15 minutes before the surgery by the intravenous route was preferred in this study. Various doses of iv clonidine have been used in the past to maintain haemodyanamics during laparoscopy. The dose of i.v clonidine in the present study is similar to the dose used in the study by Tripathi D C et. al. [7] who have compared two doses of i.v clonidine namely 1µg/kg and 2µg/kg in modulating the haemodyanamic stress response during laparoscopic surgery. They found that with a dose of 2µg/kg , there is a decrease in HR, SBP, DBP and MAP from baseline within 15 minutes of premedication ($p<0.05$), but at no time this decrease was more than 20% from baseline. This finding is comparable to our study where there was a fall in SBP by 13% after premedication with clonidine which was not significant. Marco P Zalunaedr et. al. [8] used 3µg/kg of i.v clonidine immediately before induction and compared it with a placebo. It was observed that MAP, post–intubation was significantly lower in clonidine group as compared to placebo ($p<0.05$). in our stud , we used 2µg/kg clonidine 15 minutes before induction and observed that MAP, post–induction was lower in the clonidine group when compared to control group and this difference was statistically strongly significant ($p=0.001$) immediately after intubation and $p< 0.001$ 3 minutes after intubation. In the study by Tripati D C et. al., the patients who received 2µg/kg of iv clonidine there was an increase in HR and DBP ($p>0.05$) and MAP remained comparable to the baseline. These changes were statistically not significant. These findings are comparable with the findings in our study except for the DBP. , which showed a decrease in our study.

Following institution of pneumoperitoneum , there was significant increase in HR, SBP,DBP and MAP in the control group as compared to the clonidine group ($p<0.001$) in our study (143±17.63 vs 117±18.56 for BP; 76.67±15.69 for DBP and 109±11.04 vs 87.00±15.27 for MAP). This finding is comparable is comparable to the study by Tripathi D C et. al.[7] who showed a statistically significant difference in HR, SBP, DBP and MAP, 20 minutes and 40 minutes after institution of pneumo-peritoneum ($p<0.05$) in the present study, 10 minutes after release of pneumoperitoneum, the HR in the control and clonidine group were similar ($p+0.129$). 10 minutes post extubation and 10 minutes after release of pneumoperitoneum, the HR, SBP, DBP and MAP were lower in clonidine group as compared to the control group and this difference was statistically significant in our study ($p<0.001$) in the present study, 2 patients in the clonidine (6.7%) had bradycardia. They responded well to intravenous atropine 0.6 mg. Clonidine related bradycardia has rarely been described as a side effect in commonly prescribed doses. it is more commonly associated with clonidine poisoning or overdose.

The patients who are more susceptible to bradycardia are the ones with clinical sinus node dysfunction and those already receiving sympatholytic agents. 3 patients (10%) in the clonidine group developed hypotension which was treated with ephedrine 6mg iv. Ray M et .al. [9] in their study used 3µg/kg of iv clonidine 15 minutes before induction and as infusion at 1µg/kg/min. The incidence of bradycardia and hypotension was high in their study.

The incidence of bradycardia was not significant in our study as we used a lower dose of clonidine. In the study by Kalra NK et. al. [10] there was no

bradycardia and hypotension as they used a dose lower than our study i.e 1.5µg/kg i.v. 15 minutes before induction. The analgesic effect of clonidine has been a subject to research in recent times. Mechanisms of analgesic effect either during acute pain or chronic pain management have been recently discovered and these still remain as active fields of research [4,11].

In this study we have tried to compare the time of first requirement of analgesia postoperatively in both the groups. The 1 hour postoperative 10 point VAS score was significantly lower in the patients who received clonidine (VAS 3.86±2.45 in clonidine group vs 7.36±1.54 in control group). It was observed that most of the patients who received clonidine were sleeping comfortably in the PACU but when aroused and assessed for VAS they had mild to moderate pain. The time to analgesia request was significantly higher in clonidine group (4.17±1.79 hours vs 1.65±0.95 hours) 36.7% of patients who received clonidine requested analgesia in 2- 4 hours post-operatively whereas 73.3% of patients in control group requested analgesia within 2 hours post-operatively.

Singh S et. al. [7] have used oral clonidine and have shown a decrease in postoperative analgesic requirement. The mean sedation score in clonidine group was 2.63±1.03 as compared to 1.63± 0.55 in the control group. 43.3% of the patients who received clonidine had a sedation score of 3. In spite of the high sedation scores , none of the patients in the clonidine group had respiratory depression.

In the study by Tripathi et. al. [9] a similar iv dose was used and the meam sedation scores were 2 as compared to 2.63±1.03 in the present study.

Conclusion

From the results of our study we arrived at the following conclusions.

1. Premedication with 2µg/kg intravenous clonidine, 15 minutes before surgery in ASA 1 and 2 patients was found to be relatively safe and effective in providing stable haemodyanamics intraoperatively and as protection against stress response to pneumoperitoneum.
2. Intravenous clonidine offers additional advantage of providing post-operative analgesia and sedation.
3. Intravenous clonidine at a dose of 2µg/kg can be recommended as premedication for laparoscopic surgeries in patients without cardiovascular diseases.

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Conflict of Interest: None

Abbreviations

BP- Blood pressure
CO_2- Carbon-dioxide
DBP- Diastolic blood pressure
ECG- Electrocardiogram
$ETCO_2$- End – tidal carbondioxide
IV- Intravenous
IM- Intramuscular
MAP- Mean arterial pressure
PNO- Pneumoperitoneum
SBP- Systolic blood pressure
SpO_2- Oxygen saturation
SVR- Systemic vascular resistance
TAR- Time to analgesia request

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