



## A COMPARATIVE STUDY OF EFFECTS OF CLONIDINE VERSUS MAGNESIUM SULPHATE ON HEMODYNAMICS DURING INTUBATION AND INTRAOPERATIVE PERIOD IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

### Surgery

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### KEYWORDS

#### AIM AND OBJECTIVES

The aim of this study was to compare the efficacy of intravenous clonidine 1µg/kg and intravenous magnesium sulfate 30 mg/kg in attenuation of hemodynamic response to intubation and pneumoperitoneum in intraoperative period in laparoscopy cholecystectomy patients in terms of: 1. Systolic Blood pressure 2. Diastolic blood pressure 3. Mean arterial blood pressure 4. Heart rate. The secondary objective was to observe recovery parameters such as postoperative pain, level of sedation and any adverse effects.

#### MATERIAL AND METHODS

Study Type- A hospital based double blinded, prospective study. Study Area- Guntur Medical College, Government General Hospital, Guntur. Study Duration - 2 years

#### Inclusion Criteria

ASA 1 and 2 Both sexes Age 18 – 60 years

#### Exclusion Criteria

Coronary Artery Disease Chronic Renal Failure Emergency Cases Patients on beta blockers and calcium channel blockers Laparoscopic surgery converted to open Patients not willing to give consent Severe Hepatic disease Allergy to any of the study drug

After obtaining institutional ethical committee approval and informed consent, 100 ASA physical status 1 and 2 subjects in the age group of 18 – 60 years planned for elective laparoscopic cholecystectomy were enrolled in this study. But, out of 100, four cases had to be converted into open cholecystectomy due to complications and were excluded from our study. So, we studied 60 patients, and they were randomly allocated to two study groups of 50 each as Group C (Clonidine group) and Group M (Magnesium sulfate group). 38

#### Methodology Data Collection

100 patients were randomly allocated to two different groups of 50 each using randomization method as group M and group C. The study drugs were prepared by an anaesthesiologist who had no role in the research and drugs were administered by another anaesthesiologist who was unaware of the constituent of drug and allotment of the group and similarly resident doctor keeping records of the parameters was unaware of the group allotment, thus maintaining proper blinding. All patients were assessed day before surgery and preanaesthetic check-up was done. Group M – received magnesium sulfate 30mg/kg i.v diluted in 100 ml of normal saline 10 minutes before induction. Group C – received clonidine 1µg/kg i.v diluted in 10 ml of normal saline 10 minutes before induction. Anaesthetic procedure : After coming to theatre, patient's basal parameters- BP, HR, ECG and SpO<sub>2</sub> were recorded using NIBP, ECG monitor and pulse oximeter. Intravenous access established and an IV infusion of Plasmalyte A started. Patients in each group received test drugs 10 minutes before induction and in the dose explained earlier.

The study drug was prepared by anaesthetist and the observer was blind for the study drug. 39 All patients were premedicated with inj. glycopyrrolate 0.2 mg iv and inj. midazolam 1mg iv. After adequate preoxygenation with 100% oxygen for 3 minutes, iv. Lignocaine

1.5mg/kg and inj Fentanyl 1 µg/kg was given and patients in each group were induced by inj. Propofol 2mg/kg iv. After ensuring adequate bag and mask ventilation, inj Rocuronium bromide 0.6mg/kg was given followed by laryngoscopy and intubation with appropriately sized cuffed endotracheal tube. Anaesthesia was maintained with Oxygen 50% Nitrous Oxide 50% and Desflurane 2-3 vol% based on MAC, through closed circuit on controlled ventilation with low flow of gases around 1 litre/minute. Transversus Abdominis Plane (TAP) block was given in all four quadrants using ultrasound with inj Ropivacaine 0.2%, 20 ml in each quadrant. Muscle relaxation was maintained with intermittent doses of rocuronium 0.15mg/kg if needed after 50 minutes and for analgesia iv paracetamol 15mg/kg was given. Pneumoperitoneum inflation pressures were maintained around 14 mm of Hg. Controlled ventilation was used, and end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>) was maintained between 35 and 40 mm Hg. Patients were positioned in head up tilt of 15° with left lateral tilt. Intraoperative fluid was given as per requirements. Hypotension (MAP <20% of baseline) was managed with fluid bolus or ephedrine 6 mg iv and bradycardia (HR <50 bpm) was managed with atropine 0.6 mg iv bolus. At the end of surgery, reversal was done with Glycopyrrolate (0.01mg/kg) and Neostigmine 0.05mg/kg and patient would be extubated on table. Postoperative pain based on (Visual Analogue Scale) Level of sedation was assessed with Modified Ramsay Sedation Score. Adverse effects like bradycardia, hypotension and PONV were assessed. All the parameters of the study were recorded at following stages – Baseline values, after giving the study drug that is pre-induction value, post intubation, 3 min, 5 min and 10 min after intubation, after pneumoperitoneum, 5 min, 10 min, 20 min and 30 min after pneumoperitoneum. Group M and Group C were studied for effects of drugs and results were obtained and analyzed statistically.

#### Statistical Analysis

The information related to social-demographic and other clinical variables was entered in Microsoft Excel and analysed using IBM SPSS v20.0.0. The descriptive statistics for categorical/ordinal variables were presented in the form of frequencies and percentages and in the form of mean and standard deviations for interval variables. The difference across the two groups for interval variables was explored using independent samples Wilcoxon-Mann Whitney test after testing for their distribution and other assumptions. Chi square/Fischer's exact test was used to compare categorical data across two groups and p value

#### OBSERVATIONS AND RESULTS

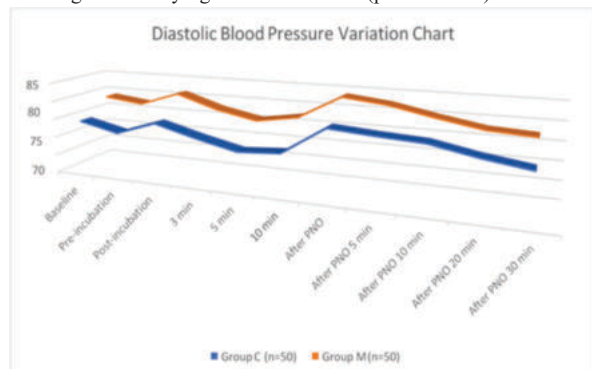
There was no statistically significant difference in age (years) in both groups (p value > 0.05). There was statistically significant difference in weight (kg) in both groups (p value < 0.05). There was no statistically significant difference in gender distribution in both groups (p value > 0.05). The baseline and preinduction (after test drug administration) mean SBP and standard deviation in group C were 122.86 ± 14.02 mm hg and 119.04 ± 14.55 mmhg while in group M were 134.53 ± 18.35 mmhg and 131.34 ± 14.67 mmhg.

**Table.1: Comparison Of SBP (mmHg) In Both Groups Analysis Of**

**Systolic Blood Pressure (SBP)**

| Systolic blood pressure (mm Hg) | Group C (n=50)<br>Mean± Standard Deviation | Group M (n=50)<br>Mean± Standard Deviation | p value | Statistical Significance  |
|---------------------------------|--|--|---------|---------------------------|
| Baseline                        | 122.86±14.02                               | 134.53±18.35                               | <0.001  | Statistically Significant |
| Pre-induction                   | 119.04±14.55                               | 131.34±14.67                               | <0.001  | Statistically Significant |
| Post intubation                 | 123.72±17.17                               | 137.76±20.91                               | <0.001  | Statistically Significant |
| 3 min                           | 119.5±18.31                                | 130.7±21.77                                | 0.006   | Statistically Significant |
| 5 min                           | 115.94±18.58                               | 126.22±21.55                               | 0.012   | Statistically Significant |
| 10 min                          | 119.24±17.45                               | 128.14±21.06                               | 0.024   | Statistically Significant |
| After Pneumo                    | 127.42±17.63                               | 138.54±22.41                               | 0.007   | Statistically Significant |
| P 5min                          | 125.76±16.40                               | 137.26±19.77                               | 0.002   | Statistically Significant |
| P 10 min                        | 123.58±15.59                               | 134.74±14.45                               | <0.00   | Statistically Significant |

The difference in pre induction SBP value between two groups was statistically significant (p value<0.05). Mean SBP recorded at post intubation in group C was 123.72±17.17 mmhg while in group M was 137.76±20.91mmhg. There was increase in SBP at post intubation in group M as compared to group C which was statistically significant (pvalue<0.05). The SBP recordings at 3, 5, 10 minutes and at pneumoperitoneum between two groups was found to be comparable and clinically significant (p-value<0.05). The mean SBP reading at intervals 5, 10, 30 minutes after pneumoperitoneum in group C were 125.76 ±16.40, 123.58 ±15.59 and 121.28± 15.58mmhg while in group M were 137.26±19.77, 134.74±14.45 and 130.46±16.79mmhg showing statistically significant difference (p value<0.05).



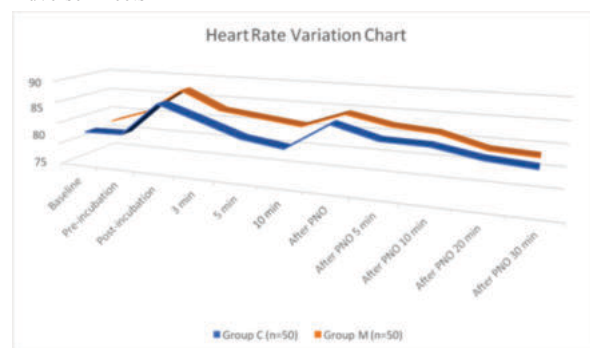
The baseline and pre induction (after test drug administration) mean DBP and standard deviation in group C were 74.2±10.03mmhg and 71.74±7.46mmhg while in group M were 78.85±10.51mmhg and 77.54±7.37mmhg. The difference in pre induction DBP value between two groups was statistically significant (p value<0.05). The postintubation after 3,5,10 minutes (after test drug administration) mean DBP and standard deviation in group C were 72.48±10.46, 69.97±11.01, 70.77±10.25 while in group M were 77.7±10.91, 75.46±11.50, 77.32± 12.67. The difference in postintubation after 3,5,10 min DBP value between two groups was statistically significant (p value<0.05). The mean DBP value after pneumoperitoneum after 10 min in Group C was 76.68± 11.43mmhg while in Group M was 80.0± 8.05mmhg. The difference in values after 10 min after pneumoperitoneum between two groups was statistically not significant (p value >0.05). The baseline (after test drug administration) mean MAP in group C was 81.9±10.62mmhg while in group M was 86.22±12.67mmhg. The preinduction mean MAP in group C was 79.82±9.43 while in Group M was 84.68±7.49. The difference in pre induction MAP value in both the groups was statistically significant (p value<0.05). The mean MAP value at post intubation 3, 5, 10 min after intubation and 5, 10, 20, 30 min after pneumoperitoneum in group C were 78.5±11.99, 76.56±12.52, 77.42±12.61, 83.98±12.23, 82.6±11.82, 80.52± 11.43, 79.5±9.83 while in group M were 83.8±11.53, 81.8±11.58, 84.34±14.12, 90.02± 13.47, 88.56±10.12, 85.78±9.36, 84.88±10.26. The mean MAP values at

these intervals between both the groups were clinically significant (p value<0.05). There was no statistically significant difference in the Heart Rate status in both the groups at any point of time during the study (p value>0.05).

**Table.2: Comparison Of Pain (Visual Analogue Scale) In Both Groups**

| Pain score | Group C (n=50)<br>Mean±Standard Deviation | Group M (n=50)<br>Mean±Standard Deviation | p value | Statistical Significance  |
|------------|---|---|---------|---------------------------|
| Pain score | 3.1±0.30                                  | 3.26±0.44                                 | 0.036   | Statistically Significant |

There was statistical difference in the postoperative pain based on (Visual Analogue Scale) in both the groups at recovery during the study (p value<0.05). Modified Ramsay Sedation Score was assessed in both the groups. Mean sedation score in group M (3.3) was more than group C (3.1) but this difference was not statistically significant (p value>0.05) 57

**Adverse Effects**

During our study, 2 patients in clonidine group had bradycardia (4.0%) and 4 patients had hypotension (8.0%) while magnesium group did not have any of these adverse effects. These side effects, however, between both the groups were insignificant (p value>0.05).

**DISCUSSION**

Sympathetic surge due to intubation and pneumoperitoneum may be well tolerated by healthy patients but it can be very harmful with patients of ischaemic heart disease having compromised cardiac reserve. Laparoscopy results in progressive and significant increases in plasma concentrations of cortisol, epinephrine, norepinephrine, and renin. Vasopressin plasma concentrations are markedly increased immediately after the beginning of pneumoperitoneum. There have been many agents used in the past for attenuation of the hemodynamic response to intubation and pneumoperitoneum such as beta blockers, calcium channel blockers, opioids, vasodilators, and alpha agonists. These drugs are not cost effective and are associated with some unwanted side effects like nausea, vomiting, prolonged sedation, and respiratory depression. Therefore, there has been a growing trend to find the most effective substitute with least side effects. Many studies have shown that alpha 2 agonists such as clonidine effectively obtunds this response in addition to providing analgesia and anxiolysis. Clonidine reduces plasma concentrations of epinephrine and norepinephrine and attenuates the changes in arterial pressure, HR, SVR and cardiac output. These benefits are mediated by a reduction of neurohormonal discharge from stress induced sympathetic hyperactivation. Magnesium sulfate is a versatile drug which produces myriad of effects like analgesia, sedation, anxiolysis and suppression of stress response. It decreases blood pressure, heart rate and SVR in dose dependent manner with preservation of cardiac output.

Most of the studies have compared the effect of intravenous clonidine or magnesium with that of control. Very few studies are available that directly compare intravenous clonidine with intravenous magnesium for attenuation of the hemodynamic responses to intubation as well as pneumoperitoneum. So, we have planned a randomized, double blinded, comparative study in Guntur medical college, Government General Hospital, Guntur to compare the effect of intravenous clonidine and magnesium sulfate on hemodynamics during intubation and pneumoperitoneum in patients undergoing laparoscopic cholecystectomy. Patient Characteristics of the groups The demographic characteristics like age and gender of the study population and duration

of the surgery were similar in both the groups, with no statistically significant difference while weight of the study population has shown significant difference. The mean age in Clonidine group was  $47.94 \pm 9.09$  years and in Magnesium group was  $49.82 \pm 6.65$  years. The mean weight in Clonidine group was  $64.66 \pm 8.03$  kg and in Magnesium group was  $67.74 \pm 7.15$  kg. The patients belonged to either ASA 1 or ASA 2 and were comparable in both groups. The mean duration of the surgery in clonidine group was 58.30 minutes and in magnesium group was 58.70 minutes which was comparable in both groups. Dosage of drug In our study we used i.v clonidine  $1 \mu\text{g/kg}$  which was diluted in 10 ml of normal saline and infused over a period of 10 minutes before induction and i.v magnesium sulfate was given in a dose of  $30\text{mg/kg}$  diluted in 100 ml of normal saline and infused over a period of 10 minutes before induction. 60 Sengupta.M et al in their study, used clonidine  $1.5 \mu\text{g/kg}$  intravenously over a period of 15 minutes before induction followed by  $1 \mu\text{g/kg/hr}$  by continuous intravenous infusion and the other group received isotonic saline (0.9%NS) in the same volume. They found that mean arterial pressure and heart rate in clonidine group was significantly less after intubation and throughout the period of pneumoperitoneum. No significant difference in the parameters of recovery were observed between the two groups. This was similar to our study. Similarly, Borokar patil et al compared magnesium sulfate  $50 \text{ mg/kg}$  with clonidine  $1.5 \mu\text{g/kg}$  in attenuation of hemodynamic response and they found clonidine  $1.5 \mu\text{g/kg}$  was better than magnesium in attenuating the response to intubation and pneumoperitoneum, but magnesium  $50\text{mg/kg}$  was better in terms of postoperative analgesia. This was similar to our study. 61 Attenuation of Hemodynamics We compared i.v clonidine with i.v magnesium sulfate in attenuation of hemodynamic parameters like systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate at various intervals such as baseline, pre induction (after giving test drug), post intubation, 3, 5, 10 min after intubation and after pneumoperitoneum, 5 min after pneumoperitoneum (P5 min), 10 min after pneumoperitoneum (P10 min), 20 min after pneumoperitoneum (P20min) and 30 min after pneumoperitoneum (P30 min). The baseline hemodynamic parameters were comparable in both the groups ( $p > 0.05$ ). MEAN ARTERIAL PRESSURE (MAP) We observed that mean arterial pressure (MAP) was lower in clonidine group than magnesium group with significant statistical difference ( $p \text{ value } 0.05$ ). Supporting to our study were the observations made by Altan A et al where they found no statistical significant difference in heart rate between clonidine and magnesium sulfate group. They, however, have used higher doses of clonidine  $3 \mu\text{g/kg}$  followed by infusion and observed increased incidences of bradycardia and hypotension. But, in our study, these incidences were insignificant probably because of single bolus dosage of clonidine as compared to continuous infusion. Yi Zhang et al studied the effects of clonidine on hemodynamic response to intubation and pneumoperitoneum in laparoscopic cholecystectomy. They compared clonidine with control group and found that clonidine intervention significantly reduced heart rate at intubation and pneumoperitoneum as compared to placebo ( $p \text{ value } 0.05$ ).

**Adverse Effects** In our study we found 2 patients had bradycardia in clonidine group at 10 minutes of intubation which was treated with inj. atropine  $0.6 \text{ mg}$  i.v stat. 4 patients 66 developed hypotension (more than 20% baseline) in clonidine group which was managed with inj. ephedrine  $6\text{mg}$  i.v bolus. This could be due to positional changes in laparoscopy where steep head up position can cause venous pooling in legs and thus hypotension. But as compared to magnesium sulfate these differences were statistically insignificant ( $p > 0.05$ ). No patient developed postoperative nausea and vomiting (PONV) in both the study groups. Altan and Turgut et al 35 used clonidine  $3 \mu\text{g/kg}$  intravenously over a period of 15 min before induction and  $2 \mu\text{g/kg/min}$  by continuous infusion intraoperatively.

They observed significant incidences of bradycardia and hypotension in their study. Similarly, Ray M et al 34 used  $3 \mu\text{g/kg}$  of clonidine intravenously over a period of 15 min before induction and  $1 \mu\text{g/kg/min}$  by continuous infusion during surgery and observed significant incidences of bradycardia and hypotension in their study. We reduced the dose of clonidine to  $1 \mu\text{g/kg}$  in our study and only 4 patients had hypotension and 2 had bradycardia in our study which were statistically insignificant. In our study we observed that clonidine was more effective in reducing systolic blood pressure, diastolic blood pressure, mean arterial pressure and pain at intubation and pneumoperitoneum as compared to magnesium sulfate. We however did not find any statistical difference in heart rate in both the groups. Recovery parameters such as sedation and PONV were also similar in both the groups. 2 patients had bradycardia and 4 patients had hypotension in clonidine group which were statistically insignificant ( $p \text{ value } > 0.05$ ).

## SUMMARY

We did a randomized, double blinded, comparative study in Guntur medical college, Government General Hospital, Guntur. 100 patients in the age ranging from 18-60 years, belonging to ASA physical status 1 and 2 planned for elective laparoscopic cholecystectomy were enrolled in our study. Our aim was to compare  $1 \mu\text{g/kg}$  clonidine and  $30\text{mg/kg}$  magnesium sulfate in attenuation of hemodynamic response to intubation and pneumoperitoneum in intraoperative period. Patients were divided into two groups of 50 each using randomization method. Group C received  $1 \mu\text{g/kg}$  clonidine diluted in 10ml of normal saline over 10 minutes prior to induction while Group M received  $30\text{mg/kg}$  magnesium sulfate diluted in 100 ml of normal saline over 10 minutes prior to induction. The heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, recovery parameters like postoperative pain, level of sedation and adverse effects were assessed in both the groups. The difference across the two groups for interval variables was explored using independent samples Wilcoxon-Mann Whitney test after testing for their distribution and other assumptions. Chi square/Fischer's exact test was used to compare categorical data across two groups and  $p \text{ value } < 0.05$  was considered statistically significant for the purpose of this study. In observations we found that systolic blood pressure, diastolic blood pressure, mean arterial pressure and pain were less in clonidine group as compared to magnesium sulfate at intubation and pneumoperitoneum. We, however, did not find any statistical difference in heart rate between the study groups. Recovery parameters such as level of sedation and PONV were also similar in both the groups. The incidence of bradycardia and hypotension in clonidine group was 4% and 8% respectively which was statistically insignificant. From our study, we concluded that clonidine  $1 \mu\text{g/kg}$  attenuated hemodynamic response to intubation and pneumoperitoneum better than magnesium sulfate  $30\text{mg/kg}$  and recovery parameters such as sedation and PONV were similar in both the groups.

## CONCLUSION

Clonidine  $1 \mu\text{g/kg}$  was superior with long lasting effects than magnesium sulfate  $30\text{mg/kg}$  during the expected times of sympathetic surge (intubation, pneumoperitoneum, changes in position etc.) of laparoscopic cholecystectomy in our study. However, both the drugs were similar in recovery parameters such as sedation and PONV. We recommend clonidine  $1 \mu\text{g/kg}$  to be used in laparoscopic cholecystectomy for attenuation of hemodynamic response during intubation and pneumoperitoneum without any major side effects.

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