

## A COMPARATIVE STUDY BETWEEN DEXMEDETOMIDINE AND MAGNESIUM SULPHATE FOR ATTENUATION OF STRESS RESPONSE DUE TO ENDOTRACHEAL INTUBATION AND PNEUMOPERITONEUM

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### Abstract

**Introduction:** Pneumoperitoneum is a surgical technique used in abdominal surgery, often involving general anesthesia. It can cause a transient sympathetic response, increased plasma catecholamines and vasopressin levels, and increased intra-abdominal pressure, potentially causing hypertension and tachycardia. Various pharmacological agents have been attempted to mitigate this response, but none have been found ideal. This study compares dexmedetomidine and magnesium sulphate in pneumoperitoneum. **Methods:** The study at Burdwan Medical College examined the effectiveness of dexmedetomidine and magnesium sulphate infusion in reducing stress during laparoscopic surgical procedures over a 1.5-year period. **Results:** The study analyzed 35 patients' changes after following the protocol, using Pearson's Chi Square test and Mann-Whitney U test. Statistical software SPSS version 20 was used, with an alpha level of 5% and p value less than 0.05 considered significant.

**Discussion:** Pneumoperitoneum, a surgical technique causing hypertension and tachycardia, can be mitigated using various pharmacological agents. Dexmedetomidine, a selective  $\alpha_2$  adrenergic agonist, provides hemodynamic stability and reduces pressor response. Magnesium sulphate, a non-competitive NMDA receptor antagonist, attenuates reflexes and vasodilation. Both drugs are equally effective in decreasing blood pressure in response to laryngoscopy and intubation. **Conclusion:** Dexmedetomidine and magnesium sulphate infusions effectively reduce stress during endotracheal intubation and pneumoperitoneum without adverse effects, maintaining heart rate and arterial pressure, and taking longer for patients in Group D.

**Keywords:** dexmedetomidine, magnesium sulphate, Pneumoperitoneum, endotracheal intubation

### Introduction

Pneumoperitoneum is a quickly developing surgical technique used in practically all abdominal surgery procedures. Worldwide, standard protocol for such interventions typically involves general anesthesia.

General Anaesthesia, including laryngoscopy, endotracheal intubation, and extubation, can cause a transient sympathetic response, increased plasma catecholamines and vasopressin levels, and increased intra-abdominal pressure, potentially causing hypertension and tachycardia.[1,2]

Various pharmacological agents, including opioids, alpha-2-adrenergic agonists, beta-blocking agents, and vasodilators, have been attempted to mitigate this response, but none have been found as ideal.[3]

Dexmedetomidine, a selective  $\alpha_2$  adrenergic agonist, provides hemodynamic stability and reduces pressor response to stress. It maintains stable heart rate and provides sedation without respiratory depression. Magnesium sulphate, a non-competitive NMDA receptor antagonist, attenuates somatic, autonomic, and endocrine reflexes by inhibiting catecholamine release and vasodilation. It can attenuate hemodynamic response during general anesthesia. [4,5,6]

This study compares dexmedetomidine and magnesium sulphate in pneumoperitoneum, evaluating their effectiveness in attenuating stress response due to endotracheal intubation and pneumoperitoneum, given the persistent effects of carbon dioxide on haemodynamics.

### Aims and Objectives

- A) General: To compare the effects of magnesium sulfate and dexmedetomidine on reducing stress during pneumoperitoneum and endotracheal intubation.
- B) B) Particular:
  - To assess differences between the two groups at various points of observation in terms of changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR).
  - To compare the levels of sedation in the first six hours following surgery between two groups.
  - To use modified Aldrete scoring to compare the post-operative recovery times of two groups.
  - To compare the incidence of any unfavorable incidents.

### Materials and Methods

This study, conducted at Burdwan Medical College, aimed to investigate the efficacy of dexmedetomidine and magnesium sulphate infusion in attenuating stress response during laparoscopic surgical procedures. The study was conducted over a 1.5-year period, focusing on patients admitted for laparoscopic surgeries, screened for exclusion criteria, and analyzed for results .

### Study variables:

**Parameters of the study:** - Heart rate (HR).

- The SBP, or systolic blood pressure.
- Blood Pressure Diastolic (DBP).
- Blood Pressure Mean (MAP).
- The Brussels Sedation Scale (BSS) score for sedation.
- Anaesthesia recovery based on the Modified Aldrete score.

**Research instruments:** - Written informed consent proforma.

- Form for gathering data.
- Questionnaires for pre-anesthesia checks.
- Modified Aldrete scale for recovery.
- The Brucellos sedation scale.

**Sample size:** The study involved 70 patients, with a sample size of 31 patients per group. The effect size was calculated to be  $5 \times SD2/d2$ , resulting in a total of 70 patients divided into two groups, assuming a 10% loss due to possible dropouts.

- Sampling design: Up until the sample size was attained in each group, successive sampling was carried out.

The study assessed the need for control and collected data through a case record form and sedation and recovery scores using a multipara monitor.

## A) Sedation scale - Brussels sedation scale (BSS) where

- 1= sedated and unarousable,  
 2= sedated but responding to painful not auditory stimuli,  
 3= sedated but responding to auditory stimuli,  
 4= awake and calm,  
 5= agitated.

## B) Recovery scale - modified Aldrete scale

<b><u>Variables Evaluated</u></b>	<b><u>Score</u></b>
<b>Activity</b>	
Able to move four extremities on command	2
Able to move two extremities on command	1
Able to move no extremities on command	0
<b>Breathing</b>	
Able to breathe deeply and cough freely	2
Dyspnea	1
Apnea	0
<b>Circulation</b>	
Systemic blood pressure $\geq$ 20% of the pre anaesthetic level	2
Systemic blood pressure is 20% to 50% of the pre anaesthetic level	1
Systemic blood pressure $<$ 50% of the pre anaesthetic level	0
<b>Consciousness</b>	
Fully awake	2
Arousable	1
Not responding	0
<b>Oxygen saturation (Pulse Oximetry)</b>	
$>$ 92% while breathing room air	2
Needs supplemental oxygen to maintain saturation $>$ 90%	1
$<$ 90% with supplemental oxygen	0

**Experiment design:** This study was a prospective, observational, comparative study on adult patients, with a one and a half-year duration. Patients were recruited, and pre-anaesthetic records were recorded. Patients with difficult intubation were excluded from the study.

**Inclusion criteria:** This study involved patients aged 18-60 years, both genders, with Mallampati grade I and II and ASA physical status. Intubation was done with atracurium besylate iv, and reversal was

done with neostigmine and glycopyrrolate. Patients received bolus doses of Magnesium Sulphate or Dexmedetomidine before and after intubation, with the infusion continuing until the pneumoperitoneum was stopped at peritoneal deflation.

**Exclusion criteria:** The study analyzed patients with major medical illnesses and pregnancy for 6 hours, observing intraoperative haemodynamic parameters, recovery time, sedation levels, and the use of premedication and maintenance drugs. The study also recorded the use of volatile anaesthetic agents and the duration of recovery from infusion of study drugs.

**Laboratory investigations:**

- Platelets, BT, CT, ESR, TC, DC, and Hb.
- View of the chest X-ray PA.
- ECG has twelve leads.
- Creatinine and urea.
- PT, INR.
- Potassium and sodium.
- FBS and PPBS.

- Parameters and the Procedures:

**Parameters -**

- Heart Rate (HR)
- Blood Pressure Systolic (SBP)
- Blood Pressure Diastolic (DBP)
- Blood Pressure Mean (MAP)
- The Brussels Sedation Scale (BSS) score for sedation.
- Anaesthesia recovery based on the Modified Aldrete score.

**Procedure -**

Procedure 1: An anesthetist performed laryngoscopy and endotracheal intubation; this procedure was not part of the study.

The surgical team performed Procedure 2: surgical pneumoperitoneum.

The null hypothesis is rejected due to a significant difference between the two agents in the definition of outcomes.

**Schedule of data collection:**

- T0: prior to the study medication's administration.
- T1: following the completion of the study drug bolus dosage.
- T2: prior to aspiration.
- T3: a minute following intubation.
- Prior to the pneumoperitoneum, T4.
- T5: Pneumoperitoneum five minutes later.
- Five minutes following peritoneal deflation is T6.

**Brussels Sedation Score:**

- Following surgery.
- 15 minutes following the conclusion of the procedure.
- 30 minutes following the conclusion of the procedure.
- Six hours following the conclusion of the procedure.
- Time till reaching Aldrete score  $\geq 9$

• **Statistical analysis plan:**

The study used Pearson's Chi Square test and Mann-Whitney U test to analyze categorical and continuous variables. The alpha level was set at 5%, with a p value less than 0.05 indicating significance.

**Result and Analysis**

The study analyzed 35 patients' changes after following the protocol, using Pearson's Chi Square test and Mann-Whitney U test. Statistical software SPSS version 20 was used, with an alpha level of 5% and p value less than 0.05 considered significant.

Results can be analysed as under:

**TABLE 1: COMPARISON OF AGE:**

DEMOGRAPHIC DATA	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
Age (IN YEARS)	34.89	33.00	9.53	35.80	35.00	9.07	<b>0.689</b>	<b>Not Significant</b>

There was no discernible age difference between the groups, as Table 1 illustrates.

**TABLE 2: COMPARISON OF WEIGHT:**

DEMOGRAPHIC DATA	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
Weight (in kgs)	51.06	50.00	9.69	53.91	52.00	11.03	<b>0.280</b>	<b>Not Significant</b>

Table 2 indicates that no discernible variation in weight was observed among the groups.

**TABLE 3: COMPARISON OF HEIGHT:**

DEMOGRAPHIC DATA	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
Height (in cms)	148.40	150.00	6.11	149.49	151.00	6.74	<b>0.287</b>	<b>Not Significant</b>

Table 3 indicates that no discernible variation in height was observed among the groups.

**TABLE 4: COMPARISON OF SEX:**

DEMOGRAPHIC DATA	Group			Total	p Value	Significance
	GROUP D	GROUP M				
Sex	FEMALE	26(74.29)	28(80)	54(77.14)	<b>0.569</b>	<b>Not Significant</b>
	MALE	9(25.71)	7(20)	16(22.86)		

Total	35(100)	35(100)	70(100)		
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Pearson's Chi Square test for Independence of Attributes

Table 4 indicates that no discernible variation in sex was observed between the groups.

**TABLE 5: COMPARISON OF ASA PS:**

DEMOGRAPHIC DATA	Group			Total	p Value	Significance
	GROUP D		GROUP M			
ASA PS	I	27(77.14)	28(80)	55(78.57)	<b>0.771</b>	<b>Not Significant</b>
	II	8(22.86)	7(20)	15(21.43)		
Total	35(100)		35(100)	70(100)		

Pearson's Chi Square test for Independence of Attributes

No significant difference was found in ASA PS across the groups, as shown in Table 5.

**TABLE 6: COMPARISON OF PERI-OPERATIVE HEART RATE:**

HEART RATE	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
HR: Baseline	81.57	80.00	13.84	80.49	82.00	7.59	<b>0.724</b>	<b>Not Significant</b>
HR: At the end of loading dose	73.51	75.00	11.27	84.49	85.00	8.29	<b>&lt;0.001</b>	<b>Significant</b>
HR: Before intubation	76.20	72.00	10.39	86.71	86.00	7.96	<b>&lt;0.001</b>	<b>Significant</b>
HR: 1 min after intubation	82.46	80.00	12.20	95.31	96.00	7.31	<b>&lt;0.001</b>	<b>Significant</b>
HR: Before pneumoperitoneum	76.11	78.00	9.15	92.14	93.00	8.14	<b>&lt;0.001</b>	<b>Significant</b>
HR: 5 mins after pneumoperitoneum	80.43	78.00	13.81	89.80	89.00	9.07	<b>0.001</b>	<b>Significant</b>
HR: 5 mins after peritoneal deflation	79.71	78.00	13.07	88.83	88.00	8.33	<b>&lt;0.001</b>	<b>Significant</b>

As shown in the above table, shortly after the loading dose ended, Group D's heart rate significantly decreased in comparison to Group M's, and it remained that way for the duration of the study.

**TABLE 7: COMPARISON OF PERI-OPERATIVE MEAN SYSTOLIC BLOOD PRESSURE:**

SYSTOLIC BLOOD PRESSURE	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
SBP: Baseline	120.17	120.00	9.15	117.40	118.00	11.61	<b>0.309</b>	<b>Not Significant</b>

SBP: At the end of loading dose	112.23	111.00	7.87	115.71	115.00	8.69	0.137	Not Significant
SBP: Before intubation	109.49	110.00	10.86	119.94	120.00	6.96	<0.001	Significant
SBP: 1 min after intubation	119.89	119.00	11.56	130.89	131.00	11.34	<0.001	Significant
SBP: Before pneumoperitoneum	114.74	115.00	8.25	120.57	119.00	10.37	0.021	Significant
SBP: 5 mins after pneumoperitoneum	120.34	119.00	9.59	128.69	128.00	12.95	0.006	Significant
SBP: 5 mins after peritoneal deflation	121.17	122.00	9.91	133.49	134.00	13.20	<0.001	Significant

As shown in the above table, a significant difference in Systolic Blood Pressure was noted between Group D and Group M beginning prior to intubation and continuing throughout the study period.

**TABLE 8: COMPARISON OF PERI-OPERATIVE MEAN DIASTOLIC BLOOD PRESSURE:**

DIASTOLIC BLOOD PRESSURE	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
DBP: Baseline	76.43	76.00	8.54	75.91	75.00	8.68	0.809	Not Significant
DBP: At the end of loading dose	71.97	72.00	7.99	73.94	74.00	6.62	0.332	Not Significant
DBP: Before intubation	71.03	72.00	10.41	76.51	76.00	5.98	0.020	Significant
DBP: 1 min after intubation	76.23	74.00	10.12	83.34	83.00	11.38	0.001	Significant
DBP: Before pneumoperitoneum	72.80	72.00	7.07	79.17	79.00	9.10	0.001	Significant
DBP: 5 mins after pneumoperitoneum	76.60	75.00	9.18	80.77	80.00	8.83	0.025	Significant
DBP: 5 mins after peritoneal deflation	75.00	74.00	7.80	83.03	84.00	10.33	<0.001	Significant

The study found a significant difference in Diastolic Blood Pressure between Group D and Group M, which persisted throughout the study period.

**TABLE 9: COMPARISON OF PERI-OPERATIVE MEAN ARTERIAL BLOOD PRESSURE:**

MEAN ARTERIAL BLOOD PRESSURE	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
MAP: Baseline	88.51	88.00	7.75	88.43	89.00	8.74	0.832	Not Significant
MAP: At the end of loading dose	83.14	83.00	7.45	86.80	85.00	9.41	0.184	Not Significant

MAP: Before intubation	81.60	82.00	11.67	87.83	85.00	8.54	<b>0.039</b>	<b>Significant</b>
MAP: 1 min after intubation	88.43	89.00	10.21	95.89	96.00	11.33	<b>0.002</b>	<b>Significant</b>
MAP: Before pneumoperitoneum	84.23	85.00	6.15	91.17	93.00	9.55	<b>&lt;0.001</b>	<b>Significant</b>
MAP: 5 mins after pneumoperitoneum	88.43	88.00	7.59	95.06	96.00	8.79	<b>&lt;0.001</b>	<b>Significant</b>
MAP: 5 mins after peritoneal deflation	87.00	88.00	8.15	95.51	99.00	10.74	<b>&lt;0.001</b>	<b>Significant</b>

The study found a significant difference in Mean Arterial Blood Pressure between Group D and Group M, which persisted throughout the study period.

**TABLE 10: COMPARISON OF PERI-OPERATIVE OXYGEN SATURATION (SpO<sub>2</sub>):**

OXYGEN SATURATION (SpO <sub>2</sub> )	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
SPO <sub>2</sub> : Baseline	99.60	100.00	0.65	99.66	100.00	0.54	<b>0.874</b>	<b>Not Significant</b>
SPO <sub>2</sub> : At the end of loading dose	99.63	100.00	0.55	99.60	100.00	0.55	<b>0.811</b>	<b>Not Significant</b>
SPO <sub>2</sub> : Before intubation	100.00	100.00	0.00	100.00	100.00	0.00	<b>1.000</b>	<b>Not Significant</b>
SPO <sub>2</sub> : 1 min after intubation	100.00	100.00	0.00	99.80	100.00	0.47	<b>0.011</b>	<b>Significant</b>
SPO <sub>2</sub> : Before pneumoperitoneum	99.91	100.00	0.37	100.00	100.00	0.00	<b>0.154</b>	<b>Not Significant</b>
SPO <sub>2</sub> : 5 mins after pneumoperitoneum	99.91	100.00	0.28	99.60	100.00	0.65	<b>0.015</b>	<b>Significant</b>
SPO <sub>2</sub> : 5 mins after peritoneal deflation	99.26	99.00	0.74	99.14	99.00	0.73	<b>0.497</b>	<b>Not Significant</b>

SpO<sub>2</sub> levels in both groups were generally similar, but became statistically significant at 1 minute post-intubation and 5 minutes post-pneumoperitoneum, as shown in the table.

**TABLE 11: COMPARISON OF POST EXTUBATION BRUSSELS SEDATION SCALE (BSS) SCORE:**

BRUSSELS SEDATION SCALE (BSS) SCORE	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
Brussels Sedation Score (BSS): At the end of surgery	1.80	2.00	0.53	2.89	3.00	0.32	<b>&lt;0.001</b>	<b>Significant</b>
Brussels Sedation Score (BSS): 15 minutes after end of surgery	2.83	3.00	0.57	3.69	4.00	0.47	<b>&lt;0.001</b>	<b>Significant</b>



Brussels Sedation Score (BSS): 30 minutes after end of surgery	3.66	4.00	0.48	4.54	5.00	0.51	<0.001	Significant
Brussels Sedation Score (BSS): 6 hours after end of surgery	4.71	5.00	0.46	4.89	5.00	0.32	0.075	Not Significant

Group D showed a significant difference in Brussels Sedation Score from surgery end to 30 minutes, becoming comparable at 6 hours post-surgery.

**TABLE 12: COMPARISON OF TIME TILL REACHING ALDRETE SCORE >= 9 IN MINS AFTER EXTUBATION:**

Time till reaching Aldrete score >= 9 in mins after extubation	Group						p Value	Significance
	GROUP D			GROUP M				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation		
	11.17	11.00	2.97	7.14	7.00	2.14		

Group D patients took significantly longer to reach an Aldrete score >= 9 after extubation compared to Group M, as shown in the table.

**Discussion**

Pneumoperitoneum is a surgical technique used in abdominal surgeries, often performed under General Anaesthesia. It creates pneumoperitoneum, causing intra-abdominal pressure elevation and arterial compression, leading to hypertension and tachycardia. The procedure also increases plasma levels of catecholamines and vasopressin, activating the renin-angiotensin-aldosterone system, causing hemodynamic alterations.[9, 10]

Vasopressin increases systemic vascular resistance, potentially causing arterial pressure rise in patients with cardiovascular disease. Various pharmacological agents, including opioids, alpha-2-adrenergic agonists, beta-blockers, and vasodilators, have been tried to mitigate this response.[3]

Dexmedetomidine, a selective α2 adrenergic agonist, provides hemodynamic stability, reduces pressor response to stress, maintains stable heart rate, and offers analgesic and anaesthetic sparing properties without respiratory depression.[7]

Magnesium sulphate, a non-competitive NMDA receptor antagonist, plays a crucial role in attenuating various reflexes, inhibiting catecholamine release, causing vasodilation, and attenuating hemodynamic responses due to endotracheal intubation.[8]

Sebastian B et al's study found 0.75 µg/kg infusion as the standard dose for attenuating stress responses to laryngoscopy and endotracheal intubation.[11]

Dexmedetomidine infusion maintains stable haemodynamics during pneumoperitoneum, reduces anesthesia maintenance agents dose, and decreases additional anesthetic requirement during perioperative periods, according to studies by Vora KS et al.[12]

Sunil R et al. found magnesium sulphate effective in reducing stress response during laryngoscopy and endotracheal intubation, attenuating arterial pressure increase during laparoscopic cholecystectomy, and ameliorating pressure response in comparison to Dexmedetomidine.[13]

This study compares dexmedetomidine and magnesium sulphate in patients with persistent carbon dioxide pneumoperitoneum. 70 patients were divided into two groups of 35 patients to receive either infusion. No significant differences were found in demographic variables. However, heart rate decreased in Group D after the loading dose and remained so throughout the study. This finding is consistent with previous studies, which found dexmedetomidine to be more effective in controlling heart rate. Both drugs were equally effective in decreasing blood pressure in response to laryngoscopy and intubation. The study's findings may be due to the continued infusion until pneumoperitoneum was continued, unlike previous studies which used only the loading dose before induction and intubation.

The study found significant differences in blood pressures in Group D compared to Group M, with Dexmedetomidine providing more effective controlled hypotension and blunting the haemodynamic response to laryngoscopy and intubation, consistent with previous studies by Modir, Borah, Lang, Srivastava, Kamal, and Bayoumy.[\[14-19\]](#)

The study found significant differences in mean systolic, diastolic, and arterial blood pressures between Group D and Group M before intubation, with Dexmedetomidine providing more effective controlled hypotension and blunting the haemodynamic response to laryngoscopy and intubation. This finding is consistent with previous studies, which found no significant difference between the groups in attenuation of pressor responses to laryngoscopy, endotracheal intubation, and pneumoperitoneum. The study also found that the mean value of SpO<sub>2</sub> in both groups was clinically comparable, but statistically significant at two intervals, which may be due to a lesser number of subjects. The intra-operative SpO<sub>2</sub> saturation of oxygen (SpO<sub>2</sub>) remains comparable in both groups, consistent with the study's findings.[\[20\]](#)

The study found that Group D subjects experienced deeper sedation compared to Group M subjects, which became comparable after 6 hours. Dexmedetomidine provided the best sedative effects, while other studies found higher Ramsay Sedation Scores. However, both groups had comparable respiratory rates and SpO<sub>2</sub> levels. The study also found that magnesium sulphate caused a delay in recovery compared to dexmedetomidine, possibly due to higher doses.[\[20,21\]](#)

The study found that dexmedetomidine patients experienced longer time to reach an Aldrete Score  $\geq 9$  compared to their non-dexmedetomidine counterparts. This is due to the unique pharmacological feature of dexmedetomidine, which induces conscious sedation and maintains it throughout the period, preventing potential hemodynamic perturbation during extubation. This finding supports previous research.[\[14.15\]](#)

#### **Adverse Effects:**

The study found no complications in 70 patients, and all were observed for 2 hours in the Post Anaesthesia Care Unit for undue side effects. Nausea and vomiting were observed in 3 patients, but no other significant adverse effects were noted.

#### **Limitations:**

The study's limitations include a small patient population, inability to subcategorize cases based on surgery type and position, and inability to accurately assess hemodynamic changes. Future studies should consider invasive hemodynamic monitoring, plasma catecholamine and vasopressin levels, and serum magnesium levels. The study only focused on ASA I and II patients, excluding hypertensive patients. Further research is needed to understand the effects of these infusions in hypertensive and ischemic heart disease patients.

#### **Conclusion:**

The study found that Dexmedetomidine and magnesium sulphate infusions effectively attenuate stress response during endotracheal intubation and pneumoperitoneum without significant adverse effects. Dexmedetomidine maintained heart rate and mean arterial pressure closer to baseline during the perioperative period, while magnesium sulphate took longer to achieve an Aldrete Score  $\geq 9$  in patients in Group D compared to Group M.

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