



## Surgery

## A COMPARITIVE STUDY ON EFFICACY OF INTRAVENOUS DEXMEDETOMIDINE AND MAGNESIUM SULPHATE IN ATTENUATING PRESSOR RESPONSE DURING INTUBATION AND PNEUMOPERITONEUM IN LAPAROSCOPIC SURGERIES: A PLACEBO-CONTROLLED RANDOMISED CLINICAL TRIAL

**Dr. Mazumdar  
Kanaka Varsha**

**Dr.A Venkateswara  
Rao\***

Professor and HOD\*Corresponding Author

**Dr.sophia**

Associate Professor

**ABSTRACT** **INTRODUCTION:** General Anaesthesia and Pneumoperitoneum during laparoscopic surgeries results in hemodynamic instability. **AIM:** To compare efficacy of intravenous Dexmedetomidine and Magnesium sulphate in attenuating hemodynamic instability during intubation and Pneumoperitoneum. **METHODS:** After written informed consent and ethics committee approval, 60 patients belonging to ASA status I or II who were posted for elective laparoscopic surgeries, were divided into 3 groups. Group D(n=20), Group M(n=20) and Group N(n=20). Group D received – Inj. Dexmedetomidine 1µg/kg bolus made to 100ml for 15 minutes. Group M received- Inj. Magnesium sulphate 2g bolus made to 100ml for 15 minutes. Group N received – 100ml saline over 15 minutes. Pre Drug (Po) ECG, BIS value, SpO<sub>2</sub>, Heart rate and Blood pressures were recorded after 5 minutes of stabilization of patient and after 5 minutes of completion of infusion. The same values were recorded a) After intubation and for every minute for 5 minutes b) Before peritoneal insufflation (PI) c) 5 minute after P.I, 10 minutes after P.I, 15 minutes after P.I, 30 minutes after P.I, 60 minutes after P.I, 90 minutes after P.I, 5 minutes after peritoneal deflation. **RESULTS:** Based on a previously published study, taking HR as the primary objective, SD obtained was 5.397 and expected difference between the means was calculated as 3.38. Assuming the power of our study 80% and an alpha error of 0.05, sample size was calculated to be 20. **CONCLUSION:** Dexmedetomidine has better hemodynamic stability compared to Magnesium sulphate..

### KEYWORDS :

#### INTRODUCTION:

- Laparoscopic surgical procedures are cost effective, have minimal blood loss due to small incision and less postoperative pulmonary complications and reduced metabolic stress compared to conventional open procedures leading to early recovery.
- In general anesthesia there is marked sympathoadrenal response during intubation, extubation.
- Pneumoperitoneum is produced by administration of carbon dioxide (CO<sub>2</sub>) into the peritoneal cavity during laparoscopic procedures which affects homeostasis and leads to alterations in cardiovascular, pulmonary physiology and stress response. Hemodynamic stability during peri-operative period is of paramount importance as there are many patients who have a compromised cardiovascular status thereby avoiding hypertension, hypotension and tachycardia.
- Dexmedetomidine, a highly selective alpha-2 adrenergic agonist, administration of dexmedetomidine before induction of anesthesia attenuates sympathoadrenal responses to laryngoscopy, endotracheal intubation, pneumoperitoneum and extubation.
- Magnesium has the ability to block the release of catecholamines from both the adrenal gland and the adrenergic nerve terminals. Magnesium sulphate as a physiological calcium antagonist as it competes with calcium for membrane channels and modifies calcium mediated responses.
- Bi-spectral index (BIS) monitoring provides a simple measure of anesthetic depth through analysis of electrocortical activity. It integrates the frequency-domain, time-domain, and bispectral analysis of raw EEG signals into a numerical value, ranging from 0 (isoelectric EEG) to 100 (fully awake). BIS values of 40–60 are preferred for surgical patients because of deep hypnotic state, unresponsiveness to verbal or surgical stimuli, and low probability of recall in this range; BIS values increase with noxious stimuli.
- The purpose of this study is to compare the effectiveness of Magnesium sulphate (physiological calcium antagonist) and Dexmedetomidine (highly selective alpha-2 adrenergic agonist) compared to placebo for attenuation of stress response in laparoscopic abdominal surgeries.

#### METHODS:

- This prospective placebo controlled randomized clinical trial conducted in tertiary health care centre from August 2022 to September 2022 after taking ethical committee approval and written informed consent from the patients.

#### INCLUSION CRITERIA:

Patients of ASA grade I and II aged between 20-60 years, either gender and who posted for elective laparoscopic abdominal surgeries were included in study.

#### EXCLUSION CRITERIA:

Patients with hypertension, severe hepatic, renal, endocrine, cardiac dysfunction, conduction defects, on beta blockers, pregnancy, morbidly obese, hypomagnesaemia and any contraindication to magnesium sulphate or dexmedetomidine were excluded from the study.

- Pre-anaesthetic evaluation and relevant investigations were carried out in all patients. On the night before the surgery, informed written consent was obtained and tablet alprazolam 0.5 mg was given to all patients and were fasted for 8 hours.
- In the operating room, non-invasive blood pressure (NIBP), electrocardiogram (ECG), pulse oximeter (SpO<sub>2</sub>) and bispectral index monitor (BIS VISTA™ monitoring system) were attached and intravenous cannula was secured.

#### BLINDING AND RANDOMIZATION:

- Eligible patients are divided into 3 groups: Group D(n=20), Group M(n=20) and Group N(n=20), each group by computer-generated random numbers, sealed in envelopes as folded slips. These slips were picked up by an independent observer who later prepared the drug solutions accordingly. This was a participant and investigator blinded study.
- PRE DRUG (P0) electrocardiogram (ECG), BIS value, SpO<sub>2</sub>, heart rate (HR) and blood pressures-systolic (SBP) and diastolic (DBP), were recorded after 5 min of stabilization of the patient.
- Intravenous line was secured with 18G cannula and premedication i.e., Inj. Glycopyrolate 0.02 mg/kg, Inj. Ondansetron 0.15 mg/kg, Inj. Midazolam, Inj. fentanyl 2 µg/kg were given and pre-oxygenated for 3 minutes.
- The study drug solution of either dexmedetomidine or Magnesium sulphate or normal saline (control) was prepared in 100 ml normal saline by an independent consultant not involved in this study; the investigator also remained blind regarding the constituents of the solution.
- Fifteen minutes prior to induction,
- Group D received Inj. Dexmedetomidine 1µg/kg bolus made to 100ml for 15 min.
- Group M received Inj. Magnesium sulphate 2g bolus made to 100 ml for 15 min.

- Group N received 100 ml saline over 15 min.
- AFTER TEST DRUG (P1) Five minutes after completion of infusion of test drug ECG, BIS value, SpO<sub>2</sub>, RSS, and vitals were recorded.
- Then, induction of anesthesia was facilitated using propofol in titrated doses to achieve BIS range 40–50, which provided adequate depth for laryngoscopy and intubation.
- AT INTUBATION(P2) : Laryngoscopy and intubation were facilitated by 2 mg/kg succinylcholine, ventilation was confirmed and end tidal carbon dioxide recorded, with continuous monitoring of all parameters.
- BIS values, SpO<sub>2</sub>, HR, and MAP were recorded after intubation every minute for 5 min intraoperatively (P3-P7)
- Muscle relaxation was achieved with inj.vecuronium bromide 0.1mg/kg bolus dose and 0.01 mg/kg maintenance dose when required.
- Controlled ventilation was maintained with sevoflurane and a mixture of 66% N<sub>2</sub>O with oxygen.
- Group D were administered Inj. Dexmedetomidine infusion at the rate of 0.2-0.4 µg/kg/hr as maintenance ,Group M were administered Inj. Magnesium sulphate at rate of 12-15 mg/kg/hr,Group N received 5ml/hr infusion.
- Oxygen saturation and end tidal carbon dioxide were maintained by controlled ventilation.
- All infusions given @5 ml/hr to achieve blinding.Ringers lactate was given as a maintenance fluid.
- Before peritoneal insufflation(P.I) (P8 ), 5 mins after P.I(P9 ), 10min after P.I (P10), 15 min after P.I(P11), 30 mins after P.I(P12), 60 min after P.I(P13), 90 min after P.I(P14), 5min after peritoneal deflation (P 15).
- Intraoperative hemodynamic parameters like BIS values, Spo<sub>2</sub>,Heart rate and Mean arterial pressures was recorded .
- Inj Paracetamol 1 g IV was given at the end of surgery. Sevoflurane and infusion of drugs were stopped at the end of surgery. Neuromuscular blockade was reversed with Inj. Glycopyrrolate 0.01mg/kg and Inj Neostigmine 0.05 mg/kg and extubated, when patients were awake, later shifted to PACU.
- Recovery time was observed in both groups as time elapsed since stoppage of sevoflurane and study drug infusion till patient achieved a modified Aldrete's score of ≥9.
- Sedation score was assessed at the end of surgery, at 15 mins, 30 mins and 60 minutes using Ramsay Sedation Scale.

**STATISTICAL ANALYSIS:**

- Based on a previously published study, taking HR as the primary objective, SD obtained was 5.397 and expected difference between the means was calculated as 3.38. Assuming the power of our study 80% and an alpha error of 0.05, sample size was calculated to be 20.
- Data were expressed using Mean±SD, and percentages. Continues variables like age, weight and duration of surgery were compared using Student t test / Mann Whitney U test Categorical variables (gender, ASA grade, bradycardia, hypotension, nausea/vomiting and shivering) were compared by chi square/ Fishers Exact test The level significance used was P<0.05.

**RESULTS:**

**TABLE 1: DEMOGRAPHIC TABLE :**

CHARACTERISTICS	GROUP D (n=20)	GROUP M (n=20)	GROUP N (n=20)	P-value
AGE (in years) (Mean±SD)	39.07±1.83	39.15±10.25	38.30±13.80	0.738
SEX (male:female)	12:8	11:9	14:6	0.08
WEIGHT(in kgs) (Mean±SD)	69.70±8.40	66.70±9.05	70.25±8.70	0.092
ASA (I:II)	11:9	13:7	12:8	0.128
Duration of surgery (min)(Mean±SD)	72.25±15.02	69.50±17.54	71.41±16.33	0.373

**Table 2: Showing comparison of sedation scores during post-operative period:**

Sedation Score	Group D	Group M	Group N	p value
End of surgery (4-6)	4.82 ± 0.81	4.92 ± 0.62	2.60 ± 0.75	0.512

At 15 min (2-5)	2.81± 0.61	2.98 ± 0.72	2.10 ± 0.75	0.137
At 30 min (2-3)	2.25 ± 0.47	2.50 ± 0.41	1.85 ± 0.48	0.144

**TABLE 3: Showing adverse effects during post operative period:**

ADVERSE EFFECTS	GROUP-D (n=20)	GROUP-M (n=20)	GROUP-N (n=20)	P VALUES
Bradycardia	2	1	0	0.162
Hypotension	2	1	1	0.265
Vomiting	1	3	0	0.740
Shivering	1	2	0	0.432
No adverse effects	14	13	19	
Total (no of patients)	20	20	20	

**DISCUSSION:**

- Dexmedetomidine acts by activating G- proteins in the brain stem which results in inhibition of norepinephrine release. The intravenous administration of dexmedetomidine before induction of anesthesia attenuates sympathoadrenal responses to laryngoscopy, endotracheal intubation, pneumoperitoneum and extubation.
- Activation of sympathetic nervous system and increased secretions of pituitary hormones are seen during surgery, there is also release of cortisol levels due to increased secretion of ACTH by stimulation of hypothalamus.
- Our above results correlate with pierre zarif et al. who found that intravenous administration of dexmedetomidine and magnesium sulphate could ameliorate the pressor response to intubation, pneumoperitoneum and extubation in laproscopic colectomies.
- In our study we administered dexmedetomidine 1 µg/kg bolus for 15 mins followed by infusion of 0.2-0.4 µg/kg/hr. Infusion rates of dexmedetomidine varying from 0.1 to 10 µg/kg/hr have been studied, higher dose of infusion was associated with high incidences of cardiac effects. In our study we have not observed biphasic response or any unexpected cardiac effects.
- Magnesium has the ability to block the release of catecholamines from both the adrenal gland and the adrenergic nerve terminals. It acts as a physiological calcium antagonist as it competes with calcium for membrane channels and modifies calcium mediated responses and also magnesium can produce vasodilatation by acting directly on blood vessels, capable of attenuating vasopressin release.
- Vasopressin concentrations raise in pneumoperitoneum due to increased compression of abdominal capacitance vessels with a consequent reduction in venous return to the heart. In our study Inj Magnesium sulphate 2g loading dose in 100 ml Normal saline over 15 minutes followed by 12-15 mg/kg/hr.
- Showket Ahmed Dar et al., found that intravenous magnesium sulphate 5 mins before pneumoperitoneum attenuates stress response and significantly lower the heart rate and arterial pressures during laproscopic abdominal surgeries and this attenuation is related to the effect of magnesium sulphate as a physiological calcium antagonist as it competes with calcium for membrane channels and modifies many calcium mediated responses.
- Another study by Rania M Ali found that intraperitoneal insufflations of magnesium sulphate attenuated hemodynamic stress response to pneumoperitoneum which reduced postoperative pain, nausea, vomiting in patients undergoing laparoscopic cholecystectomy when compared to placebo.
- Ray et al. in their study concluded that magnesium sulphate and clonidine were effective in attenuating stress response and also observed delayed recovery in magnesium sulphate group. Rebie Soliman showed that dexmedetomidine has better control of heart rate and blood pressure, provides better exposure of surgical field with minimal blood loss compared to magnesium sulphate.
- According to studies by Mohamed F Mostafa et al. and Rafat Shamim et al. observed that dexmedetomidine group patients maintained better hemodynamic stability compared to placebo. Mean pulse rate was decreased more in group D compared to group M, from P 1 -P 10 which was not statistically significant except at P 7 (60 mins after peritoneal insufflations) and at P10 (PACU). Mean arterial pressure was found statistically significant difference in group D when compared to group M from P1 – P5 and at P8.
- Sedation was higher in group M compared to group D which resulted in delayed emergence and extubation time. Vomiting and shivering was found to be more in group M. Patients in group M

required more time to reach an aldrete score of  $\geq 9$  and to be discharged from PACU.

- Limitations of the study: 1. Both upper abdominal and lower abdominal cases included in the study, positioning of patient which is different may affect hemodynamic parameters. 2. ASA grade I and II only included in the study.

#### CONCLUSION:

- Dexmedetomidine and Magnesium sulphate attenuated stress response to surgery and pneumoperitoneum. Dexmedetomidine has better hemodynamic stability compared to Magnesium sulphate.
- Early post operative recovery was found in dexmedetomidine group.

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