Original Research Paper

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# A COMPARATIVE STUDY ON THE EFFICACY OF INTRAVENOUS DEXMEDETOMIDINE AND MAGNESIUM SULFATE IN ATTENUATING PRESSOR RESPONSE DURING INTUBATION AND PNEUMOPERITONEUM UNDER BISPECTRAL INDEX-CONTROLLED ANAESTHESIA IN LAPAROSCOPIC ABDOMINAL SURGERIES: A PLACEBO-CONTROLLED RANDOMISED CLINICAL TRIAL

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**ABSTRACT** **Background:** Maintenance of adequate depth of anaesthesia is important to prevent awareness and stress response associated with surgery. The aim of this study is to evaluate dexmedetomidine and magnesium sulphate to attenuate stress response in abdominal laparoscopic surgeries when the depth of anaesthesia is maintained under a constant BIS range of 40-60 (±5). **Methods:** Patients of ASA grade I and II aged between 20 and 60 years, either gender, and who underwent elective laparoscopic abdominal surgeries were included in the study and divided into 3groups, Group D (n=20), GroupM(n=20), Group N (n=20). Group D received Inj. Dexmedetomidine 1µg/kg bolus for 15 min followed by 0.2-0.4µg/kg /hr. infusion and group M patients received Inj. Magnesium sulfate 2g bolus for 15 min followed by 12-15mg/kg /hr. infusion, Group N received 100 ml saline over 15 min followed by 8-10ml/kg/hr. Depth of anaesthesia maintained constantly under BIS range 40-60 (±5) throughout the surgery. Intraoperative hemodynamic parameters like Heart rate, and mean arterial pressure were recorded and emergence time, extubation time, and sedation scores were assessed. Statistical analysis was done using the Chi-square test. **Results:** During maintenance, significantly lower HR, MAP, and BIS values were seen in groups D and M than in N($p < 0.001$). No significant differences were seen regarding baseline hemodynamics, sedation score and BIS values in all groups. At end of the surgery, the sedation score was $4.82 \pm 0.81$ in the dexmedetomidine group compared to $4.92 \pm 0.62$ and $2.60 \pm 0.75$ in groups M and N. Time to reach Aldrete score ≥9 was significantly more in group M compared to groups D and N. **Conclusions:** Dexmedetomidine and Magnesium sulphate attenuated stress response to surgery and pneumoperitoneum. Dexmedetomidine had better hemodynamic stability, early post-operative recovery compared to Magnesium sulphate.

**KEYWORDS :** Dexmedetomidine; Magnesium sulphate; Bispectral index-controlled Anaesthesia; Elective laparoscopic abdominal surgeries; Pressor response.

## INTRODUCTION

Laparoscopic surgical procedures are cost-effective, have minimal blood loss due to small incisions and fewer postoperative pulmonary complications, and reduced metabolic stress compared to conventional open procedures leading to early recovery[1,2]. In general anaesthesia there is a marked sympathoadrenal response which results in increased heart rate and blood pressure during intubation and extubation.

Pneumoperitoneum is produced by the administration of carbon dioxide (CO2) into the peritoneal cavity during laparoscopic procedures which affects homeostasis and leads to alterations in cardiovascular, pulmonary physiology, and stress response. Hemodynamic stability during the 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 anaesthesia attenuates sympathoadrenal responses to laryngoscopy, endotracheal intubation, pneumoperitoneum, and extubation. Magnesium can block the release of catecholamines from both the adrenal gland and the adrenergic nerve terminals. Magnesium sulfate is 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[3]. It integrates the frequency-domain, time-domain, and bi-spectral analysis of raw EEG signals into a numerical value, ranging from 0 (isoelectric EEG) to 100 (fully awake)[4]. BIS values of 40–60 is 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[5].

The purpose of this study is to compare the effectiveness of Magnesium sulfate and Dexmedetomidine compared to placebo for attenuation of stress response in laparoscopic abdominal surgeries when the depth of anesthesia is maintained under a constant BIS range 40-60 (±5).

## METHODS

**Study Design:** Prospective Placebo-controlled Randomized clinical trial

**Study Location**: This was a tertiary care teaching hospital-based study done in the Department of Anaesthesiology, Government General Hospital, Rangaraya Medical College, Kakinada, Andhra Pradesh.

**Study Duration:** January 2021 to August 2021.
**Sampling design:** Purposive Sampling.
**Sample size:** 60 patients.

**Subjects & selection method**: The study population was drawn from the patients who were posted for elective laparoscopic abdominal surgeries presented to Government General Hospital, Kakinada between January 2021 to August 2021. Patients were divided into three groups (each group had 20 patients) according to Blinding and Randomization. Eligible patients are divided into 3 groups as follows:

Group D (n=20) received Inj.Dexmedetomidine 1µg/kg bolus made to 100ml for 15 min.

Group M (n=20) received Inj. Magnesium sulfate 2g bolus made to 100 ml for 15 min.

Group N (n=20) received 100 ml saline over 15 min.

Patients in each group were selected by computer-generated random numbers, sealed in envelopes as folded slips in the OT complex. These slips were picked up by an independent observer who later prepared the drug solutions accordingly. This was a participant and investigator-blinded study.

**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 the 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 sulfate or dexmedetomidine were excluded from the study.

**Procedure and methodology:**
Pre-anaesthetic evaluation and relevant investigations were carried out in all patients. On the night before the surgery, informed written consent was obtained and a tablet of 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 ($SpO_2$), and Bispectral index monitor (BIS VISTA™ monitoring system) were attached and an intravenous cannula was secured.

After written informed consent was obtained, the following data of the recruited patients were collected prospectively:

**PRE-DRUG ($P_0$):** Electrocardiogram (ECG), BIS value, $SpO_2$, Heart Rate (HR), and Blood Pressures-Systolic (SBP) and Diastolic (DBP), were recorded after 5 min of stabilization of the patient.

The intravenous line was secured with an 18G cannula and premedication i.e., Inj. Glycopyrrolate 0.02 mg/ kg, Inj. Ondansetron 0.15 mg/kg, Inj. Midazolam and Inj. Fentanyl 2 µg/kg was given and pre-oxygenated for 3 minutes.

The study drug solution of either Dexmedetomidine Magnesium sulfate 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.Dexmedetomidine1µg/kg bolus made to 100ml for 15 min.

Group M received Inj. Magnesium sulfate 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, $SpO_2$, RSS, and vitals were recorded.
Then, induction of anesthesia was facilitated using propofol 2mg/kg body weight in titrated doses to achieve a BIS range of 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 was recorded, with continuous monitoring of all parameters.

BIS values, SpO2, 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% N2O with oxygen.

Group D was administered Inj. Dexmedetomidine infusion at the rate of 0.2-0.4 µg/kg/hr as maintenance, Group M was administered Inj. Magnesium sulfate at the 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 were given at @5 ml/hr to achieve blinding. Ringer lactate was given as a maintenance fluid. Before Peritoneal Insufflation (P.I) (P8), 5 mins after P.I(P9), 10 min 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, Spo2, Heart rate, and mean arterial pressures were 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, and later shifted to PACU.

Recovery time was observed in both groups as time elapsed since the stoppage of sevoflurane and study drug infusion till the patient achieved a modified Aldrete's score of ≥ 9. The sedation score was assessed at the end of the surgery, at 15 mins, 30 mins, and 60 minutes using Ramsay Sedation Scale.

**Statistical analysis**
Data were expressed using Mean ± SD, and percentages. Continues variables like age, weight, and duration of surgery were compared using the student t-test / Mann-Whitney U test. Categorical variables (gender, ASA grade, bradycardia, hypotension, nausea/vomiting, and shivering) were compared by chi-square/ Fisher's Exact test The level significance used was $P < 0.05$. Data were analyzed using SPSS version 24.0 (SPSS Inc., Chicago, IL).

## RESULTS
A total of 60 patients were included in the study and demographic variables such as age, gender, weight, ASA grading, and duration of surgery were comparable. There was no statistically significant difference among the three groups (Table 1).

**Table no 1: Shows Demographic and various variables**

| 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 |

**Figure-1: Line diagram showing the comparison of Heart rate in the Intraoperative period**

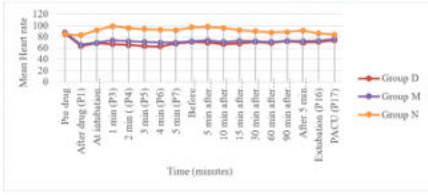


**Table no 2: Showing comparison of sedation scores during the postoperative period**

| 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 |

**Figure-2: Line diagram showing the comparison of BIS values Intraoperatively at various time intervals**

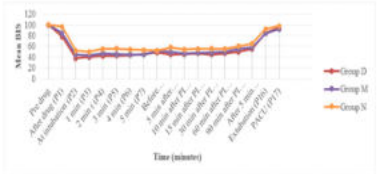


**Figure-3: Line diagram showing the comparison of MAP values Intraoperatively at various time intervals**

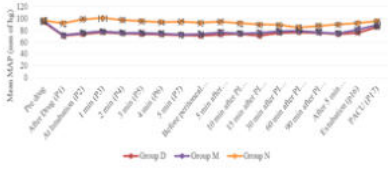


**Table no 3: Comparison of sedation scores during the postoperative period**

| 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 no 4: Showing adverse effects during the postoperative 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 the inhibition of norepinephrine release [6,7]. The intravenous administration of dexmedetomidine before induction of anaesthesia attenuates sympathoadrenal responses to laryngoscopy, endotracheal intubation, pneumoperitoneum, and extubation.

Activation of the sympathetic nervous system and increased secretions of pituitary hormones are seen during surgery, there is also the release of cortisol levels due to increased secretion of ACTH by stimulation of the 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 laparoscopic colectomies.

In our study, we administered dexmedetomidine 1 µg/kg bolus for 15 mins followed by an 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, and the higher dose of infusion was associated with high incidences of cardiac effects. In our study, we have not observed a biphasic response or any unexpected cardiac effects.

Magnesium can 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, also magnesium can produce vasodilatation by acting directly on blood vessels, and is capable of attenuating vasopressin release.

Vasopressin concentrations raise in the 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. [8] found that intravenous magnesium sulfate 5mins before pneumoperitoneum attenuates stress response and significantly lowers the heart rate and arterial pressures during laparoscopic abdominal surgeries and this attenuation is related to the effect of magnesium sulfate 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 [9] found that intraperitoneal insufflation of magnesium sulfate attenuated hemodynamic stress response to pneumoperitoneum which reduced postoperative pain, nausea, and vomiting in patients undergoing laparoscopic cholecystectomy when compared to placebo.

Ray et al. in their study concluded that magnesium sulfate and clonidine were effective in attenuating stress response and observed delayed recovery in the Magnesium sulfate group.

Rebie Soliman [10] showed that dexmedetomidine has better control of heart rate and blood pressure, and provides better exposure to the surgical field with minimal blood loss compared to Magnesium sulfate.

Studies by Mohamed F Mostafa et al. [11] and Rafat Shamim et al. [12] observed that dexmedetomidine group patients maintained better hemodynamic stability compared to placebo.

The 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 were found to be more in group M. Patients in group M required more time to reach an Aldrete score of ≥ 9 and to be discharged from PACU.

**Limitations of the study:**

In both upper abdominal and lower abdominal cases included in the study, the positioning of the patient which is different may affect hemodynamic parameters.

ASA grades I and II were only included in the study.

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## DECLARATIONS

**Funding:** Nil

**Conflict of interest:** Nil

**Ethical approval:** Nil

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