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EFFECT OF INTRAVENOUSLY ADMINISTERED MAGNESIUM SULPHATE AND CLONIDINE IN ATTENUATING HEMODYNAMIC RESPONSE TO INTUBATION IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY- A RANDOMIZED DOUBLE BLINDED COMPARATIVE STUDY.

Anaesthesiology

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ABSTRACT

BACKGROUND: Laryngoscopy and endotracheal intubation result in sympatho-adrenal stimulation leading to transient increase in heart rate and blood pressure, which can be deleterious in some patient populations. Both magnesium sulphate and clonidine are known to attenuate these hemodynamic responses. We conducted this randomized, double blinded study to compare the effectiveness of these drugs in attenuating the sympathetic response to laryngoscopy and intubation.

MATERIALS AND METHODS: Fifty ASA physical status I patients posted for elective laparoscopic cholecystectomy were randomized into two groups of 25 each. Group A patients received IV magnesium sulphate 50 mg/kg, while Group B patients received IV clonidine 1 µg/kg 15 minutes prior to intubation. Systolic, Diastolic and Mean blood pressure and Heart rate were recorded at baseline (prior to administration of drugs) and at 0 min, 5 min, 10 min, 15 min and 20 min after intubation. Data was analyzed using SPSS version 22 software.

RESULTS: There was comparable decrease in mean heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure in both magnesium sulphate and clonidine groups.

CONCLUSION: Both magnesium sulfate 50 mg/kg and clonidine 1 µg/kg are equally effective in blunting hemodynamic response to intubation in patients undergoing laparoscopic cholecystectomy.

KEYWORDS

Clonidine; intubation; laparoscopic cholecystectomy; laryngoscopy; magnesium sulphate

INTRODUCTION

Laryngoscopy and endotracheal intubation are associated with sympathetic stimulation leading to transient increases in heart rate and blood pressure[1]. The resulting hemodynamic responses do not pose problems in majority of patients, but may be deleterious in select patient groups such as, patients with heart disease, head injury patients etc. Various techniques and pharmacological agents have been used to blunt these responses. Magnesium sulphate and clonidine are two such drugs which have been shown to attenuate these effects of intubation helping in maintaining hemodynamic stability.

Magnesium sulphate has been shown to block the release of catecholamines from adrenal medulla as well as from nerve terminals and directly blocks catecholamine receptors. This results in sympathetic blockade, indirectly causing vasodilatation and thus, fall in blood pressure.[2] Thus, it has a role in blunting sympathetic response to laryngoscopy and intubation.

Clonidine is an antihypertensive agent that reduces sympathetic outflow from CNS via α2-adrenergic receptor agonism in nucleus tractus solitarii[3] resulting in decrease in arterial blood pressure. So, it can also be used for attenuating hemodynamic response to endotracheal intubation.

We hypothesized that both clonidine and magnesium sulphate may be effective in attenuating hemodynamic responses to laryngoscopy and intubation in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODOLOGY

The study was conducted as a prospective, open-labelled, double-blinded randomized comparative trial after obtaining approval from Institutional Ethical Committee (IEC REF NO/ DMR/ IMSSH/ SOA/ 180247). 50 ASA-1 patients of age 18-60 years of either sex, posted for elective laparoscopic cholecystectomy, were included in this study. Based on a previous study, [4] for achieving a power of study equal to 80% and a confidence interval of 95% (p-value of 0.05), total sample size was calculated to be 50. Patients were randomized to be included in one of the two groups using computer-generated random number table. Patients in Group A (n=25) received IV MgSO4 50 mg/kg while patients in Group B (n=25) received IV Clonidine1 µg/kg, 15 minutes prior to intubation. Total volume of test drugs was adjusted to 50 ml and administered over a period of 15 minutes before intubation in both the groups. Study drug preparation was done by a resident anesthesiologist who was blinded to the study protocol and was not involved further in the study for any data collection. Patients refusing to participate in study, belonging to ASA grade II/III/IV, having allergy to any of the study drugs or in whom laparoscopy was converted into laparotomy were excluded.

Written informed consent was taken from all the patients. Patients were kept nil per oral for 8 hours (solids) and 2 hours (clear liquids). Patients were premedicated with tablet pantoprazole 40 mg on the morning of surgery and glycopyrrolate 0.2 mg intravenously in pre-operative room.

After shifting to OT, patients were attached to standard monitors i.e. pulse oximetry, non-invasive blood pressure and electrocardiogram. Baseline parameters i.e. heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure were recorded. Study drugs were infused over 15 minutes prior to intubation with IV MgSO4 50 mg/kg in group A and IV clonidine 1 µg/kg in Group B.

Rest of the anesthesia protocol was similar in both the groups. All the patients received 2 µg/kg body weight of fentanyl citrate intravenously as pre-anaesthesia medication and they were pre-oxygenated with 100% oxygen for 3 minutes. Induction was done with propofol 2 mg/kg body weight and endotracheal intubation was facilitated by vecuronium bromide 0.1 mg/kg body weight. Maintenance of anesthesia was done using nitrous oxide and oxygen in 1:1 ratio and isoflurane. Vecuronium bromide 0.02 mg/kg body weight was used intravenously for maintenance of adequate muscle relaxation. Intermittent positive pressure ventilation was done with a target end-tidal CO2 of 30-35 mm Hg by adjusting adequate tidal volume and respiratory rate. Intraoperative fluid management was done according to 4-2-1 rule of Holiday and Segar formula. Patient's heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were assessed prior to administration of drugs (baseline), immediately after intubation (0 min) and at 5, 10, 15 and 20 minutes after intubation. More than or equal to 20% increase or decrease from baseline values of any parameter was considered as clinically significant. At the end of surgery, reversal of neuromuscular blockade was achieved with intravenous neostigmine 0.05 mg/kg and intravenous glycopyrrolate 0.01 mg/kg and patients were extubated and shifted to PACU. Occurrence of any intraoperative or postoperative adverse event was noted.

Data was statistically analyzed using SPSS Version 22 software. For qualitative data, the Chi-Square test was applied and for inter-group comparison, ANOVA was used. Results were presented as Mean ± SD or as absolute numbers. A p-value of <0.05 was considered statistically significant and p- value of <0.001 was considered as statistically highly significant.

RESULTS

Demographic characteristics of the patients in two groups were similar [Table 1]. Decrease in mean heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure from the baseline values was observed in both the groups, but there was no statistically significant difference between the two groups [Tables 2, 3, 4, 5].

Table 1 Demographic profile of the study population

Parameters	Group A	Group B	P value
Age (years)	41.77 ± 10.99	40.23 ±8.7	0.671
Weight (kg)	59.17 ± 5.5	60.43 ± 9.3	0.293
Height(cm)	159.97 ± 3.8	160.83 ±4.5	0.177
Gender (M/F)	16/9	17/8	0.182

Table 2 Comparison of mean heart rate at different time intervals between the groups

Heart rate	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	98.67	6.2	97.8	5.8	0.58
0 min	94.73	4.3	92.93	4.6	0.121
5 min	93.73	4.5	91.6	4.4	0.069
10 min	90.53	4.3	90.13	4.1	0.712
15 min	85.8	2.5	88.53	2.1	0.981
20 min	84.33	1.7	86.13	2.2	0.517

Table 3 Comparison of mean systolic blood pressure at different time intervals between the groups

SBP	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	134	5.8	136	5.1	0.427
0 min	134	4.1	135	4.8	0.399
5 min	133	3.1	134	6.7	0.516
10 min	132	3.2	132	5.6	0.352
15 min	129	3.4	132	5.5	0.971
20 min	131	4.9	130	4.8	0.101

Table 4 Comparison of mean diastolic blood pressure at different time intervals between the groups

DBP	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	81.87	3.3	82.67	6.4	0.543
0 min	80.27	2.7	82.73	2.0	0.981
5 min	77.27	2.7	78.73	2.1	0.367
10 min	78.33	2.5	77.8	1.9	0.267
15 min	77.73	2.7	76.93	2.0	0.471
20 min	76.27	2.6	75.2	4.1	0.233

Table 5 Comparison of average mean arterial pressure at different time intervals between the Groups

MAP	Group A		Group B		P value
	Mean	SD	Mean	SD	
Baseline	89.47	6.0	92.13	5.5	0.079
0 min	89.53	5.7	90.33	3.6	0.671
5 min	89.33	5.8	88.4	2.7	0.381
10 min	85.8	5.0	86.93	2.9	0.288
15 min	83	2.6	85.2	3.0	0.786
20 min	80.93	4.4	79.33	3.6	0.125

DISCUSSION

In present study, reduction in heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was observed in both Group A and Group B, though the difference between two groups was statistically insignificant suggesting both magnesium sulphate and clonidine were equally effective in attenuating hemodynamic response to intubation. Also, reduction in values of the observed hemodynamic parameters from baseline values suggested effective mitigation of sympathetic response to intubation. This decrease was not clinically significant (≥20% from baseline value) ascertaining that both the drugs, in used doses, did not result in exaggerated fall of various observed hemodynamic parameters and thus, maintained hemodynamic stability.

We found that there was no statistically significant difference in mean heart rate between both the groups. Also changes in heart rate in both the groups from baseline values were clinically not significant (≥20% from baseline). Similar findings were seen in a study conducted by Bidyut Bohra et al[5] who also observed clinically insignificant changes in heart rate at baseline, 5 min and 10 min after intubation (85.7±6.8, 94.6±7.7, 93.6±7.4 for magnesium group & 87.6±6.8, 98.9±6.6, 99.1±7.1 for clonidine group). In a study by Arnab Bakshi et al[6], clonidine 3 µg/kg was administered via intravenous infusion over a period of 15 minutes by infusion pumps before induction. They observed significant decrease in heart rate from baseline, after induction ($p<0.05$) and 5 minutes after intubation ($p<0.01$). This is in agreement to our findings. Although in our study, reduction in mean heart rate was not clinically significant in patients receiving clonidine which may be due to the reason that we used lesser dose of clonidine (1 µg/kg).

We observed a decrease in systolic blood pressure, diastolic blood pressure and mean arterial pressure in Group A and B, though the difference between the groups remained statistically insignificant and decrease in values of all parameters (SBP, DBP & MAP) from baseline value was not clinically significant. This reinforces the fact that magnesium sulphate and clonidine both are equally effective in providing hemodynamic stability by blunting sympathetic response to intubation and at the same time, did not result in profound decrease in pressure values from baseline values, in the used doses. In a study conducted by NS Siwalkar et al[7], it was observed that both clonidine 2 µg/kg and magnesium sulphate 50 mg/kg were effective in preventing the increase in systolic, diastolic and mean arterial pressures following laryngoscopy. These observations were similar to our results. They also observed that clonidine showed better results than magnesium sulphate. This is, in contrast to our findings and can be explained due to the higher dose of clonidine (2 µg/kg) used in the said study compared to our study (1 µg/kg).

In another study conducted by VPB Patil et al[8], there was no significant difference in the mean diastolic BP in both the groups immediately at intubation (76.17±10.74 for group M and 78.86±10.48 for group C with $p>0.05$) and 5 min after intubation (63.03±7.909 for magnesium sulphate and 67.69±13.588 for clonidine with $p>0.05$), which is in agreement to our findings in present study. Corresponding observations noted in our study were 80.27±2.7 in Group A vs 82.73±2.0 in Group B ($p>0.001$) immediately after intubation and 77.27±2.7 in Group A vs 77.73±2.1 in Group B ($p>0.001$) 5 min after intubation.

Bhavna Soni et al[9] conducted a study in patients undergoing laparoscopic surgery in which patients were randomized to receive either clonidine or magnesium sulphate. They observed no significant difference in mean arterial blood pressure between groups. In yet another study conducted by Zhang et al[10], it was found that clonidine infusion significantly reduced mean arterial blood pressure following intubation in patients undergoing laparoscopic cholecystectomy, supporting the findings of our study.

We did not encounter any serious adverse events (bradycardia, hypotension, delayed recovery etc.) in our patients. In a study by M Ray et al[11],patients were administered clonidine 3 µg/kg i/v 15 minutes before induction followed by continuous infusion of clonidine @ 1 µg/kg/hour intraoperatively. They observed significant increase in incidence of bradycardia and hypotension which can be attributed to use of higher dose and continuous infusion of clonidine. They also observed delayed recovery in patients who received magnesium sulphate which again may be attributed to continuous intraoperative infusion of magnesium sulphate @ 10 mg/kg/hour after giving a loading dose of 30 mg/kg. All these findings suggest that use of higher dose and continuous infusion of these drugs may result in increased risk of adverse effects and thus, prompted us to use lesser dose of these drugs in our study. Even with the smaller dose used, both magnesium sulphate and clonidine were effective in mitigating the hemodynamic response to laryngoscopy and endotracheal intubation without any increase in adverse events.

Limitations of the study are small sample size and inclusion of only ASA-I patients.

CONCLUSION

We conclude that both magnesium sulfate 50 mg/kg and clonidine 1 µg/kg are equally effective in blunting hemodynamic response to intubation and have safe patient profile in the used doses.

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Conflict of Interest: None

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