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Original Research Paper

Anaesthesiology

TO OBSERVE THE EFFICACY OF INTRAVENOUS MAGNESIUM SULFATE GIVEN AFTER INTUBATION AND BEFORE CREATING PNEUMOPERITONEUM TO ATTENUATE HEMODYNAMIC CHANGES DUE TO PNEUMOPERITONEUM IN LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT In a randomized, double-blind trial study, 60 patients were divided into two groups. Group M received 50 mg/kg i.v. magnesium sulphate in 100 ml, 0.9% normal saline, Group C received the same volume of normal saline during intraoperative period. HR, MAP, Rate pressure product, were recorded prior to induction, intubation, 3 and 5 minutes post intubation, prior and during to pneumoperitoneum, 5 minutes after release of pneumoperitoneum, 5 and 10 minutes after extubation. There were sustained decreases in Systolic and Diastolic blood pressures after Endotracheal intubation in Group M in comparison to Group C contributing to lower mean arterial pressures in group M. In Group C, MAP were 13% higher than baseline. MAP increased to 25%, after extubation, which imputes stress response, but which was attenuated in group M which assures better outcome. In conclusion, Magnesium sulfate attenuated reflex tachycardia, hypertensive response, decreased RPP, and hence myocardial oxygen consumption.

KEYWORDS : Magnesium sulfate, Laparoscopic Cholecystectomy, Stress response, Pneumoperitoneum

INTRODUCTION

The rising popularity of laparoscopic surgery is one of the most spectacular events in modern surgical sojourn putting an end to the era of *"Big surgeons' Big incisions"*.

Laparoscopy results in multiple postoperative benefits, quicker recovery, avoidance of big incisions, less tissue damage and shorter hospital stay.[1].Pneumoperitoneum with CO_2 and patient positions required for different laparoscopic surgeries adversely affect due to elevation of plasma noradrenaline by sympathetic stimulation[2]. Peritoneal insufflations also results in respiratory changes and can contribute to stress response.[3][4]

Attenuation of circulatory response to Pneumoperitoneum is usually done by opioids,[5] vasodilators,[6] beta blocking agents,[7] and alpha-2 adrenergic agonists,[8] reducing anaesthetic and analgesics agents attenuating the stress responses.

Magnesium in its wide spectrum actions also has the ability to block the release of catecholamines from both the adrenal gland and the adrenergic nerve terminals.[9] Apart from that, magnesium can produce vasodilatation by acting directly on blood vessels[10] Intravenously administered magnesium sulphate is capable of attenuating the adverse hemodynamic response associated with endotracheal intubation.[11] and it also capable of attenuating vasopressin-stimulated vasoconstriction.[12] In the present study an attempt has been made to evaluate magnesium sulphate as i.v. adjunct to reduce hemodynamic instabilities during laparoscopic cholecystectomy

MATERIALS AND METHODS:

After obtaining Institutional Ethics Committee approval and written informed consent from patients, the study was conducted at Ispat General Hospital, Rourkela, Odisha.

The study was prospective, randomized, placebo controlled and double blinded. Sixty American Society of Anaesthesiologists (ASA) grade I and II patients, aged 18-65 years, undergoing elective laparoscopic cholecystectomy were assigned (using a computer derived random number sequence) to one of the two groups (each containing 30 patients).

EXCLUSION CRITERIA:

- Patient Refusal
- Patients with renal, hepatic, cardiovascular, and endocrinal disorders.
- Patients on beta blockers, methyldopa or Monoamine oxidase inhibitors.
- Patients with drug allergies,pregnant and lactating patient

MATERIALS:

- 50%.Magnesium Sulphate in 2ml ampoule.
- 100 ml Normal Saline as diluent.

METHOD OF STUDY

The patients were assigned to one of the groups by computer generated random numbers

Group M (n=30):--Intravenous Magnesium Sulfate 50mg/kg IBW

Group C (n=30):-- Placebo 0.9% NS

Magnesium sulphate as available in 50% solution is made 20% and was **diluted in 100 ml normal saline and was given intravenously over** 3 minutes immediately after intubation before insufflation of abdomen. Placebo group was administered 100ml of 0.9% NS over 3 min.

IN THE OPERATION THEATRE

On arrival, all baseline vitals were recorede, Intravenous access was secured, Invasive Recording of Systolic (SAP), and Diastolic Arterial Pressures (DAP), Heart rate (HR) were recorded and Mean Arterial Pressure (MAP), Rate Pressure Product (RPP) ere calculated.

ANAESTHETIC TECHNIQUE:

Premedication:

All patients were premedicated with inj.Glycopyrrolate0.2mg , inj.Midazolam0.05mg/Kg and inj. fentanyl 2 mcg/kg i.v 5 minutes prior to induction.

Induction and Intubation:

Pre-oxygenation with 100% O_2, induction with inj.Propofol 2mg/Kg. inj.Rocuronium 1mg/Kg was given i.v to facilitate endotracheal intubation.The study drug solution is infused over 3 min immediately after intubation and before insufflating pneumoperitoneum.

Maintenance:

Anaesthesia was maintained with N_2O and O_2(50:50) and Isoflurane 1%. End tidal CO_2 maintained between 30-40 mm

Hg. Muscle relaxation with inj. vecuronium. Isoflurane vaporizer was turned off about 10 minutes before the end of surgery. N_2O was discontinued after the last skin stitch was placed.

Intraoperatively the following parameters were monitored and recorded:

A. Continuous ECG, HR, SPO_2, NIBP, $EtCO_2$.
B. Continuous intraperitoneal pressure at 12mm of Hg.

Rise of MAP (> 25% of baseline) was titrated to maintain MAP Inj.labetalol Fall of MAP (> 25% of baseline) was treated by decreasing the dial setting of the Isoflurane vaporizer, IV fluids and supplemented with an Ephedrine 5mg i.v bolus as and when necessary.

Bradycardia, defined as HR < 60 beats $min^{-1,}$ was treated with Atropine 0.6mg i.v and repeated if necessary.

Reversal:

Neuromuscular block was reversed with Neostigmine, 50 μg Kg^{-1}IV and Glycopyrrolate, 10μg kg^{-1} IV.

STUDYPARAMETERS

1). HR, MAP, Rate pressure product:were recorded at the followingpoints of time

- Before premedication,
- prior to induction,
- prior to intubation,
- 3 and 5 minutes post intubation,
- prior to pneumoperitoneum,
- during pneumoperitoneum (5, 10, 15, 30, 45, 60 minutes),
- 5 minutes after release of pneumoperitoneum ,
- 5 and 10 minutes after extubation.

2). The number of patients needing active intervention for hypotension, hypertension, tachycardia and Bradycardia was noted.

STATISTICS:

Power calculations based on web based sample size calculators https://www.dssresearch.com/ KnowledgeCenter/ toolkitcalculators/samplesizecalculators.aspx suggested that with (α=0.05, β=0.70) ,to detect 15% difference in mean values{ in percentages} expected between two groups after administration of magnesium sulphate suggested minimum of 28 subjects per group.so rounded off to include 30 patients per group. Intra-group differences and inter group differences were evaluated by repeated measures of two-way analysis of variance (ANOVA), and inter-group differences using the unpaired *t*-test. *P*-values of <0.05 were considered significant. Statistical analysis was performed using SPSS® 22.0. Software (SPSS Inc., Chicago, IL, USA),Microsoft excel 2007. Data are expressed as mean (SD) , percentages (%), and numbers (*n)*

RESULTS

A total of 60 patients consented to participate at the preoperative anaesthesia visit and no patient was excluded at any stage of the study.

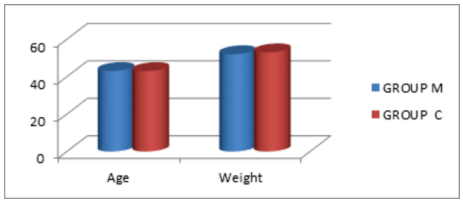
The groups were similar to

- Age,
- Weight,
- Gender (Table 1) and
- Duration of anaesthesia (Table 2).

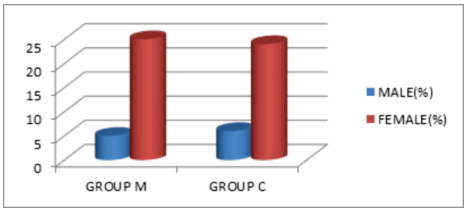
PATIENT CHARACTERISTICS

TABLE-1 SEX, AGE & WEIGHT DISTRIBUTION

	GROUPM	GROUPC	P*
MALE (%)	5(16.5)	6(19.8)	0.3679
FEMALE (%)	25(83.5)	24(79.2)	0.3679
Age(Years)M±SD	43.73±8.17	43.73±8.17	0.6919
Weight(Kg) M±Sd	52.47±6.14	53.5±6.27	0.3679



GRAPH 1:AGE AND WEIGHT IN GROUPS

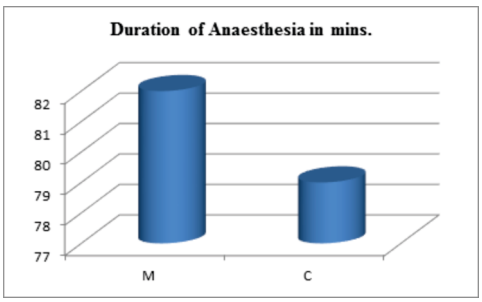


GRAPH 2: GENDER AMONG GROUPS

TABLE-2 DURATION OF ANAESTHESIA

GROUPS	No. of cases	Duration of Anaesthesia In mins.	P*
M	30	82.1±22.02	0.9036
C	30	79.67±19.34	

*p>0.05 statistically not significant.



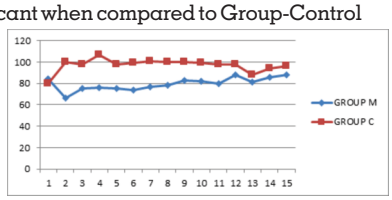
GRAPH 3: DURATION OF ANAESTHESIA

TABLE-3 PERIOPERATIVE HEART RATE (Mean ±SD)

TIME	Group M	GROUP C	M vsC
Pre operative	84.7±8.8	80.2±6.7	0.0002
Pre induction	66.8±9.1*©	99.9±7.6*	0.0001
Pre intubation	75.8±14.7*©	98.9±5.3*	0.0001
3minafter intubation	76.2±14.3*©	107.1±7.7*	0.0001
5minafter intubation	74.1±14.6*©	98.6±5.5*	0.0001
Pre pneumoperitoneum	74.4±15.2*©	99.9±6.2*	0.0001
During pneumoperitoneum			
5min	74.3±17.2 ©	101.4±7.7*	0.0001
10min	81.9±17.9©	100.8±9.2*	0.0001
15min	83.0±14.3©	97.0±17.8*	0.0001
30min	81.1.±21.1©	99.3±6.4 *	0.0001
45min	82.5.±15.3	98.3±5.1 *	0.0001
60min	83.4±9.1	97.6±3.2*	0.0001
5min after Release of pneumoperitoneum	81.0±9.30©	88.5±9.7	0.0001
POST EXTUBATION			
5min	82.4±8.4	94.9±6.4*	0.0001
10min	88.4±7.2	96.0±8.3*	0.0001

* - Significant change from base line (p<0.05)

©- Significant when compared to Group-Control



GRAPH 4 : PERIOPERATIVE HEART RATE

1-Base line 6-Pre PP 11-45 min PP
2-Pre induction 7-5min PP 12-60 min PP
3-Pre intubation 8-10 min PP 13-5 min PP
4-3 min. post intubation 9-15min PP 14-5 min. post extubation
5-5 min. post intubation 10-30 min PP 15-10min. post extubation

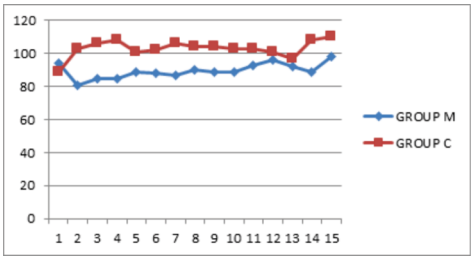
TABLE-4: Repeated measures ANOVA: Heart rate

Heart rate	F	P
Between Group	276.917	P<0.001**
With in Group	5.647	P<0.001**

TABLE-5 PERIOPERATIVE MEAN ARTERIAL PRESSURE (Mean ±SD)

TIME	GROUPM	GROUP C	M vs C
Pre operative	94.8±7.53	87.4±5.07	0.0008
Pre induction	81.1±8.37*©	103.43± 6.11*	0.0001
Pre intubation	85.53±7.4*©	107.03±4.54 *	0.0001
3min after intubation	85.86±7.85*	108.20±7.35*	0.0001
5min after intubation	86.4.± 7.24*	101.76±4.86	0.0001
Pre pneumoperitoneum	88.1±5.85*	102.13±4.55	0.0001
During pneumoperitoneum			
5min	87.63±5.51©	106.5±7.14*	0.0001
10min	90.23± 6.35	104.07± 6.23 *	0.0001
15min	90.8± 7.88	104.20± 5.54 *	0.0001
30min	91.3± 7.75	103.76± 4.77	0.0001
45min	92.7±7.88	103.63 ±5.24	0.0001
60min	94.0± 6.71	101.26 ±3.55	0.0001
5min after Releaseof pneumoperitoneum	91.1± 9.42	98.2± 4.53	0.0001
Post extubation			
5min	88.9± 7.27 *	108.83 ± 8.7*	0.0001
10min	96.7 ± 11.7	111.0±7.7	0.0001

*- Significant change from base line (p<0.05)
©- Significant when compared to Group-C



GRAPH5PERIOPERATIVE MEAN ARTERIAL PRESSURE

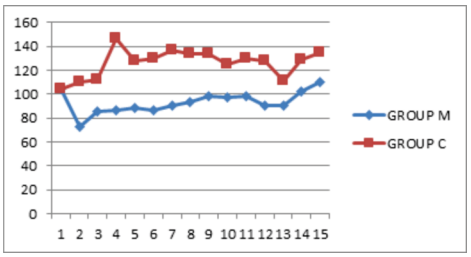
TABLE-6 Repeated Measures Of ANOVA: Mean Arterial Pressure

Mean Arterial Pressure	F	P
Between Group	349.365	P<0.001**
With In Group	12.571	P<0.001**

TABLE-7 PERIOPERATIVE RATE PRESSURE PRODUCT (Mean ±SD)

TIME	M	C	M vs C
Pre operative	100.8±5.3	105.5±4.6	0.98
Pre induction	75.7±5.4	108.7±5.9	0.0001
Pre intubation	92.2±10.4	111.7±3.9	0.0001
3min after intubation	87.9±4.6	146.9±3.2	0.0001
5min after intubation	91.3±3.4	128.0±2.5	0.0001
Pre pneumoperitoneum	87.1±1.8	123.27±27.0	0.0001
During pneumoperitoneum			
5min	87.2±15.2	137.0±4.2	0.0001
10min	92.9±3.6	135.2±3.4	0.0001
15min	98.7±5.6	133.6±4.7	0.0001
30min	91.6±22.2	125.0±2.7	0.0001
45min	97.8±1.6	129.9±2.3	0.0001
60min	104.6±7.8	125.3±18.8	0.0001
5min after Release of pneumoperitoneum	89.1±5.8	110.5±5.4	0.0001
Post extubation			
5min	101.7±5.5	125.0±18.5	0.0001
10min	108.3±4.6	136.8±4.4	0.0001

Significant change from base line (p<0.05)
©- Significant when compared to Group-C



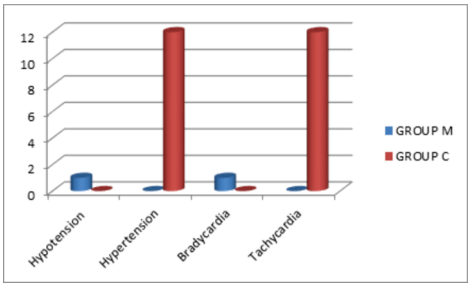
GRAPH 6 PERIOPERATIVE RATE PRESSURE PRODUCT (Mean ±SD)

TABLE-8 Repeated measures ANOVA: RATE PRESSURE PRODUCT

Rate Pressure Product	F	P
Between Group	6100.82	P<0.001**
Within Group	101.804;	P<0.001**

TABLE-9 PERIOPERATIVE SIDE EFFECTS

Group	Hypotension	Hypertension	Bradycardia	Tachycardia
M	1	0	1	0
C	0	12	0	12



GRAPH 7 : PERIOPERATIVE SIDE EFFECTS

In Table 9, 1 patient in Group M developed intra-operative hypotension and Bradycardia whereasIn the control group, 12 patients developed intraoperative Hypertension and Tachycardia throughout the surgery.

DISCUSSION

The aim of our study was to observe the effectiveness of Magnesium sulfate on attenuation of hemodynamic changes in patients undergoing laparoscopic cholecystectomy.

Vitals recorded on the preoperative day was considered as a baseline.

In the Study, CO2 was used to create Pneumoperitoneum(PP) IAP was maintained at 12 mm Hg and effects of magnesium sulphate were studied. Immediately after PP, the prepared solution was administered and the variables were recorded, being alert observing for any side effects.

In our Study, there were sustained decreases in Systolic and Diastolic blood pressures after Endotracheal intubation in Group M in comparison to Group C contributing to lower mean arterial pressures in group M in similarity with, James et al.[12]where i.v. magnesium sulphate was able to attenuate the adverse hemodynamic response of Endotracheal intubation We have not used for continuous infusion of magnesium

sulphate as in Telci and et al.[13] where 10 mg/kg/h continuous i.v. infusion was used.

Diamant et al.[14]reported 35% decrease in cardiac output in dog with a raised IAP of 40 mmHg. Ishizaki et al.[15] observed significant fall in cardiac output at 16 mmHg of IAP and hemodynamic alterations reduced at 12 mm Hg of IAP. So in our study, we kept IAP 12 mm Hg.

In this study the HR throughout PP in group M were lower than Group C which is in contrary to study by D. JEE C.LEE et al.[16]where no effect on heart rate was observed.

On assessing for MAP in Group M there were decrease in MAP during pre induction period when compared to base line. During PP, there were a well maintained trend with no increases in MAP on comparison to base line.Then 5 minutes after release of pneumoperitoneum the MAP decreased and remained at 2% below the base line.

In Group C, the preinduction MAP were 13% higher than the baseline and it remained in that range throughout the PP. After that MAP decreased, but 9% higher than baseline. MAP increased to 20% and 25%, 5 and 10 minutes after extubation, respectively which imputes a severe stress response, but which was attenuated in group M which could improve the better outcome. The probable reason being magnesium to reduce release of norepinephrine, epinephrine and vasopressin in post PP contributing for the blunting of hemodynamic response.

In an attempt to assess the burden of the hemodynamic fluctuations on cardiovascular system, we have studied Rate Pressure Product in both the groups as Fredarick L. Gobel, et al[17] suggested that Rate-Pressure Product as an Index of Myocardial Oxygen consumption. So this stress reducing response indirectly unburden the cardiac load.

In Group C, pre-induction RPP was 6% higher than base line and the pre-intubation RPP was 7% higher than the preoperative value. It was increased further during PP and 5 minutes after release of PP the RPP was 6% higher than the base line. Post extubation, the RPP increased significantly which was up to 27.5% when compared to base line.

In Group M, RPP was significantly lower compared to base line values at all the measurement times except 5minutes and 10 minutes after extubation. RPP was low in group M due to moderate decrease in systolic blood pressure but probably attributable to decrease in heart rate in greater extent. So RPP were lower in group M than group C.

So In Our Study repeated measues of ANOVA Of Heart Rate, Mean Arterial Pressure, Rate Pressure product $P<0.001$ was observed with in the group and between the groups and significance of intervention was observed.

Regarding the incidence of adverse effects, 1 patient in Group M developed intra-operative hypotension and Bradycardia whereas In the control group, 12 patients developed intraoperative Hypertension and Tachycardia throughout the surgery.

Following conclusions:

- Magnesium sulfate attenuated the reflex tachycardia and hypertensive response to PP significantly when compared to placebo.
- RPP which is a major determinant of myocardial oxygen consumption. Magnesium sulfate offered the advantage of reduction in RPP, and hence myocardial oxygen consumption which subsequently decrease myocardial burden.
- There were significantly more episodes of hypertension needing antihypertensive drug treatment in the placebo group.

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