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EFFICACY OF DEXMEDITOMIDINE AND MAGNESIUM AS ADJUNCTS TO EPIDURAL BUPIVACAINE FOR UPPER ABDOMINAL SURGERIES

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ABSTRACT

Background: This prospective, randomized, double-blind study was undertaken to establish the effect of addition of magnesium or dexmedetomidine, as an adjunct, to epidural bupivacaine in upper abdominal surgeries. **Materials and Methods**: Sixty ASA (American Society of Anesthesiologists) class I and II patients undergoing upper abdominal surgeries were enrolled to receive either magnesium sulfate (Group M) or dexmedetomidine (Group D) along with epidural bupivacaine for surgical anesthesia. All the study subjects received an epidural anesthesia with 8 ml of 0.5% bupivacaine along with either MgSO4 50 mg (Group M) or dexmedetomidine 1 μg/kg (Group D). Duration of analgesia, total rescue analgesic requirement, hemodynamic parameters and any adverse events were monitored. **Results**: Analgesia in the postoperative period was better in Group BD, rescue analgesic requirement was less in Group BD and incidence of sedation was more in Group BD. **Conclusion**: Hence, addition of dexemedetomidine to epidural bupivacaine can be advantageous with respect to better analgesia and arousable sedation.

KEYWORDS: Dexmedetomidine, magnesium sulphate, bupivacaine.

INTRODUCTION

Painful surgical incisions involving the upper abdomen result in reflex mediated increase in tone in abdominal muscles during expiration and decrease in diaphragmatic functions. The result is reduced pulmonary compliance, muscle splinting and inability to breathe deeply or cough forcefully phrenic reflex activity is an important component of decreased postoperative pulmonary functionand in some cases hypoxia, hypercarbia, retention of secretions, atelectasis and pneumonia. Suprasegmental reflex responses to pain results in increased sympathetic tone, hypothalamic stimulation, increased catecholamine and catabolic hormone secretion and decreased secretion of anabolic hormones.[1] Sympathetic activation may also delay return of postoperative gastrointestinal motility, which may develop into paralytic ileus. Epidural blockade is becoming one of the most useful and versatile procedures in modern anaesthesiology. It is unique because it can be given virtually at any level of the spine, adding more flexibility in its application to clinical practice. It provides postoperative pain control and more rapid recovery from surgery. Thoracic epidural analgesia has been shown to decrease the incidence of myocardial infarction and postoperative pulmonary complications.[2,3,4,5]

Dexmeditomidine is a highly selective α_2 adrenoceptor agonist that has sedative and analgesic properties with associated reduction in opioid and anesthetic requirements.[6–16] One significant advantage of dexmedetomidine is that in the clinical dose range there is no respiratory depression.[17-19] The hypnotic and supraspinal analgesic effects of dexmedetomidine are mediated by the hyperpolarisation of noradrenergic neurons, which suppresses neuronal firing in the locus ceruleus along with inhibition of norepinephrine release and activity in the descending medullospinal noradrenergic pathway, secondary to activation of central alpha2A adrenergic receptors.

Neurophysiological studies have demonstrated that Mg is a physiological and pharmacological blocker of NMDA receptors in neuronal tissue. As the role of the NMDA receptor in pain perception has become apparent, there is increasing use of Mg for the management of both acute andchronic pain.[20,21] Magnesium inhibits calcium entry into neuronal cells at avariety of calcium channels including acting as an NMDA antagonist.[22]

MATERIALS AND METHODS

This clinical study entitled to compare the “efficacy of magnesium and dexmeditomidine as adjuncts to bupivacaine in epidural anesthesia in upper abdominal surgeries” was conducted

after approval by the Institutional Ethical Committee and an informed written consent was obtained from all the patients for participation in this study. A total number of 60 patients of physical status ASA I and II of either sex belonging to age group 20-60 years posted for elective upper abdominal surgery (hepatobiliary, pancreatic and gastric) were enrolled for the surgery. Preanaesthetic evaluation was done for all patients. Patient refusal, raised intracranial tension, bleeding disorders or anticoagulation, infection at local site, hypersensitivity to drugs in study, deformity of lumbar spine and heart blocks were considered as contraindications and these patients were excluded from the study. All the patients were premedicated with oral ranitidine 150mg night before surgery. On arrival to operation theatre, intravenous line was secured with 18g cannula. Standard anesthetic monitoring viz electrocardiogram, non invasive blood pressure, pulse oximetry was instituted to all patients. All the baseline parameters (heart rate, blood pressure and oxygen saturation, respiratory rate) were recorded prior to epidural block. All the patients were preloaded with lactated ringers solution 20 ml/kg body weight prior to epidural block. Patients were allocated randomly to two groups by systematic random sampling to receive one of the two solutions in epidural anesthesia. Group BM received bupivacaine 0.5%(8ml)+ magnesium sulphate 50mg(2ml) and Group BD recievedbupivacaine 0.5%(20ml +Dexmeditomidine(1 mcg/kg) (2ml) respectively. The study solutions were prepared by an anesthesiologist not involved in study. The procedure was carried out in lateral decubitus or sitting position whichever was comfortable for the patienusing 18 gauge Tuohy epidural needle. Epidural space was identified at T8-T9 space with loss of resistance to air technique. A 20 gauge catheter was advanced for 3-5 cm into the epidural space. Correct placement of epidural catheter was verified with test dose of 3 ml lignocaine (2%), with epinephrine 1:200,000. In case of any motor block or significant rise in heart rate, patients were excluded from the study. Patients received test solution after test dose of local anesthetic. In order to prevent patient discomfort due to prolonged positioning and gut manipulation general anesthesia was given to all patients. Patients were induced with propofol 1.5-2.5 mg/kg, fentanyl 2mcg/kg, atracurium 0.5mg/kg and intubated with appropriate sized endotracheal tube. Anesthesia was maintained with O2 30%, N2O 70% and isoflurane 1%. Hypotension was defined systolic blood pressure of <90mmHg or drop of more than 20% basal mean arterial blood pressure and bradycardia as heart rate less than 60 beats per minute and was treated with intravenous ephedrine 5- 10 mg bolus doses and atropine IV 0.01 mg/kg bodyweight respectively. Patients were reversed with neostigmine and glycopyrrolate and extubated once fully conscious. Patients were evaluated for 24 hours after completion of surgery regarding total duration of analgesia and

post operative analgesic requirements. Rise in mean arterial pressure by >20% of baseline MAP associated with tachycardia (Heart rate >100bpm) despite adequate level of anesthesia during intraoperative period was considered as pain. Postoperatively pain was recorded by using Visual Analogue Scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain). Rescue analgesia was given for intraoperative pain and postoperative VAS Score of ≥4. For rescue analgesia 10ml of tramadol (100mg) was administered through epidural catheter. In case pain was unrelieved in 20 mins injection diclofeac 75 mg was given slowly in 100 ml of normal saline. Total consumption of tramadol and diclofenac was calculated. Sedation was assessed at intervals of 2 hour postoperatively. Sedation was assessed by Subjective Sedation Scale as: Grade 0 = Awake conscious no sedation to slightly restless, Grade 1= Calm and compose, Grade 2 = Awake on verbal command, Grade 3= Awake on gentle tactile stimulation, Grade 4= Awake on vigorous shakig and Grade 5= Unarousable. Any untoward incident or side effect like nausea, vomiting, hypotension, respiratory depression, drowsiness, headache, dizziness, urinary retension was recorded.

Descriptive statistical analysis was carried out. Independent sample *t*-test, Pearson Chi-square/Fisher Exact test are used to find the significance of study parameters on categorical scale. P value ≤0.05 was considered statistically Significancant. The statistical software namely SPSS 17.0, was used for analysis.

RESULTS

Demographic patterns and pre-operative vital parameters were comparable between the groups [Table 1].

Parameters	Group BM (*n*=30)	Group BD (*n*=30)	*P* value
Age (years)	42.97±4.19	44.31±7.67	0.4
Weight (kg)	62.37±6.47	64.94±7.10	0.18
ASA status(I/II)$	14/1618/120.89		
Preoperativepulse (bpm)	95.30±5.33	96.13±5.39	0.45
Preoperative MAP (mmHg)	104.24±4.99	102.31±4.4	0.123
Preoperative SpO2 (%)	99.57±0.82	99.61±0.72	0.87

Data are given as mean±SD, except ASA physical status. Test done:

Independent sample *t*-test, $Pearson Chi square. *n*: Number of patient;

bpm: Beats per minute; MAP: Mean arterial pressure

Durations of surgery were 208.31±4.34 and 204.56±5.33min in group BM and group BD, respectively, the values being comparable (*P*>0.05). Intra/postoperative vital parameterswere comparable in the two groups (*P*>0.05)(Table 2).

Parameters Group	BM (*n*=30)	Group BD (*n*=30)	*P* value
Duration of surgery(mins)	208.31±4.34	204.56±5.330.78	
Intra/postoperative pulse(bpm)	79.36±2.1	0.35±3.19	<0.01
Intra/postoperative MAP (mmHg)	89.05±2.78	86.72±3.54	1.24
Intraoperative SpO2 (%)	98.21±5.92	98.38±4.62	1.33

Data are given as mean±SD. *n*: Number of patient, Test done: Independent sample *t*-test. *Statistically significant; bpm: Beats per minute; mins: Minutes.

Time to request for analgesic for the first time wasconsidered as the duration of postoperative analgesia. It ranged from 193 to 505 min in group group BM and from 279 to 568 min in group BD. The mean duration of post-operative analgesia was 303.67±2.31min in group group BM and 485.31±15.33 min in group BD, the difference being statistically significant (*P*<0.001). Total dose of tramadol as rescue analgesic during the first 24 h was 356.38±5.52mg in group group BMas compared with 252.13±3.89 mg in group BD(*P*<0.001). Back-up analgesic in the form of intramuscular diclofenac sodium had to be used in three patients (10%) in group BMas compared with none in group BD(*P*=0.01). The VAS scores in the immediate post-operativeperiod and after 2, 4, 6, 12 and 24 h in the post-operative period were significantly higher in group BM(*P*<0.05).{Table 3}.

Parameters	Group BM (*n*=30)	Group BD(*n*=30)	*P* value
Time to first analgesic at VAS≥4 (mins)	303.67±2.31	485.31±15.33	<0.001*
Patients receiving diclofenac [*n* (%)]$	3	0	0.01*
VAS score in immediate postoperative period	2.27±3.22	1.05±6.33	<0.0001*
VAS score at 2 hrs	2.35±1.34	1.41±8.22	<0.0001*
VAS score at 4 hrs	3.73±5.31	1.79±1.42	<0.0001
VAS score at 6 hrs	3.12±1.12	2.66±3.21	<0.0001
VAS score at 12 hrs	3.87±1.46	2.03±1.38	<0.0001
VAS score at 24 hrs	3.38±8.52	2.13±3.89	<0.0001
Total Tramadol received(mg)	356.38±5.52	252.13±3.89	<0.0001

Data are given as mean±SD, *n*: Number of patient; Test done: Independent sample *t*-test, $Pearson Chi square. *: Statistically significant. mgs: Milligrams; VAS: Visual analogue scale

Sedation score 0 was found in 1(3%) patients in Group BM and 0(0%) in Group BD.

Sedation score 1 was found in 27(90%) patients in Group BMand 6(20%) in Group BD. Sedation score 2 was found in 2(7%) patients in Group BM and 10(33%) in Group BD. Sedation score 3 was found in 0(0%) patients in Group BM and 14(47%) in Group BD. Sedation score 4 and 5 was not found in any patient. Statistically the relation between groups is significant (p <0.01)(Table 4).

Table 4: Sedation scores

Characteristics	Group BM (n = 30)		Group BD(n = 30)		
	No.	%	No.	%	
Sedation scores	0	1	03 00	00	
Sedation scores	1	27	90	06	20
Sedation scores	2	02	0710	33	
Sedation scores	3	00	0014	47	
Sedation scores	4	00	00	00	00
Sedation scores	5	00	00	00	00

Table 5: Incidence of side effects in patients of all the three groups

Parameters	Group BM	Group BD
Nausea / Vomiting	4	3
Hypotension	1 0	1 2
Bradycardia	6	8
Respiratory depression	0	0
Headache	3	3
Shivering	3	4

DISCUSSION

Epidural analgesia offers superior pain relief and early mobilization especially when local anesthetic dose is combined with an adjuvant as compared to LA used alone.[23] Selection of exclusive epidural route during this study was done to avoid invasive dural penetration technique with spinal needle as well as to provide postoperative pain relief. Also Christopher L *et al* performed a meta-analysis and found that epidural analgesia overall provided superior postoperative analgesia compared with intravenous patient-controlled analgesia for all types of surgeries.[24]

Brown *et al.* [25](1990) and **Brockway *et al.*[26]** comparedeffect of 0.5% ropivacaine (20ml) and 0.5% bupivacaine and concluded that 0.5% bupivacaine produced a quicker onset, longer duration and more intense motor block than same concentration of ropivacaine. **Buvanendran A et al.[27] (2002)** found that intrathecal magnesium prolongs spinal opioid analgesia in humans and suggested that the availability of an intrathecal N-methyl-d-aspartate

antagonist could be of clinical importance for pain management. Later **Bilir A et al.[28] (2007)** found that co-administration of magnesium for postoperative epidural analgesia results in a reduction in fentanyl consumption without any side-effects. **Bajwa SJS et al.[29] (2011**) found that Dexmedetomidine seems to be a better alternative to fentanyl as an epidural adjuvant as it provides comparable stable hemodynamics, early onset and establishment of sensory anesthesia, prolonged post-op analgesia, lower consumption of post-op LA for epidural analgesia and much better sedation levels.

Keeping in view the above mentioned properties of bupivacaine, magnesium and dexmeditomidine we selected these drugs to be administered to our patients in epidural anesthesia.

In our study patients were comparable with respect to their demographic profile i.e., age, gender, ASA status and weight. Baseline cardiorespiratory parameters were comparable between the study groups. We observed non significant change in systolic and diastolic blood pressure, mean arterial pressure, respiratory rate and oxygen saturation from baseline values during intra-operative and post-operative period respectively. There was a significant change in mean pulse rate ($p \leq 0.0001$) between Group BM and Group BD. The decrease in heart rate caused by α_2 agonist can be explained on the basis of their central action by decreasing sympathetic outflow and norepinephrine release.

Although wide variations were seen in postoperative pain score, however, dexmeditomidine group had lowest VAS score compared to Magnesium group. VAS at different time intervals was significant between the two groups ($P < 0.01$). 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. This antinociceptive effect may explain the prolongation of the sensory block when added to spinal or epidural anesthetics. Motor and sensory blockade effects of local anesthetics are enhanced by dexmeditomidine. We found in our study that the time gap between initial epidural medication and the time to 1st epidural top-up was significantly higher in Group BD compared to Group BM. The number of top-ups was also reduced in Group BD as compared to Group BM ($p = < 0.01$). Our results are consistent with the results of Shahi V et al.[30] (2014) as they found analgesia in the postoperative period was better and statistically significant in paients receiving bupivacaine with dexmeditomidine as compared

to patients receiving bupivacaine with saline and bupivacaine with magnesium. Gupta K et al.[31] (2014) studied epidural 0.5% levobupivacaine with dexmedetomidine vand fentanyl for vaginal hysterectomy. Postoperative analgesia was significantly prolonged in patients receiving levobupivacaine with dexmeditomidine. We also found significant prolongation of analgesia with addition of dexmeditomidine as adjuvant to bupivacaine in our study. Thus addition of dexmeditomidine as adjuvant to bupivacaine or levobupivacaine can prolong postoperative analgesia.

Eskandar A M et al.[32] (2014) studied effects of epidural dexmedetomidine and low-volume bupivacaine on postoperative analgesia after total knee replacement. The demographic data were comparable in both groups. Visual analogue scale of pain showed a significant reduction between the two groups at both rest and movement and the total dose of nalbuphine consumption during the study period was significantly reduced ($P < 0.002$) in group receiving dexmeditomidine (5 ± 5.15) than in group receiving bupivacaine (11 ± 7.63). Thus our results are also consistent with Eskandar A M et al. R Arcioni et al.[33] (2007) undertook a randomized trial in patients undergoing major orthopedic surgery and studied the effect of combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia on post-operative analgesic requirements. They enrolled 120 patients undergoing orthopaedic surgery during spinal anesthesia. Patients were randomly assigned to receive intrathecal MgSO4, epidural MgSO4, intrathecal and epidural MgSO4 combined or spinal anesthesia alone (controls). Post-operative morphine consumption was assessed. They observed that in patients undergoing orthopedic surgery, supplementation of spinal anesthesia with combined intrathecal and epidural MgSO4 significantly reduces patients' post-operative analgesic requirements.[33] **Yousef AA et al.[34] (2010)** studied the effect of adding magnesium sulphate to epidural bupivacaine and fentanyl in elective caesarean section using combined spinal-epidural anaesthesia in a prospective double-blind randomized study and concluded that addition of magnesium sulphate to epidural bupivacaine and fentanyl in women undergoing elective caesarean section with combined spinal-epidural anaesthesia improved intraoperative conditions and the quality of postoperative analgesia.

Sedation is a side effect frequently associated with use of dexmeditomidine in post-operative analgesia often in conjunction with opioids. In our study sedation score 3 was significantly higher in Group BD patients compared to Group BM patients. Higher sedation score gives better patient satisfaction. Dexmedetomidine acts on pre and post-synaptic sympathetic nerve

terminal and central nervous system thereby decreasing the sympathetic outflow and norepinephrine release to cause sedation, analgesia and hemodynamic effects. It acts peripherally by blocking conduction through Aα and C fibers to enhance the eff ects of local anesthetics without increasing the incidence of side effects.

The patients were continuously observed for respiratory depression i.e., SpO2 (< 90%) and RR (< 10) in the postoperative period. No case of respiratory depression was observed in any group, consistent with other studies.

There was no significant difference between the three groups regarding nausea, vomiting, urinary retention, pruritis, dizziness, dry mouth, shivering, headache, hypotension and bradycardia ($p>0.05$).

Limitations of study

Patient consent is a problem as patients are not easily ready for experimental study. Study is limited to 24hours only.

CONCLUSION

Dexmeditomidine and dexmeditomidine are safe adjuncts in epidural anesthesia. Dexmeditomidine prolongs the duration of analgesia and produces significant sedation. Quality of analgesia is excellent in dexmeditomidine group as compared to magnesium group as adjunct to bupivacaine in epidural anesthesia.

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