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"REDUCING OPIOID DEPENDENCE IN ANESTHESIA: A STUDY ON DEXMEDETOMIDINE AND MAGNESIUM SULFATE AS ALTERNATIVES"

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Abstract

Background: The rising concerns over opioid-related complications, such as addiction, tolerance, and adverse effects, have fueled the pursuit of opioid-free general anesthesia. This has led to the exploration of alternative anesthetic strategies, including the use of dexmedetomidine and magnesium sulphate.

Objective: This study aims to evaluate the efficacy of dexmedetomidine and magnesium sulphate as components of opioid-free general anesthesia, focusing on their impact on anesthetic agent consumption, hemodynamic stability, postoperative recovery, and side effects.

Methods: A prospective, randomized, placebo-controlled study was conducted with 135 patients aged 20-50 years, classified as ASA physical status I or II, undergoing elective surgery under general anesthesia. Patients were randomly allocated into three groups: Group D received dexmedetomidine loading dose 1 µg/kg + inj diclofenac 75mg before induction over a period of 15 min and maintenance 0.5 µg/kg/h throughout the surgery. Group M received magnesium sulphate loading dose 30 mg/kg + inj diclofenac 75mg before induction over a period of 15 min and maintenance 10 mg/kg/h throughout the surgery, and Group C (Control group) – Inj fentanyl of 2mcg/kg + inj diclofenac 75mg before induction and maintenance 1mcg/kg/hr throughout the surgery. The primary outcomes measured included propofol and vecuronium doses, hemodynamic parameters, sedation scores, postoperative analgesia requirements, and side effects.

Results: Dexmedetomidine and magnesium sulphate significantly reduced the doses of propofol and vecuronium compared to the control group. Both agents provided better hemodynamic stability with minimal intraoperative fluctuations. Dexmedetomidine demonstrated superior postoperative analgesic efficacy, reducing the need for rescue analgesia. Group D had higher sedation scores, while Group M had a lower incidence of postoperative shivering. The control group exhibited higher rates of postoperative pain, nausea, and vomiting.

Conclusion: The use of dexmedetomidine and magnesium sulphate in opioid-free general anesthesia effectively reduces the need for opioids and anesthetic agents while maintaining hemodynamic stability and minimizing side effects. This approach offers a promising alternative to traditional opioid-based anesthesia, enhancing patient safety and postoperative recovery.

INTRODUCTION-

The pursuit of opioid-free general anesthesia has gained significant momentum due to increasing concerns about opioid-related complications, including addiction, tolerance, and adverse effects. In

response, researchers and clinicians have been exploring alternative anesthetic strategies that minimize or eliminate the need for opioids while maintaining effective analgesia and ensuring patient safety.

Dexmedetomidine, a selective α2-adrenergic agonist, has emerged as a promising agent in this context. It is known for its sedative, anxiolytic, and analgesic properties, making it a valuable tool in opioid-sparing anesthesia regimens. Dexmedetomidine offers the advantage of providing sedation and analgesia without the respiratory depression commonly associated with opioids, thereby enhancing patient safety.

Magnesium sulfate, traditionally used for its neuromuscular blocking and anticonvulsant effects, has also been recognized for its potential analgesic properties. Magnesium is involved in various physiological processes that can modulate pain perception and neuromuscular transmission. Its role in opioid-free anesthesia involves providing additional analgesic effects and potentially reducing the overall need for opioids.

Combining dexmedetomidine and magnesium sulfate in opioid-free general anesthesia protocols represents a novel approach to managing surgical pain and anesthesia. This combination aims to leverage the distinct mechanisms of action of both agents to achieve effective pain control, reduce opioid consumption, and improve overall patient outcomes.

This introduction explores the rationale behind using dexmedetomidine and magnesium sulfate for opioid-free general anesthesia, reviewing their pharmacological profiles, benefits, and potential challenges. By understanding these aspects, clinicians can better assess the feasibility and effectiveness of this approach in various surgical settings, ultimately advancing the practice of anesthesia and patient care.

MATERIALS AND METHODS-

This prospective, randomized, placebo-controlled study was conducted after approval from the Institutional Ethics Committee and written informed consent from the patients.

A total of 135 patients 20-50 years of age, ASA physical status I or II, of either sex, and scheduled for elective surgery under general anesthesia were included in this study. Patients with a history of preoperative neuromuscular disease, hepatic, renal, endocrinal, hematological disorder or cardiovascular dysfunction, any degree of heart block, BMI>30 kg/m^2, patients receiving magnesium supplementation, drugs known to have a significant interaction with NMDAs, chronic use of opioids and current treatment with a β-blocker or calcium channel blocker were excluded from the study. The 135 patients were randomly allocated to three groups of 45 each with the help of a computer generated table of random numbers.

Group D – Dexmedetomidine loading dose 1 µg/kg + inj diclofenac 75mg before induction over a period of 15 min and maintenance 0.5 µg/kg/h throughout the surgery.

Group M – Magnesium sulfate loading dose 30 mg/kg + inj diclofenac 75mg before induction over a period of 15 min and maintenance 10 mg/kg/h throughout the surgery.

Group C (Control group) – Inj fentanyl of 2mcg/kg + inj diclofenac 75mg before induction and maintenance 1mcg/kg/hr throughout the surgery.

Preoperative Assessment: Comprehensive medical history, physical examination, and laboratory tests including CBC, blood tests, chest X-ray, ECG, and renal/liver function tests as needed.

Procedure:

1. **Preoperative Check-Up:** Included a detailed medical history, physical examination, airway evaluation, and necessary lab tests. Informed consent was obtained.

2. **Preparation:** Patients fasted for 8 hours. IV line and normal saline drip were started. Baseline monitoring (3-lead ECG, NIBP, SpO_2) was established.

3. Induction:
- 20 minutes after drug loading, pre-medication with GPL (0.2 mg IV), diclofenac (75 mg IV), ranitidine (50 mg IV), and midazolam (1 mg IV).
- Pre-oxygenation with 100% O_2 for 3 mins.
- Induction with propofol (2 mg/kg) and succinylcholine (2 mg/kg) for intubation. Endotracheal intubation was done with a lubricated cuffed tube.
- Anesthesia maintained with N_2O and O_2 (50:50), sevoflurane (0.5-1 vol%), and vecuronium (0.01 mg/kg). Ventilation adjusted to maintain $EtCO_2$ at 35-40 mm Hg.

4. Monitoring: HR, SBP, DBP, MAP recorded at various intervals: post-drug administration, induction, intubation, every 20 mins during surgery, and post-extubation.

5. Postoperative Care:
- Reversal of neuromuscular blockade with neostigmine (0.05 mg/kg) and GPL (0.01 mg/kg).
- Patients extubated upon recovery (hand grip, head lift, etc.).
- Postoperative monitoring in PACU for 24 hours, including pain assessment (VAS), sedation level (MOAA/S), vital signs, and rescue analgesia use.
- Hypotension and bradycardia managed with ephedrine, normal saline, and atropine. Oral intake resumed after 4 hours.

Data Collection:
- Total dose of propofol and muscle relaxants used.
- Heart rate, SBP, DBP, RR, SpO_2.
- Sedation quality (OAA/S scale).
- Time to first rescue analgesia.
- Pain (VAS scores).
- Postoperative side effects (nausea, vomiting, shivering, respiratory depression).

RESULTS-

There was no significant difference amongst the groups with regard to demographic variables (P>0.05) (Table 1)

Table 1. Demographic data

-	Group C (n=30)	Group D (n=30)	Group M (n=30)	P Value
Mean age (yrs)	46.57 ±8.73	45.93±9.19	48.30±7.70	0.543
Weight (Kg)	60.22±10.19	56.20 ±5.66	58.11 ±4.12	0.071
Male/Female	10/35	15/30	10/35	0.239
Duration of surgery (hrs)	114.7±8.62	113.44±12.26	110.9±10.38	0.159

Propofol induction dose were significantly lower in the group D and group M than in the group C (P<0.05). Vecuronium doses were also significantly lower in the group D and group M than in the group C (P<0.05) (Table 2).

Table 2. Induction dose of propofol and maintenance dose of propofol, vecuronium and fentanyl

Variable	Group C (n=45)	Group D (n=45)	Group M (n=45)	P value		
				C vs D	C vs M	D vsM
Propofol Induction dose (mg)	95.00±16.00	80.00±7.38	88.44±14.29	<0.001	<0.05	<0.001
Vecuronium Maintenance dose (mg/hr)	5.13±0.75	4.51±0.50	4.91±0.82	<0.05	<0.001	<0.05

There was no significant difference in preoperative hemodynamic parameters between the groups. After administration of the study drugs, there was a significant decrease in heart rate in group D ($p<0.05$). After induction, there was no change in HR in group M only. There was no significant increase in HR in group D after intubation ($p>0.05$). HR in group D and group M were significantly decreased ($p<0.05$) during the whole intraoperative period except 20 min in group M, however, this decrease was not seen in group C, compared to preoperative values. There was no significant change in HR after surgery and extubation in all groups except in group D after surgery ($p<0.05$). There was a significant difference in HR values between group C, D and M, during the whole intraoperaive period ($p<0.05$) (figure 1.).

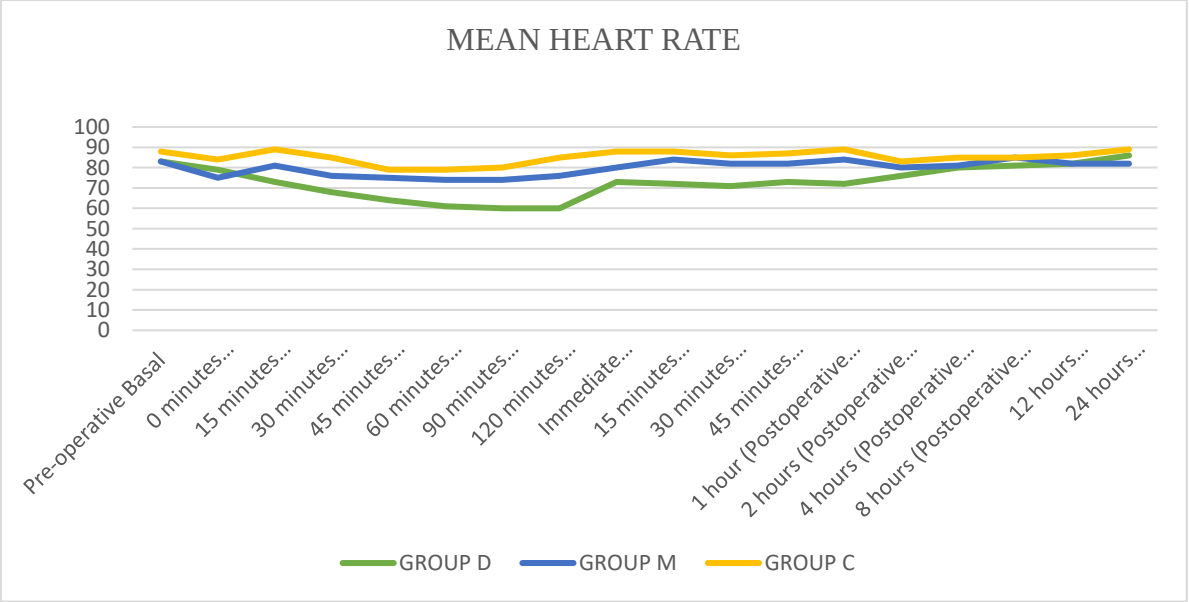

Fig 1. Comparison of Heart Rate Between Study Groups

MAP values were statistically significantly lower in the group D and group M comparative to group C after intubation and all time observations of surgery ($p<0.05$). There was a significant decrease in MAP in all groups, compared to preoperative values at all time intervals of surgery ($p<0.05$). There was no significant difference in MAP after surgery between the group C and M ($p=0.237$). MAP values difference were more when compared the group D with group C ($p<0.001$), than group M with group C ($p<0.05$) (Figure 3.)

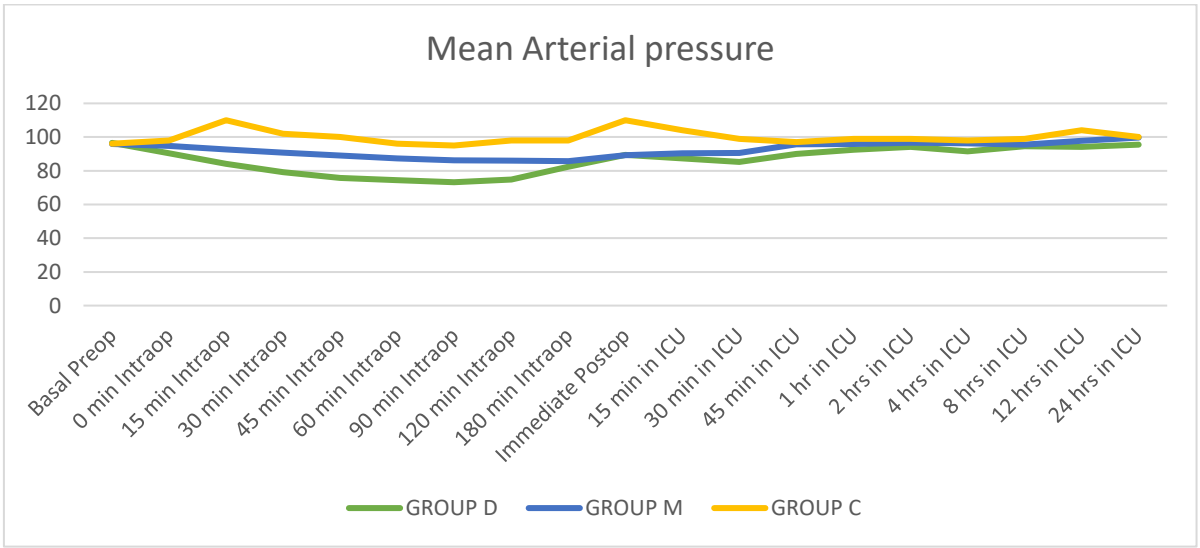

Fig 2. Comparison of Mean Arterial Pressure Between Study Groups

Group D had a significantly higher mean sedation score than Group M and Group C. This indicates that patients in Group D were, on average, less sedated immediately after surgery than those in Group M and GroupC (Fig 4.)

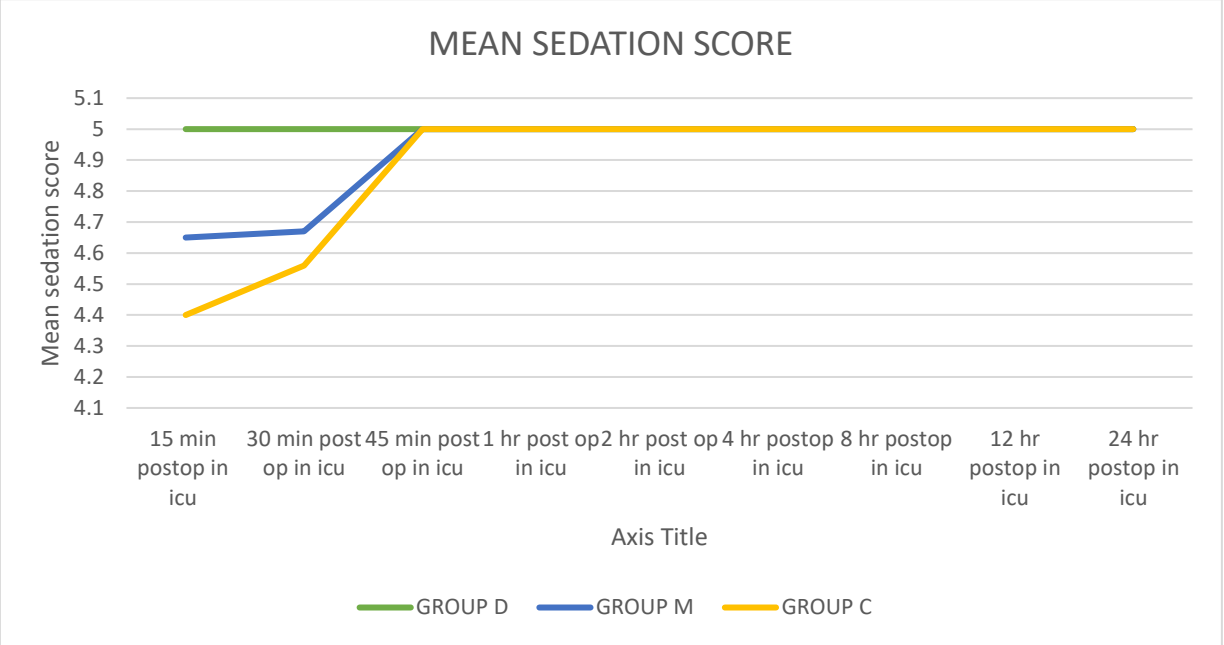

Fig.3 Mean sedation score among study groups.

Group D required less total dose of rescue analgesia compared to group M and group C postoperatively (figure 4). Dexmedetomidine may offer superior analgesic efficacy or reduce the need for additional pain relief compared to Group M and Group C in the post-operative recovery period.

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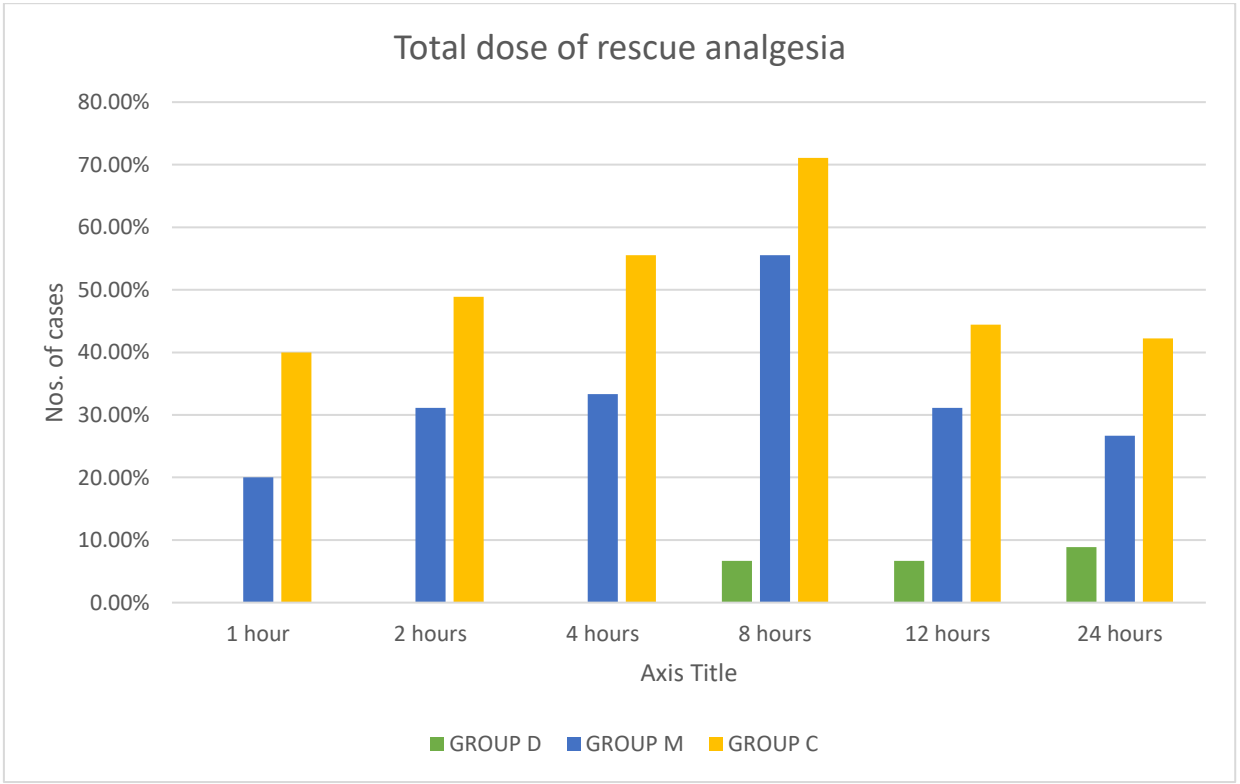

Fig. 4 Total dose of rescue analgesia among study groups.

Postoperatively, Group M and Group C showed a notably higher incidence of shivering compared to Group D. Group C reported higher rates of pain and nausea/vomiting compared to Group M and to Group D.

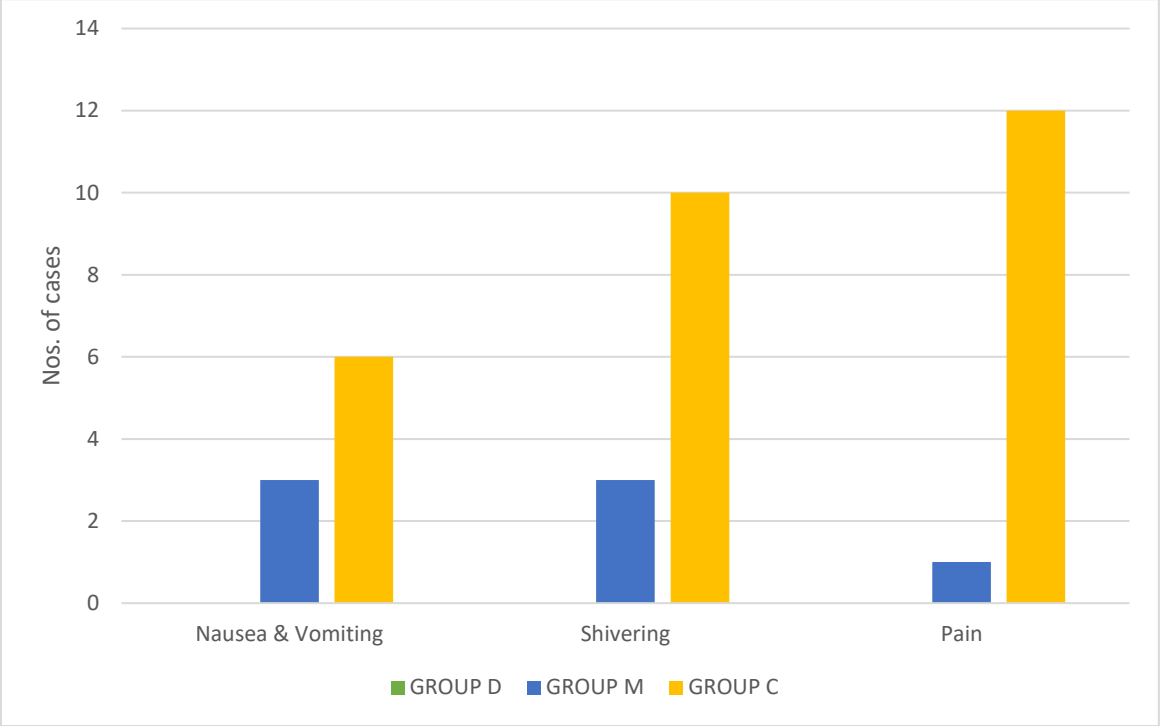

Fig.5 Comparison of Immediate Postoperative Side Effects between Study Groups

DISCUSSION-

Post-operative pain is a significant concern that can hinder a patient's comfort and recovery. The primary goal in post-operative management is to minimize the dosage of medications while reducing side effects, yet still achieving adequate pain relief. In this context, Dexmedetomedine and magnesium sulphate has emerged as a promising option. It has been reported to be effective in perioperative pain management, blunting somatic, autonomic, and endocrine reflexes triggered by noxious stimuli. Additionally, dexmedetomidine and magnesium sulphate has been shown to reduce the need for anesthetics and muscle relaxants during surgery.

In our study, dexmedetomidine was associated with a higher incidence of hypotension and bradycardia, with these effects being dose-dependent. We selected a dose of 1 µg/kg over a 15-minute duration, followed by a maintenance dose of 0.5 µg/kg/h, supported by various studies. Magnesium sulfate was also used safely as an adjuvant, though cases of magnesium toxicity leading to cardiac arrest and death have been reported. However, magnesium toxicity typically begins at serum concentrations of 2.5–5.0 mmol/liter, which is much higher than the levels observed in the magnesium group of our study. **Goral et al.** noted that toxic serum magnesium concentrations were not reached even after administering a bolus dose of 50 mg/kg and a continuous infusion of 20 mg/kg/hr. In our study, we administered a magnesium sulfate bolus dose of 30 mg/kg and a maintenance dose of 10 mg/kg/hr, based on previous research.

In this study, the dexmedetomidine group achieved a 20% greater reduction in propofol and fentanyl requirements compared to the magnesium and control groups. This reduction is attributed to the hypnotic, sedative, analgesic, and anesthetic-sparing effects of dexmedetomidine. The interaction between α2-adrenoreceptors and opioids led to a decrease in fentanyl dosage. Specifically, α2-adrenoceptors, particularly α2A and α2C, modulate descending noradrenergic pathways, resulting in a reduction in opioid requirements. Our findings align with previous studies. Magnesium's role in

modulating anesthesia likely involves several mechanisms, including its analgesic effects through interference with calcium channels and antagonism of NMDA receptors in the central nervous system. Calcium channel blockers are known to have antinociceptive actions and enhance opiate analgesia in patients treated chronically with morphine. Magnesium blocks NMDA-induced currents in a voltage-dependent manner, which is another possible explanation for its analgesic effects.

It is well established that magnesium sulfate prolongs and potentiates neuromuscular block by non-depolarizing neuromuscular blocking agents. Consistent with previous studies, our study also showed lower vecuronium requirements with magnesium use. **Fuchs-Buder et al**. reported that an intravenous infusion of magnesium at 40 mg/kg significantly potentiated the neuromuscular blockade of vecuronium, with significant increases in plasma magnesium concentrations. However, no symptoms of muscle weakness were observed in any patients. Similarly, **Baraka and Yazigi** found no clinical or electromyographic signs of muscle weakness, even at slightly higher plasma magnesium concentrations (1.7–2.5 mmol/L).

In the present study, both dexmedetomidine and magnesium sulfate provided better hemodynamic stability with minimal fluctuations throughout the intraoperative period. The dexmedetomidine group experienced a greater decrease in heart rate, likely due to the drug's sympatholytic effects and vagal mimetic properties. From post-intubation to the end of surgery, mean arterial pressure (MAP) remained significantly lower in the dexmedetomidine and magnesium sulfate groups compared to controls, likely due to the analgesic properties of both drugs reducing sympathetic stimulation. Magnesium induces vasodilation by acting directly on blood vessels and interfering with various vasoconstrictor substances. Additionally, elevated serum magnesium levels may reduce peripheral vascular tone through mechanisms such as sympathetic blockade and inhibition of catecholamine release. Dexmedetomidine also decreases sympathetic outflow and circulating catecholamine levels, leading to a reduction in MAP similar to that of magnesium. The hypotension and bradycardia observed in the dexmedetomidine group are well-documented effects of α2 agonists and have been confirmed in previous studies.

The mean induction dose of propofol was significantly lower in Group D(80.00±7.38) compared to Group M (88.44±14.29) and to Group C (95.00±16.00), with a statistically significant difference (P = 0.001). This finding is consistent with studies by **Kaur et al (2016)** they found that propofol consumption was much more in Control group as compared to Dexmed group.[p value <0.05]. A study by **J.E. Vieira et al.** found higher propofol consumption in the magnesium group compared to the fentanyl group, which contrasts with our findings.
The mean dose of total muscle relaxants (vecuronium) used was 4.51±0.50. mg in Group D, 4.91±0.82. mg in Group M and in group C was 5.13±0.75. The difference in muscle relaxant dosage was statistically significant (P = 0.001), with Group C requiring a higher dose than Group M and least requirement in Group D. This finding aligns with a study by **Srivastava et al (2016)** requirement of Vecuronium were also suggestively lesser in group Dexmedetomidine & MgSO4 than in C group (P<0.05) similar to our study findings.

Group C required significantly more rescue analgesia than Group M and Group D. The total number of analgesic requirements was higher in Group C compared to Group D and Group M, with the difference being statistically significant (P = 0.002). This suggests Dexmedetomidine may offer superior analgesic efficacy or reduce the need for additional pain relief in post- operative recovery period. And magnesium sulphate may help prevent and treat pain by inhibiting NMDA receptors**. Elyazed and Mogahed (2018)** What they found that Dexmedetomidine decreased the time taken by SB and MB but had extended durations of SB, MB, & analgesia as well as reduced requirements of post-operative rescue analgesics. **Sayed et al (2018)** they found that the addition of dexmedetomidine & Mgso4 to bupivacaine caudal block prolongs time to first analgesia request.

Most patients in both groups, 100.0% in Group D & 86.7% in Group M, reported no side effects postoperatively but Group C 33.6% reported side effects like nausea and vomiting and pain.
The existing literature provides valuable insights into the effects of these adjuvants on opioid free anaesthesia, anesthetic agent consumption, hemodynamics, and postoperative recovery. However, a closer examination of the literature reveals several specific gaps that warrant further investigation. Addressing these gaps through well-designed comparative studies, dose optimization, long-term follow-up, safety assessments, economic evaluations, and consideration of patient-centered outcomes can advance our understanding and enhance the evidence-based practice of anesthesia management in a broader range of clinical scenarios. Closing these literature gaps will ultimately contribute to safer, more efficient, and patient-centered general anesthesia practices.

CONCLUSION -

Through our study we concluded that use of intravenous Dexmedetomidne and magnesium sulphate infusion allows us to provide opioid free general anaethesia and opioid related side effects .It also reduces the dose of anaesthetic agents , provides good hemodynamic stability without any side effects as well as it is cost effective .Hence Dexmedetomidine and magnesium sulphate has shown efficiency in reducing opioid consumption .

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