



RESEARCH ARTICLE

A COMPARATIVE STUDY OF DEXMEDETOMIDINE AND MAGNESIUM SULPHATE AS AN ADJUVANT TO BUPIVACAINE FOR POSTOPERATIVE EPIDURAL ANALGESIA IN LOWER LIMB SURGERIES

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Abstract

Background: Pain is pathologic entity, noxious stimulus and a most common problems challenging the anaesthetist. Regional anaesthesia is a safe, inexpensive technique that inhibits the nerve transmission to relieve pain and also provide postoperative analgesia. Magnesium is N-methyl D-aspartate receptor and physiological calcium antagonist. Dexmedetomidine is α_2 receptor antagonist with analgesic and sedative properties.

Objectives: To compare the duration of postoperative analgesia, time of administration of first rescue analgesia, systemic side effects of epidural bupivacaine with Magnesium sulphate and dexmedetomidine.

Methods: After approval of ethical committee and informed written consent A prospective randomised study was conducted with Sixty ASA grade I and II patients aged between 18-60 years undergoing lower limb surgeries were divided into two groups of 30 each. Group BM and Group BD received 10ml of 0.125% bupivacaine with 100mg of 20% MgSO₄ and 12.5mcg of dexmedetomidine respectively. Heart rate, mean arterial pressure, VAS score, time for first rescue analgesia were recorded postoperatively. Epidural analgesia was given when VAS score was more than 4.

Results: VAS was significantly less in group BM, time for first rescue analgesia was more in group BM compared to group BD without any systemic side effects.

Conclusion: Administration of Magnesium sulphate with bupivacaine provides prolonged postoperative analgesia compared with Dexmedetomidine without any systemic side effects.

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Introduction:-

Pain is a consistent and predominant complain of individuals following most surgical interventions. Anaesthesiologists, the health care providers have, the first and foremost, a moral and ethical obligation to help all patients manage their pain adequately, which may lead to better outcomes for both the patient

and the health care system. Various modalities have been tried to relieve the post-operative pain. Epidural analgesia with various drugs have been tried. It has become a common practice to use a polypharmacological approach for the treatment of postoperative pain, because no drug has yet been identified that specifically inhibits nociception without associated side effects.¹

Epidural analgesia is often used to supplement general anaesthesia (GA), regional anaesthesia for surgical procedures in patients of all ages with moderate to severe comorbid disease; provide analgesia in the intraoperative, postoperative, peripartum, and end-of-life settings; and can be used as the primary anaesthetic for surgeries from the mediastinum to the lower extremities

Epidural LA drugs administered alone have never become widely used for routine postoperative analgesia because of the significant failure rate resulting from regression of the sensory block² and the unacceptable incidence of motor blockade and hypotension.

Bupivacaine is the indicated local anaesthetic in caudal, epidural, spinal anaesthesia and also provides epidural post-operative analgesia, hence is widely used clinically to manage acute and chronic pain with long duration of action of 180-300 minutes. In addition to blocking Na channels, bupivacaine affects the activity of many other channels, including NMDA receptors. Importantly, bupivacaine inhibits NMDA receptor-mediated synaptic transmission in the dorsal horn of the spinal cord, an area critically involved in central sensitization of bupivacaine would decrease the peak and accelerate the decay of synaptic NMDA receptor currents during normal synaptic transmission. These quantitative predictions inform possible applications of bupivacaine as preventative and therapeutic approaches in chronic pain³ It has also less incidence of nausea, vomiting and pruritis when compared with opioids. However it can cause some amount of motor blockade and hypotension.

Magnesium sulphate has been shown to have anti nociceptive effects in animal and human models by blocking the N-methyl-D-aspartate (NMDA) receptor and associated calcium channels, thus preventing central sensitization caused by peripheral nociceptive stimulation. In addition to their central location, recent studies identified peripheral NMDA receptors in the skin, muscles, and knee joints and found that they play a role in sensory transmission of noxious signals⁴. The addition of magnesium sulphate to local anaesthetics for neuraxial anaesthesia prolongs the duration of anaesthesia and improves the quality of analgesia. It has been accepted as an adjuvant for intra- and postoperative analgesia. Perioperative magnesium sulphate reduces the need for anaesthetics and improves postoperative analgesia⁵

Dexmedetomidine is an imidazole compound. It is 8 times more specific for α_2 adrenergic receptors when compared to clonidine⁶ Dexmedetomidine has sedative, analgesic, and sympatholytic effects that blunt many of the cardiovascular responses seen during the perioperative period. Patients remain sedated when undisturbed but arouse readily with stimulation⁷

Hence this clinical study is undertaken for comparing duration for post-operative analgesia, time for first rescue analgesia of epidural bupivacaine with magnesium sulphate and dexmedetomidine as adjuvants and also to evaluate systemic side effects.

Materials And Methods:-

After obtaining approval from the institutional ethical committee and after obtaining written informed consent from each patient, the study was conducted which consist of 60 ASA I & ASA II patients of both sexes aged between 18 years to 60 years undergoing elective lower limb surgeries were enrolled in this prospective randomised controlled study. Those who had renal, hepatic impairment, cardiac disease, coagulopathy or receiving anticoagulants or opioids, spine deformity or neuropathy for any cause were excluded from the study.

The patients were explained prior to surgery about the epidural technique as well as visual analogue scale (VAS: 0- no pain, 10- worst pain). All patients were assessed with regards to haemodynamics including heart (HR), mean arterial pressure and oxygen saturation (SPO2). Intravenous access had been established and an infusion of crystalloid commenced, all patients had a combined spinal-epidural anaesthetic. The epidural space was identified at L3-L4 or L4-L5 intervertebral space using a loss-of-resistance technique. An epidural catheter was then inserted into the epidural space and correct position was confirmed by injection lidocaine 2% with epinephrine in concentration of

1:200000(3ml).The levels to be achieved was upto T10. When surgery was complete, patients were randomized, by a sealed envelope technique, into one of the two groups.

Group BD received 10ml of bupivacaine 0.125% plus 12.5mcg of dexmedetomidine .

Group BM (Magnesium) received 10ml of bupivacaine 0.125% plus 0.5ml of 20%Magnesium sulphate[100mg].Total epidurally injected volume is 10.5ml.Postoperatively heart rate,mean arterial pressure were recorded every 2 hourly at 0,2,4,6,8,10,12 hours.The duration of analgesia,time for first rescue analgesia was assessed in both groups and comparison was done.

Duration of analgesia: was taken from the time of administration of drug to the time of giving first rescue analgesia.The patients were taught to assess the intensity of pain using visual analog scale(VAS) for post operative pain assesment and systemic side effects related to the drugs and epidural technique were recorded

VAS was monitored every 2nd hourly in the post operative period. Post operative analgesia with bupivacaine was given with magnesium sulphate or dexmedetomidine when the patient complaints of moderate pain (VAS>4)

Statistical Analysis

Statistical data was analyzed by IBM SPSS 25.0 version software. Collected data were spread on excel sheet and master chart was prepared. Through the master chart tables and graphs were constructed.

For quantitative data analysis,descriptive statistics were done like mean, standard deviation . Independent samples “t” test was used to compare the mean values between two variables for statistical significance.

For qualitative data analysis chi-square test and Fisher exact probability tests were applied for statistically significant data. $P \leq 0.05$ was considered statistically significant for all comparisons.

Results:-

The study groups did not show any statistical difference as regards to demographic data,postoperative haemodynamics such as heart rate(HR),mean arterial pressure(MAP),ASA grade [Table :1] $P>0.05$,Figure 1 and Figure2.

There was no statistically significant data with regards to surgical procedure [Table:2] $P>0.05$

The time for first rescue analgesia was 5.76 ± 0.62 hours in group BD and 10.93 ± 1.02 hours in group BM which was statistically highly significant ($P<0.001$)Figure 5,[Table :4]

Pain intensity was assessed using the visual analogue scale (VAS) post-operatively at 0,2,4,6,8,10 and 12 hours.The mean VAS pain score was significantly higher in group BD as compared to Group BM at 2 and 4 hours.Thereafter first rescue analgesia was given to group BD at 4th and 6th hour and Group BM at 10th and 12th hour.There was no statistical significant difference of mean VAS pain score between group A and Group B at 0 and 12th hour post operatively.[Table:3]

There was statistically highly significant difference of mean VAS score between Group BM and Group BD at 2,4,6,8and 10 hours of postoperative period ($P<0.001$).Figure 4

No significant differences were recorded regarding incidence of any side effects such as nausea,vomiting,hypotension,bradycardia between two groups .[Table :1]

Demographic Data

	GROUP BD		GROUP BM		P VALUE
Gender	No	%	No	%	
Male	14	46.7	21	70	0.073
Female	16	53.3	09	30	
Age	46.50 ± 13.3		48.06 ± 13.95		P = 0.658

Weight	61.50±5.84		61.13±8.26		P= 0.843		
Height	161.70±5.70		158.3±5.34		P= 0.095		
ASA grade							
I	12	40	12	40	P= 1.000		
II	18	60	18	60			
Side effects							
Hypotension	0	0	2	6.7	P= 0.023		
Bradycardia	0	0	0	0	P= 0.006		
Nausea and vomiting	4	13.3	2	6.7	P= 0.478		
Surgical procedure		Group BD		Group BM		Total	
		No.	%	No.	%	No.	%
HEMIARHTROPLASTY		9	30.0	7	23.3	16	26.7
ARTHROSCOPIC REPAIR		4	13.3	2	6.7	6	10.0
TOTAL HIPREPLACEMENT		3	10.0	8	26.7	11	18.3
CLOSED-REDUCTION&INTERNAL FIXATION		8	26.7	4	13.3	12	20.0
OPEN-REDUCTION&INTERNAL FIXATION		6	20.0	9	30.0	15	25.0
Total		30	100.0	30	100.0	60	100.0
X ² -test value, P-value		X ² = 1.943 P = 0.251					

Table 2:- Surgical procedure wise distribution of cases among Group BM and Group BD.

Fig 1:- Line diagram representing mean heart rate of the cases.

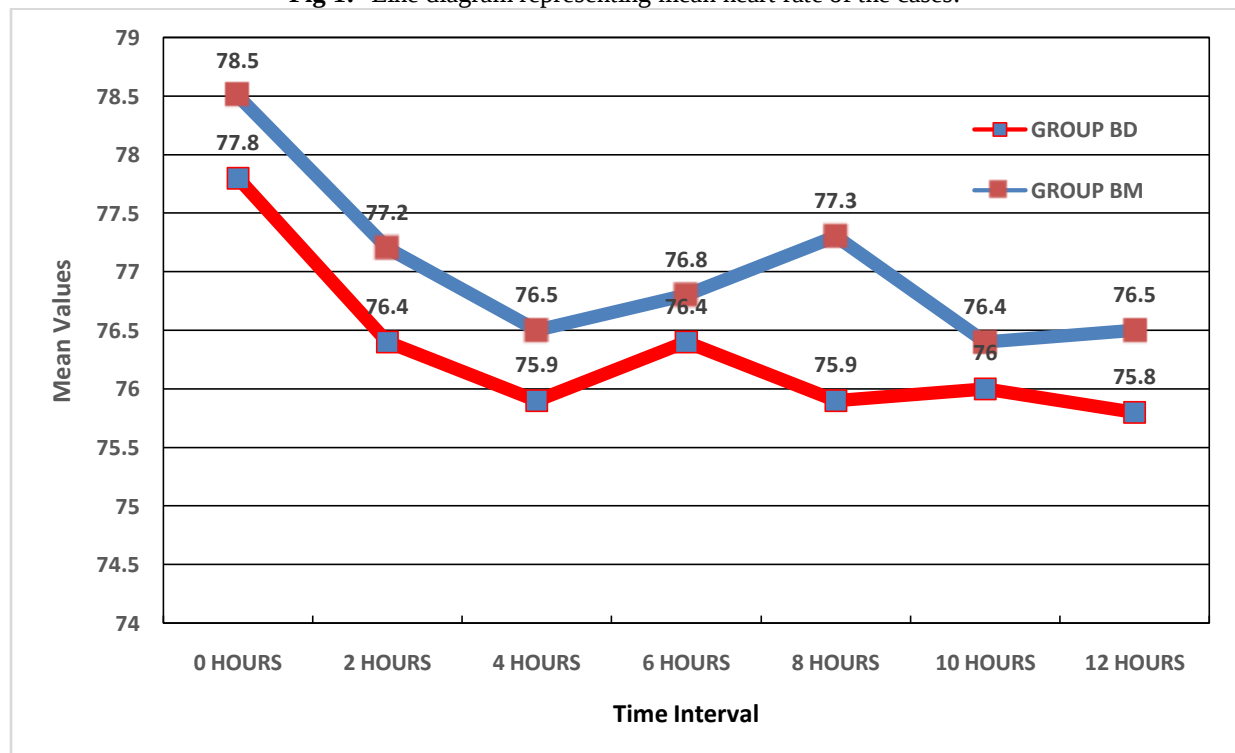


Fig 2:- Line diagram represents mean arterial pressure of two groups.

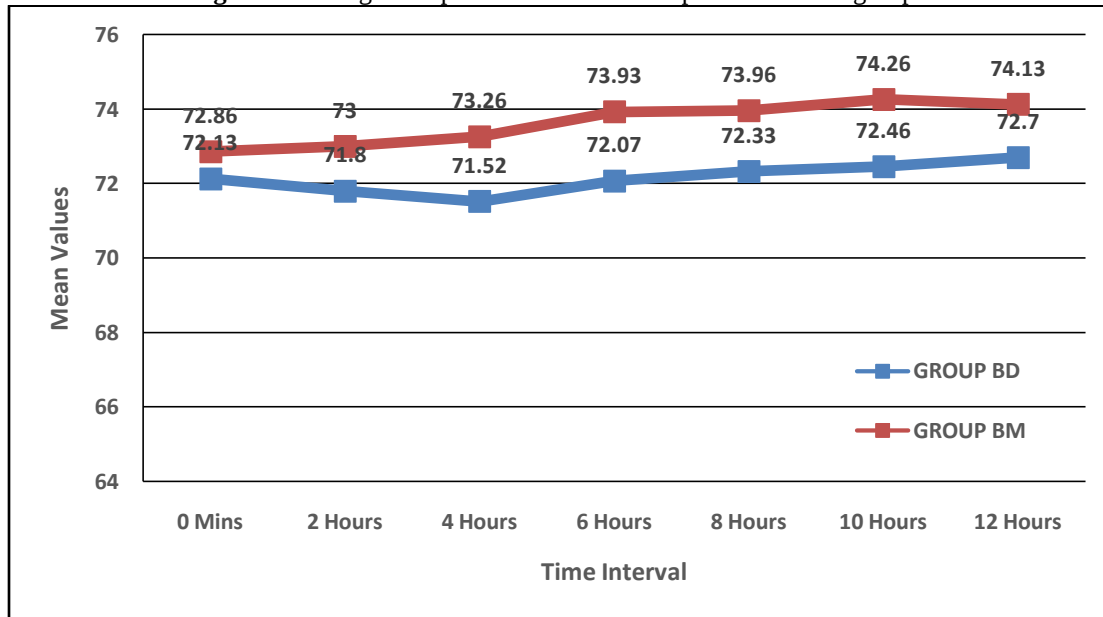


Table 3:- Comparison of Mean VAS score of pain of cases between Group BD and Group BM.

Time Period	VAS score		Std. Error	t –test value	P- value & Significance
	Group BD	Group BM			
	Mean $\pm$ SD	Mean $\pm$ SD			
0 hours	0.57 $\pm$ 0.67	0.2 $\pm$ 0.40	0.123	t = 2.137	P = 0.091, NS
2 hours	1.86 $\pm$ 0.63	1.16 $\pm$ 0.37	0.114	t = 5.222	P = 0.002, HS
4 hours	3.00 $\pm$ 0.78	1.50 $\pm$ 0.57	0.143	t = 8.437	P = 0.000, HS
6 hours	4.26 $\pm$ 1.11	2.03 $\pm$ 0.49	0.203	t = 10.065	P = 0.000, HS
8 hours	1.70 $\pm$ 0.46	2.67 $\pm$ 0.47	0.085	t = -7.918	P = 0.000, HS
10 hours	1.96 $\pm$ 0.18	3.76 $\pm$ 0.81	0.274	t = -11.774	P = 0.000, HS
12 hours	2.96 $\pm$ 0.18	2.16 $\pm$ 2.37	0.434	t = 1.786	P = 0.089, NS

Figure4:- Line diagram represents mean VAS pain score of the cases.

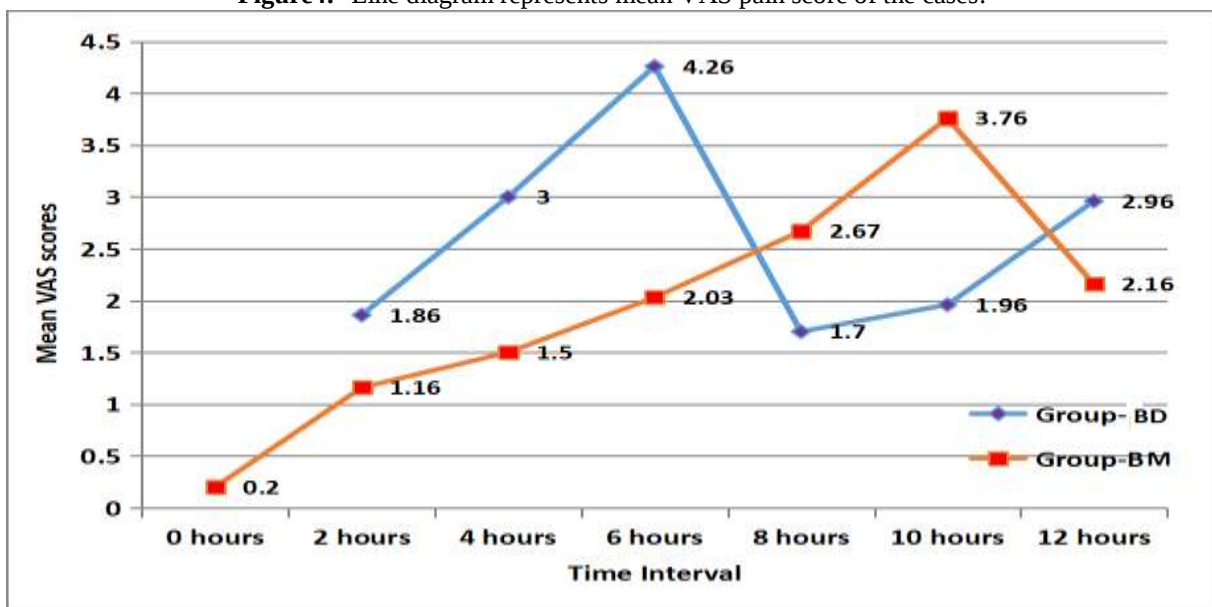


Figure 5:- Simple bar diagram representing the comparison of duration of time for first rescue analgesia between the two groups.

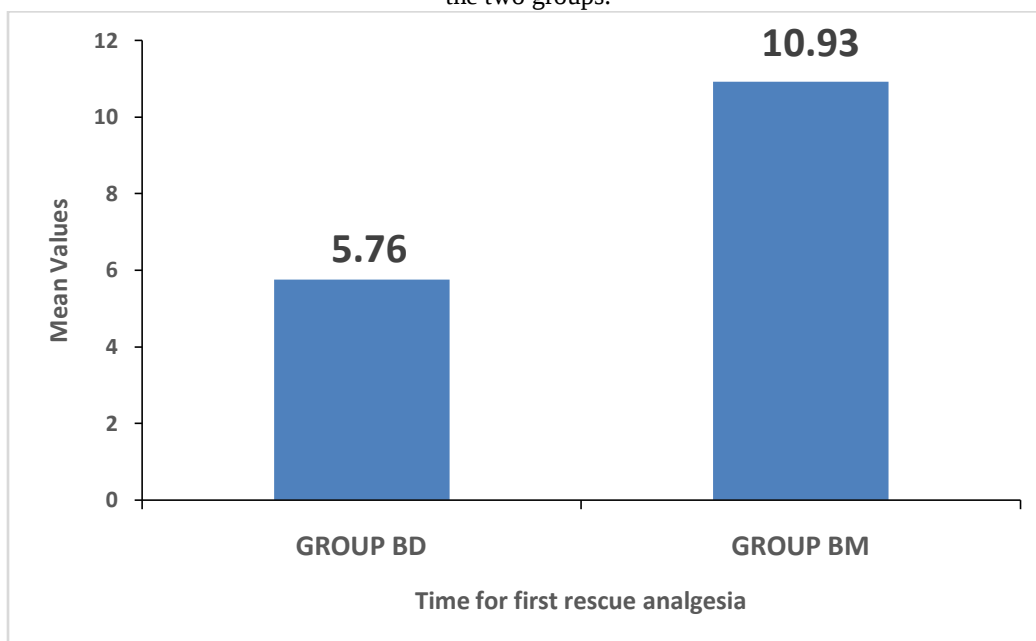


Table 4:- Comparison of Time of rescue analgesia in hours between the groups.

Groups	Time of rescue analgesia	t –test value	P- value & Significance
	Mean $\pm$ SD		
Group-BD	5.76 $\pm$ 0.62	t = 23.733	P = 0.000, HS (highly significant)
Group-BM	10.93 $\pm$ 1.02		

Discussion:-

Management of post-operative pain still poses lot of challenge to anaesthetists paradoxically after all the efforts taken to make the intra-operative period pain free and stress free, the patients are left to fend themselves in the post-operative period. Hence, its relief undoubtedly decreases morbidity and mortality

The safety of epidural magnesium administration has been evaluated in animal and human studies that concluded that magnesium has a good safety profile with no serious side effects^{3,8}. Since the amount of magnesium used in this study was only 100 mg epidurally, serum magnesium levels was not monitored during the study. NMDA receptor signaling may be important in determining the duration of acute pain⁹ Magnesium blocks calcium influx and noncompetitively antagonizes NMDA receptor channels¹⁰

The dose of epidural dexmedetomidine reported is in the range of 1.5-2 μ g/kg in humans. We preferred lower dose of dexmedetomidine as higher doses results in more side effects such as bradycardia¹¹. The local anesthetic acts by blocking sodium channels, whereas the α 2-adrenoceptor agonist acts by binding to presynaptic C fibers and postsynaptic dorsal horn neurons. The α 2-adrenoceptor agonists produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons.¹²⁻¹⁶

In this prospective interventional randomised study, the analgesic efficacy of bupivacaine with magnesium sulphate and dexmedetomidine given through epidural in patient undergoing elective lower limb surgeries was evaluated.

In the present study, there were no significant haemodynamic changes between groups

This was observed in study conducted by Bilir A et al¹, Kerdawy H et al¹⁷, there were no significant side effects observed in the study

Zara Wani et al¹⁸ evaluated that concomitant administration of magnesium also reduces the requirement for rescue analgesic with no increased incidence of side effects.

The mean VAS pain score was significantly higher in group BD as compared to Group BM at 2 and 4 hours. Thereafter first rescue analgesia was given to group BD at 4th and 6th hour and Group BM at 10th and 12th hour. There was no statistical significant difference of mean VAS pain score between group BD and Group BM at 0 and 12th hour post operatively.

There was statistically highly significant difference of mean VAS score between Group BD and Group BM at 2,4,6,8 and 10 hours of postoperative period ($P < 0.001$)

Similarly study done by Aishwarya Guru et al ¹⁹ showed reduced postoperative visual analogue score and prolonged duration of analgesia with bupivacaine and magnesium sulphate group than bupivacaine group in patients undergoing abdominal hysterectomy

Fukushima, et al. ²⁰ administered 2 µg/kg epidural dexmedetomidine for postoperative analgesia in humans without any reports of neurological deficits. Moreover, Maroof, et al. ²¹ used epidural dexmedetomidine, approximately 1.5 µg/kg, to decrease the incidence of postoperative shivering, without any reports of neurological deficits.

In our study, time for first rescue analgesia (TFA) in (magnesium group) Group BM is 10.93 ± 1.02 hours and Group BD is 5.76 ± 0.62 hours.

This study reveals that there was statistically highly significant difference of mean time of rescue analgesia in hours between Group BD and Group BM ($P < 0.001$) and prolongs the duration of analgesia.

Kerdawy et al ¹⁷ defined time for first rescue analgesia as the time from the completion of surgery till the time of first use of rescue medication by PCEA. Since each surgery may have different durations, in our study, we defined time for first rescue analgesia as the time from the injection of the study drug through epidural to the time when visual analogue score reaches 4 in the postoperative period

Li-Qin-lil et al ²², found that epidural bupivacaine with magnesium sulphate could prolong the time for first rescue analgesics.

Mohamed Ibrahim El-Desoukey Mohamed et al ⁸ conducted a study on 60 patients of ASA I and II scheduled for lower limb orthopedic surgery in which patients were allocated into two equal groups of 30 each. The duration of analgesia was more prolonged in magnesium sulphate group (75mg) than in the fentanyl group (1mg/kg) and this difference was statistically significant.

Zara Wani et al ¹⁸ conducted a study on 40 Patients of ASA grade I and II aged 20 to 60 years of either gender undergoing Total Knee replacement surgery. And concluded that the administration of epidural magnesium (75 mg) as an adjuvant to epidural fentanyl (50µg) for postoperative analgesia resulted in prolonged duration of analgesia when compared with epidural fentanyl (50µg) alone.

Arcioni, et al ²³ observed that intrathecal and epidural magnesium sulfate potentiated and prolonged motor block. [21] They concluded that patients undergoing orthopedic surgery, supplementation of spinal anesthesia with combined intrathecal and epidural MgSO₄ significantly reduces patients' postoperative analgesic requirements

Conclusion:-

This study establishes the role of dexmedetomidine as an adjunct to bupivacaine in comparison to magnesium. In conclusion, Noncompetitive NMDA antagonist magnesium sulfate, administered epidurally, prolongs the duration of analgesia, more than epidural dexmedetomidine. 12.5 µg epidural dexmedetomidine seems to be an attractive alternative as adjuvant to epidural bupivacaine for prolonged surgeries, with minimal side effects and excellent postoperative analgesia.

Further studies are required to determine whether larger doses of epidural dexmedetomidine can produce greater potentiation of analgesia.

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