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EFFECT OF MAGNESIUM SULFATE AND CLONIDINE IN ATTENUATING HEMODYNAMIC RESPONSE IN LAPAROSCOPIC CHOLECYSTECTOMY -A CLINICAL COMPARATIVE STUDY

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ABSTRACT

INTRODUCTION - Laryngoscopy and tracheal intubation invariably causes hypertension and tachycardia and subsequent pneumoperitoneum and changes in patient position required during laparoscopic surgeries add to the insult. In patients with cardiovascular co-morbididities, such alterations can cause severe life threatening situations perioperatively[1]. Various drugs have been tried to attenuate these effects and in this regard, clonidine, and magnesium sulfate have shown promising results.

AIM- This study was aimed at comparing the efficacy of clonidine and magnesium sulphate in attenuating the hemodynamic responses to laryngoscopy, intubation and pneumoperitoneum, assessed in terms of heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure.

INCLUSION CRITERIA: Patients between age 18-60 years, of both sexes, ASA grade I&II and scheduled for elective laparoscopic cholecystectomy under general anesthesia.

EXCLUSION CRITERIA: Refusal to informed consent, anticipated difficult airway,ASA grade III&IV,history of allergy to study drug, pregnant and lactating mother, any disorders of cardiovascular system, respiratory system, renal system, hepatic and neuromuscular condition.

METHODS-: A randomized prospective study was conducted in Silchar Medical College and Hospital, Silchar, and 80 patients were randomly allocated to two groups of 40 patients each. One group received clonidine 1.5mcg/kg whereas other group received MgSO4 50mg/kg. HR, SBP, DBP, and MAP were recorded at baseline, after infusion of the study drug, just before intubation, after intubation at 1min,3mins,and5mins, after pneumoperitoneum at 5min,10min,20min,and 30min. All analyses were done by using two tailed test p-value.

RESULTS: The mean values in HR,SBP, and MAP values at at various intervals were statistically significant ($p<0.05$) in clonidine group when compared to MGSO4 group.

CONCLUSION: Clonidine was found more effective than MGSO4 during laryngoscopy and intubation while both were equally effective during pneumoperitoneum which correlated with other similar studies.

INTRODUCTION-

The manifestations observed during laryngoscopy and intubation result from stress response in the form of laryngo-sympathetic stimulation with the manifestions being hypertension, tachycardia and cardiac arrhythmias. Use of premedication and anaesthetic agents, the duration of laryngoscopy, and intubation, and depth of anaesthesia usually determine the magnitude of these manifestations. In a healthy individual, these hemodynamic responses are well tolerated. But in patients with co-morbid conditions such as hypertension, coronary artery disease, stroke and cerebral aneurysms, such alterations can lead to ventricular failure, pulmonary edema, myocardial ischemia, ventricular dysrhythmias and cerebral hemorrhage.[1]

Laparoscopic cholecystectomy involves creation of pneumoperitoneum by insufflation of gas followed by trendelenburg positioning of the patient. Pneumoperitoneum causes increase in the abdominal pressure and elevation of diaphragm bringing about decrease in cardiac output, alteration in various vascular pressures, increase in resistance as well as fall in functional residual capacity of the lungs.[2] Absorbtion of CO2 from the abdomen causes hypercarbia and respiratory acidosis. Further increase in cardiac output occurs due to change in position required for better exposure of surgical field.

As evident from above, hemodynamic changes during endotracheal intubation as well as pneumoperitoneum are not desirable and need to be attenuated especially in high risk patients. The use of intravenous anaesthetic agent before intubation does help in this regard but it is usually inadequate and accompanied with other undesirable effects.

Clonidine acts on the Alpha-2 adrenergic inhibitory neurons present mainly in the medullary vasomotor centre causes decrease in the sympathetic nervous system outflow from the CNS to the peripheral tissues which is manifested as peripheral vasodilatation and a decrease in systolic blood pressure, heart rate and cardiac output.[3,4]

Magnesium has also been shown to attenuate the hemodyanmic responses by blocking the release of catecholamines from both adrenergic nerve terminals and adrenal gland. Also, it produces vasodilation by acting directly on blood vessels. In high doses, it attenuates vasopressin mediated vasoconstriction.[5,6]

As the hemodynamic changes occur due to increased sympathetic activity on heart, we aimed to compare an alpha2 adrenergic agonist clonidine with magnesium sulfate in attenuating cardiovascular stress response to laryngoscopy, intubation amd pneumoperitoneum. Pretreatment with these drugs infused over 10 minutes and administered 15 minutes prior to induction blunts the hemodynamic response seen during the peri-operative period.

METHOD-

A randomized, double blinded prospective study was undertaken at Silchar Medical College and Hospital, Silchar, Assam, after Institutional Ethical Committee approval and written informed consent from 80 patients of age between 18-60 and ASA grade I and II undergoing laparoscopic cholecystectomy.

On the day prior to surgery, all patients had a thorough clinical examination of all organ systems was performed

followed by tablet alprazolam 0.5 mg orally at bed time and kept NPO for 8 hours prior surgery.

On arrival of the patient in the operating room, a 20-gauge intravenous cannula was secured and connected to IV fluid ringer lactate. The patients was then connected to Drager multi parameter monitor which recorded heart rate, SPO2, non-invasive measurements of SBP, DBP, MAP, and ECG monitoring. The baseline(BL) systolic, diastolic blood pressure, mean arterial pressure and heart rate were recorded after 5 mins of settling in the operative room. After recording the baseline reading, all patients were premedicated with intravenous (IV) glycopyrrolate 0.005 mg/kg, midazolam 0.03 mg/kg and IV fentanyl 1 mcg/kg.

For the purpose of double blinding, one anesthetist who knew the study drug being used in each patient prepared the study drugs and labeled them as either Group A or Group B while another anesthetist who was oblivious to the identity of the study drug administered them in the patients and recorded the findings in each case. 150 mcg of inj. Clonidine (1ml) added to 9.0 ml of normal saline and made to 10 ml with each ml containing 15 mcg of Clonidine. Subsequently the required dose according to body weight was calculated and added to the normal saline to make 100 ml of the drug and infused in group A over 10 mins. 1000mg of Magnesium sulfate (2ml) added to 8.0ml of normal saline and made to 10 ml with each ml containing 100mg of magnesium sulfate. Subsequently the required dose according to body weight was calculated and added to the normal saline to make 100 ml of the drug and infused in group B over 10 mins.

Following this vital parameters(ATD) were recorded. The patients were then preoxygenated for 3 minutes, parameters again recorded and anesthesia was induced with propofol (titrated till loss of verbal response) and IV Veccuronium 0.1 mg/kg. Parameters were again taken just prior to laryngoscopy and intubation (T0). After intubation, maintenance was done with sevoflorane 0.5-0.6 % and N2O and O2 at 67% and 33% respectively and hemodynamic parameters were recorded at 1min after intubation(T1), 3min after intubation(T2), 5min after intubation(T3), 5min after pneumoperitoneum(P1), 10mins after pneumo peritoneum (P2), 20mins after pneumo peritoneum(P3) and 30 mins after pneumoperitoneum(P4). No surgical or any other stimulus was applied during 10 minutes of study period. At the end of the surgical procedure patients was reversed with neostigmine 0.05 mg/kg body weight and glycopyrrolate 0.01mg/kg. Any perioperative complication was also noted.

STATISTICAL METHOD-

All data are presented as Mean ± SD (Standard Deviation). All Quantitative data are assessed using Student's t - test to analyse changes over a period of time. Qualitative data are assessed using Fisher exact Test or Chi- square test.P value < 0 .05 is considered significant. The statistical software GRAPHPAD INSAT-3 was used for the analysis of data.

RESULTS:

The mean age,weight,height and duration of surgery of both the groups were comparable. There was no significant difference amongst the groups with regard to demographic variables (P value < 0.05).

Changes in heart rate

INTERVAL	Heart Rate (beats/min)				P-value
	Group A (CLONIDINE) N=50		Group B (MgSO4) N=50		
	Mean	SD	Mean	SD	
HR BL (Baseline)	81.27	8.77	81.62	9.06	0.861
HR ATD (After the drug)	77.00	8.91	81.80	8.26	**0.014**
HR T0 (Before Intubation)	76.5	8.96	80	8.70	0.083
HR T1 (1 Min After Intubation)	99.05	7.79	100.08	3.79	0.187
HR T2 (3 min After Intubation)	93.85	2.24	95.27	2.55	**0.009**
HR T3 (5 min After Intubation)	88.45	2.01	90.25	3.20	**0.003**
HR P1(5 min After Pneumoperitoneum)	93.37	3.82	94.17	3.63	0.340
HR P2 (10mins After Pneumoperitoneum)	90.35	4.41	91.12	6.60	0.538
HR P3 (20mins After Pneumoperitoneum)	90	3.26	90.4	7.57	0.759
HR P4 (30mins After Intubation)	89.25	3.87	90.37	6.87	0.369

Table- Comparison of mean heart rate between two groups.

The mean HR decrease observed after the drug (ATD), at 3 and 5 min after intubation which was statistically significant in Group A when compared to mean Heart Rate in group B. No other interval showed any significant difference.

CHANGE IN SYSTOLIC BLOOD PRESURE

	SBP				P-value
	Group A (CLONIDINE) N=50		Group B (MgSO4) N=50		
	Mean	SD	Mean	SD	
SBP BL (Baseline)	128.15	6.87	129.75	5.88	0.267
SBP ATD (After the drug)	123.52	6.93	127.85	6.22	**0.004**
SBP T0 (Before Intubation)	109.17	4.30	109.22	4.73	0.960
SBP T1 (1 Min After Intubation)	132.65	4.65	136.07	8.65	**0.030**
SBP T2 (3 min After Intubation)	124.45	4.90	125.97	8.49	0.328
SBP T3 (5 min After Intubation)	119.47	4.69	119.75	7.84	0.849
SBP P1(5 min After Pneumoperitoneum)	129.32	6.07	129.90	7.69	0.711
SBP P2 (10mins After Pneumoperitoneum)	127.10	6.99	127.42	7.26	0.839
SBP P3 (20mins After Pneumoperitoneum)	125.35	6.95	125.20	7.18	0.924
SBP P4 (30mins After Intubation)	124.72	6.86	124.20	6.61	0.728

Table- Comparison of mean systolic blood pressure in between two groups

The mean fall in SBP at the time of drug was significantly more in group A. Also, the rise in SBP at 1 minute after intubation was significantly lesser in group A.

DIASTOLIC BLOOD PRESSURE

Table- Comparison of mean diastolic blood pressure between the two groups.

	DBP				P-value
	Group A (CLONIDINE) N=40		Group B (MgSO4) N=40		
	Mean	SD	Mean	SD	
DBP BL (Baseline)	82.55	4.10	82.82	3.52	0.748
DBP ATD (After the drug)	80.82	4.39	80.57	3.37	0.776
DBP T0 (Before Intubation)	72.65	4.06	74.17	3.28	0.068
DBP T1 (1 Min After Intubation)	77.2	5.20	78.67	3.81	0.152
DBP T2 (3 min After Intubation)	74.7	5.15	76.55	4.48	0.090

DBP T3 (5 min After Intubation)	72.4	4.31	72.8	4.93	0.700
DBP P1(5 min After Pneumoperitoneum)	79.5	4.35	80.37	5.13	0.427
DBP P2 (10mins After Pneumoperitoneum)	77.52	4.35	78.94	3.53	0.131
DBP P3 (20mins After Pneumoperitoneum)	75.82	4.27	76.9	3.49	0.221
DBP P4 (30mins After Intubation)	75.15	4.22	75.27	3.47	0.885

The fall in mean DBP values were statistically insignificant at all intervals.

MEAN ARTERIAL PRESSURE

	MAP				**P-value**
	Group A (CLONIDINE) N=40		**Group B (MgSO4) N=40**		
	Mean	**SD**	**Mean**	**SD**	
MAP BL (Baseline)	98.05	4.13	98.77	3.35	0.391
MAP ATD (After the drug)	95.34	4.36	95.03	3.33	0.725
MAP T0 (Before Intubation)	85.06	3.21	86.09	2.97	0.143
MAP T1 (1 Min After Intubation)	96.05	3.80	98.19	4.29	**0.020**
MAP T2 (3 min After Intubation)	91.61	4.07	93.35	4.38	0.069
MAP T3 (5 min After Intubation)	88.40	3.28	88.76	4.13	0.669
MAP P1(5 min After Pneumoperitoneum)	96.45	4.11	97.21	4.85	0.454
MAP P2 (10 min After Pneumoperitoneum)	94.38	4.35	95.24	3.77	0.345
MAP P3 (20 min After Pneumoperitoneum)	92.66	4.25	93.32	3.21	0.437
MAP P4 (30mins After Intubation)	92.00	4.21	91.90	3.10	0.908

Table- Comparison of mean arterial pressure between the two groups.

The rise in mean MAP values in group A at 1 minute of intubation was significantly lesser when compared to group B.

SIDE EFFECTS

Side effects	**Group A (CLONIDINE)**		**Group B (MgSO4)**		**P-Value**
	No of Patients	**Percentage (%)**	**No of Patients**	**Percentage (%)**	
BRADYCARDIA	2	5	1	2.5	0.797
HYPOTENSION	2	5	1	2.5	
PONV	1	2.5	2	5	
NIL	35	87.5	36	90	

Table– Comparison of side effects in between two groups.

Bradycardia, Hypotension and PONV were seen in both the groups, and on comparing the two groups statistically using chi - square test, the difference was found to be non-significant.

DISCUSSION:

Hypertension and tachycardia subsequent to tracheal intubation and pneumoperitoneum is associated with poor outcomes in patients with compromoised cardiovascular system and the present study is aimed at comparing intravenous administration of Clonidine and Magnesium sulfate for attenuation of this hemodynamic response.

Clonidine, an alpha-2 adrenoreceptor agonist, acts on the pre and post -synaptic alpha-2 receptors both centrally and peripherally thereby causing vasodilatation, reduction in BP and HR, thus increasing the hemodynamic stability during the stress induced sympatho-adrenal responses to laryngoscopy and intubation during surgery and emergence from anesthesia.[7-16]

Magnesium sulfate, on the other hand, has been described as the physiological calcium antagonist because it competes with calcium for membrane channels and can modify many calcium-mediated responses.[17] Magnesium ions can inhibit the release of catecholamines from both the adrenal gland and peripheral adrenergic nerve terminals.[18] So, magnesium sulfate can significantly attenuate the release of catecholamines at the time of laryngoscopy and tracheal intubation and thus reduce the severity of cardiovascular disturbances. Magnesium also acts by slowing the atrial rate by inhibiting the calcium mediated depolarizing current in pacemaker tissue[19,20] and, therefore, the overall effect is the mild increase in heart rate.

In our study, we have used clonidine in a dose of 1.5 mcg/kg and magnesium sulfate in a dose of 50mg/kg in 2 groups selected randomly. The mean HR decrease observed after the drug (ATD), at 3 and 5 min after intubation was significantly more in clonidine. The mean decrease in SBP at the time of drug was significantly more clonidine. Also, the rise in SBP at 1 minute after intubation was significantly lesser in clonidine. The fall in mean DBP values were statistically insignificant at all intervals. The rise in mean MAP values with clonidine at 1 minute of intubation was significantly less (p=0.020) compared to MgSO4. At all intervals during pneumoperitoneum, no significant differences were found between the two drugs for all parameters observed.

Bradycardia, Hypotension and PONV were seen in both the groups, and on comparing the two groups statistically using chi - square test, the difference was found to be non-significant.

Thus, during laryngoscopy and intubation, clonidine provided better attenuation of heart rate, systolic and mean arterial blood pressure compared to $MgSO_4$ at various whereas both were equally effective for diastolic blood pressure. Also, during pneumoperitoneum, both the drugs were equally effective at all intervals for all evaluated parameters. These findings were corroborated by similar studies.

Vijaya P. Borkar Patil et al[21] concluded that between the two, IV Clonidine 1.5mcg/kg attenuated the haemodynamic response to laryngoscopy andintubation better than IV Magnesium sulphate 50mg/kg which was similar to our study. Palak P. Sheth et al[22] concluded that administration of IV clonidine 1.5mcg/kg was more effective than IV magnesium sulphate 50mg/kg given 30min before induction while both equally attenuate hemodynamic stress response to pneumoperitoneum.This was also seen in our study.

CONCLUSION-

From this study it was observed that Inj. clonidine 1.5mcg/kg caused better attenuation of cardiovascular response to laryngoscopy and intubation when compared to magnesium sulfate 50mg/kg. It provided more stable HR, SBP, and MAP during the stressful period following laryngoscopy and intubation. There were minimal side effects with no significant difference in the two groups.

On the basis of our present clinical comparative study, we can come to conclusion that:

1. Both clonidine and magnesium sulfate attenuate the cardiovascular response to laryngoscopy, intubation and

pneumoperitoneum.

2. Inj clonidine 1.5mcg/kg is more efficient than inj. MgSO4 50mg/kg for attenuation of the cardiovascular response to laryngoscopy and intubation.
3. Both the drugs have side effects and neither of the drug is superior over the other in this aspect.
4. More studies are needed to determine the optimum clonidine dose and regimen which can show significant benefit over MgSO4 in attenuating the cardiovascular response to laryngoscopy, intubation and especially pneumoperitonium.

1. Conflict of Interest- none
2. Sourse of Support - none

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