Original Article

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A Comparative Study of Epidural Fentanyl Citrate Alone and Fentanyl Citrate with Magnesium Sulphate for Post Operative Analgesia

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Abstract

Background: This study was done to evaluate the efficacy of single bolus administration of Magnesium Sulphate epidurally as an adjuvant to epidural fentanyl citrate for post-operative analgesia with consideration of duration of analgesia and hemodynamic stability after abdominal surgeries and to compare the side effects of both groups. *Method:* One hundred patients received standard general anaesthesia with epidural anesthesia using 10 ml of 0.5% Bupivacaine. After the surgery, patients were randomized into Group-I [Epidural Fentanyl-1µg/ kg in 10 ml saline] and Group- II [Epidural Magnesium-75 mg along with Fentanyl-1 µg/ kg in 10 ml saline]. Supplementary analgesia was provided by Inj. Tramadol- 50 mg when Verbal Rating Score (VRS) was > 4. Patient's first analgesic requirement and duration of analgesia were recorded. *Results:* The duration of analgesia was significantly longer in Group- II (290 ± 50 min) as compared to Group- I (160± 30 min) (*P*- 0.001). The frequency of rescue analgesics required in Group- II (2.1±0.5) was significantly less than that in Group-I (3.3±0.5) (*P*- 0.001). VRS was lower in Group-II up to 4 hours postoperatively (*P*- 0.001). *Conclusion:* The Administration of Magnesium- 75 mg as an adjuvant to Epidural Fentanyl- 1 µg/ kg significantly lowers the Verbal Rating Score (VRS) with prolonged duration of postoperative analgesia as compared with Epidural Fentanyl (1 µg/ kg) alone. Concomitant administration of Magnesium also reduces the requirement of breakthrough analgesics without any significant side effects.

Keywords: Epidural Adjuvants; Fentanyl; Magnesium; Postoperative Analgesia.

Introduction

Post-operative pain, especially when poorly controlled, results in harmful acute effects (adverse physiological responses) and chronic effects (delayed recovery and chronic pain). The main aim of pain management is to ensure that the patient gets pain relief at appropriate time.

Abdominal analgesia may assist in improving post-operative outcome in cases of abdominal surgeries. The analgesic regimen needs to meet the goal of providing safe, effective analgesia with minimal side effects & allowing the patients to breathe, cough, and move easily with early hospital discharge. These effects reduce pulmonary, cardiovascular, thromboembolism and other complications that may affect the patient.

Providing postoperative pain relief is a challenge task for anesthesiologists. Various adjuvants in addition to opioids have been used epidurally to prolong analgesia and reduced the incidence of adverse events observed when opioids are used alone [1]. NMDA, an excitatory amino acid receptor has been implicated in transmission of noxious stimulus from periphery leading to central sensitization. The duration and intensity of postoperative analgesia is dependent on the degree of inhibition of NMDA receptor signal transmission. Calcium channel blockers and NMDA receptor antagonist have shown to be beneficial in preventing initiation of pain. Magnesium, a divalent cation, through non-competitive mechanism blocks the NMDA receptor in a voltage dependent manner and results in natural calcium antagonism [2,3]. Magnesium has been used as an adjuvant by various routes, including intrathecal, epidural and intravenous in different dosage regimens [4,5,6]. Fentanyl

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is a potent opioid agonist and has been widely used in the management of post-operative pain and it is found that epidural route is more effective than Intravenous infusion [7].

We hypothesized that a single bolus dose of Epidural Magnesium will prolong the duration of postoperative analgesia. Thus, we planned a prospective randomized, double-blind study to evaluate the efficacy of single bolus administration of Magnesium-75 mg epidurally as an adjuvant to Epidural Fentanyl- 1 mcg/kg for postoperative analgesia.

Method

After obtaining ethical committee approval and written informed consent, 100 patients of ASA [American Society of Anesthesiologists] physical status I or II patients, 18–65 years of age, undergoing elective abdominal surgery under general anaesthesia were enrolled for the study. Exclusion criteria- History of drug allergy, Cardio-respiratory and liver disease, Regular consumption of analgesics, calcium channel blockers or drug abuse and dependent on narcotic and contraindication to epidural procedure.

A day before surgery, patients were instructed about Verbal Rating Score (VRS) [0: No pain, 10: worst pain). They were advised over night fasting. Tab Lorazepam- 1 mg a night before surgery and Tab Diazepam- 5 mg in the morning on the day of surgery were given orally.

In the operating room monitors were attached for temperature, electrocardiogram, non-invasive blood pressure and pulse oximeter. An intravenous access was established. Inj. Glycopyrrolate- 40 mcg/ kg IV was given before placement of epidural catheter**.** Epidural catheter was placed in L2-L3 or L3-L4 space in lateral position using hanging drop technique and catheter was guided cephalad. Test dose of Inj. Lignocaine hydrochloride (with adrenaline-1:2, 00,000) 3ml 2% with was given. After preoxygenation with 100% oxygen, general anaesthesia was induced with Inj. Fentanyl citrate 2 mcg/ kg, Inj. Thiopentone 5 mg/ kg, Inj. Succinyl choline 2 mg/ kg and Inj. Lignocaine hydrochloride (2%) 2 mg/ kg intravenously.

Patients were intubated with appropriate sized portex tube and cuff was inflated. Anaesthesia was maintained with O_2:N_2O (50%:50%) and Isoflurane. Muscle relaxation was achieved with Vecuronium bromide 0.1 mg/ kg IV initial dose followed by 0.04 mg/ kg/ hr intravenous infusion. Intra-operative epidurally inj. Bupivacaine hydrochloride 0.5% 10 cc was administered. After completion of surgery patients, all patients were reversed with inj. Neostigmine 0.05 mg/ kg with inj. Glycopyrrolate 80 mcg/ kg intravenously, were extubated and transferred to post-operative ward.

Patients were randomized by computer generated random number assignment into 2 groups of 50 each. Group- I (n=50) patients who received Epidural Fentanyl-1 mcg/ kg in 10 mL isotonic normal saline, while patients in Group- II (n=50) who received Epidural Magnesium - 75 mg along with fentanyl- 1 mcg/ kg diluted in isotonic saline to a total volume of 10 mL. The drug was prepared by an independent investigator who was not involved in the perioperative management of the patient. Further observations were noted by an independent investigator who was unaware of the randomization. VRS ≤ 4 was considered adequate pain relief. Whenever patient had VRS > 4, supplementary analgesia was provided by Inj. Tramadol- 50 mg IV. Patient's first analgesic requirement was recorded. The duration of postoperative epidural analgesia was defined as the time from administration of epidural study drug postoperatively to the time to first demand of additional/ rescue analgesia. The frequency of rescue analgesics during 24 hours postoperative period was also noted. Pulse, BP, respiratory rate, verbal rating score, sedation score and SpO_2 were noted initially at 0 and 30 min, then hourly till 6 hours and then at 8 hour, 12 hour and 24 hour duration.

Sedation was evaluated by four point scale:

- 1 = Awake & alert
- 2 = mildly sedated, easy to wake up when spoken
- 3 = moderately sedated, easy to wake up when stimulated
- 4 = deeply sedated, difficult to wake up when stimulated

Patients were monitored continuously for side effects after administration of drug.

Statistical analysis was performed using the statistical software package. Data comparisons were made using unpaired student's t-test and fisher's exact test.

Results

The demographic data were almost comparable in both the groups (P> 0.05). The total numbers and types

Table 1: Demographic data

	Groups	
	Group I	**Group II**
N	50	50
Age (yrs)	54 ±7	56 ± 8
Height (Cm)	159 ± 4	158 ± 8
Weight (Kg)	49 ± 6	50 ± 5
Sex (male/female)	18:32	19:31

Cm-centimeter, Kg-kilogram, Values are mean ± SD

Table 2: Type of surgery

Diagnosis	Surgery	Group I	Group II
Ca. ovary	TAH+BSO	18	20
Ca. cervix	Wertheim's Hysterectomy	8	6
Ca. stomach	Total Gastrectomy	3	5
Ca. colon	Colectomy	9	9
Obstructive jaundice	Whipple's procedure	6	4
Obstructive jaundice	Triple bypass	6	6
Total		50	50

TAH+ BSO-Total abdominal hysterectomy and Bilateral Salpingo-ophorectomy

Table 3: Post-operative VRS Score

Time	Group I	Group II	P value
t = 0	7.1±0.3	7.2±0.4	0.1605
30 min	2.6±0.4	2.5±0.2	0.1171
1 hr	2.4±0.3	1.9±0.6	0.0001
2 hr	3.1±0.6	2.4±0.2	0.0001
3 hr	5.2±0.3	2.8±0.4	0.0001
4 hr	3.8±0.4	3.0±0.2	0.0001
5 hr	3.1±0.2	3.9±0.8	0.0001
6 hr	3.5±0.3	4.8±0.3	0.0001
8 hr	2.8±0.2	1.9±0.3	0.0001
12 hr	3.2±0.4	2.4±0.3	0.0001
24 hr	3.6±0.1	3.7±0.4	0.0895

t-time, Min-minute, hr-hour, mean ± SD

Table 4: Changes in vital parameters

Pulse Rate											
Time	T=0	30 min	1 hr.	2 hrs.	3hrs.	4 hrs.	5 hrs.	6hrs.	8 hrs.	12 hrs.	24 hrs.
Group I	87±9	86±9	83±8	84±10	82±8	80±8	76±7	73±2	78±9	76±10	70±7
Group II	87±12	84±7	83±7	82±6	81±8	78±5	73±6	71±6	74±7	73±7	69±6
P value	1.00	0.24	0.85	0.16		0.17	1.00	0.12	0.04	0.16	0.53
Blood Pressure											
Time	T=0	30 min	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	8 hrs.	12 hrs.	24 hrs.
Group I	90±10	86±9	78±8	77±2	76±5	77±7	71±6	72±5	75±6	72±7	72±5
Group II	92±8	85±7	75±10	75±8	74±8	74±8	69±8	72±9	74±2	77±6	75±6
P value	0.12	0.08	0.10	0.12	0.15	0.33	0.10	0.07	0.08	0.18	0.37
Respiratory Rate											
Time	T=0	30 min	1 hr.	2 hrs.	3 hrs.	4 hrs.	5 hrs.	6 hrs.	8 hrs.	12 hrs.	24 hrs.
Group I	15.4±1.4	15.5±2.2	15.2±2.7	14.7±2.2	14.5±1.2	14.8±1.1	14.6±1.2	14.1±0.9	15.5±0.9	15.0±0.7	15.0±1.8
Group II	15.2±1.3	15.2±1.4	15.0±1.3	14.1±1.3	14.2±1.3	14.4±1.0	14.1±1.4	13.8±1.2	15.0±1.2	14.9±0.6	14.6±2.1
P value	0.46	0.41	0.63	0.10	0.12	0.06	0.05	0.16	0.16	0.44	0.30

t- time, Min-minute, hr-hour, mean ± SD

Table 5: Side effects

	Groups	
Side Effects	**Group I**	**Group II**
Hypotension	2	0
Bradycardia	3	1
Sedation	1	1
Nausea	3	2
Vomiting	1	Nil
Pruritus	Nil	Nil
Urinary retention	Nil	Nil

of surgeries in both groups were comparable. The difference in VRS score was not statistically significant between the two groups at 0 min and 30 min. Both groups had decrease in VRS score. VRS score was significantly lower in Group- II at 1, 2, 3, and 4 hr in the postoperative period (P=0.001). The first breakthrough analgesic requirement of Tramadol- 50 mg in Group- II was between 4 and 6 hrs with average duration of 290 ± 50 min which was significantly longer as compared to Group- I in which first analgesic requirement of Tramadol- 50 mg was between 2 and 3 hrs with average duration of 160 ± 30 min. The frequency of rescue analgesics (Tramadol- 50 mg) required in 24 hrs postoperative period in Group- II was 2.1 ± 0.5 and in Group- I was 3.3 ± 0.5 (P=0.001). Both groups were comparable (P > 0.05) in relation to pulse rate, mean blood pressure and respiratory rate (P > 0.05). Motor blockade was not observed in the study due to the low dose of magnesium. No grave complications were observed in any patient.

Discussion

Post-operative pain is an unpleasant experience for the patient, associated with number of physiological responses and may contribute to post-operative morbidity. Regional anesthesia is a safe, less expensive technique with the advantage of prolonged post-operative pain relief [8]. Epidural analgesia is considered by many as the gold standard analgesic technique for major abdominal surgery [9]. Intra-operatively epidural analgesia reduces stress response, improves quality of muscle relaxation and helps minimize blood loss. Postoperatively epidural analgesia helps in early mobilization of patients and improves gastrointestinal function especially in abdominal surgery.

Epidural fentanyl citrate is selected as 1 mcg/ kg because higher dose of fentanyl citrate may have greater adverse effects than beneficial effect. G. Lyons et al stated that incidence of pruritus was increased significantly with fentanyl citrate 4 mcg/ml [10]. Magnesium, a noncompetitive NMDA receptor antagonist, has a role in prevention of central sensitization from peripheral noxious stimulus. Magnesium has anti-nociceptive effects in animal and human models of pain [11,12].

The results of our study showed that a single bolus of epidural magnesium as an adjuvant to epidural fentanyl results in prolonged duration of analgesia with lower VRS as compared with epidural fentanyl (1 mcg/ kg) alone.

Bilir and colleagues demonstrated that 50 mg epidural bolus magnesium followed by 100 mg/ day epidural infusion resulted in lower VAS score only at first hour postoperatively [16]. This difference of lower VRS score could be due to higher bolus dose of epidural magnesium in our study.

In a study by El-Kerdawy, patients received CSE followed by epidural infusion of magnesium (100 mg/ hr) [13]. They concluded that the time to first analgesic requirement was significantly prolonged in magnesium group when compared with control/ placebo group. The duration of analgesia in their study was much less than in our study (79 vs. 290 min). This may be explained by the fact that we administered epidural magnesium in addition to fentanyl, which could prolong the requirement of rescue analgesia.

Recently this was also confirmed in patients scheduled for cesarean section. Yousef *et al*. administered 10 mL of 5% magnesium epidurally and concluded that the addition of magnesium to epidural bupivacaine and fentanyl in women undergoing elective cesarean section with combined spinal epidural anesthesia improved intra-operative conditions and quality of postoperative analgesia [14].

The frequency of rescue analgesics (intravenous Tramadol 50 mg) required in 24 hrs post-operative period in Group- II and in Group- I were 2.1 ± 0.5 and 3.3 ± 0.5 respectively (P=0.001). Different studies observed that administration of epidural magnesium reduces the rescue analgesic requirement in the postoperative period [5,15,16].

No impact was noted on motor function in our study when magnesium was administered epidurally. There were no increased incidences of side effects in the magnesium group which would be explained by low dose of magnesium sulphate via epidural route. There were no differences in the incidence of side effects between the groups in the studies, nor were any additional adverse events [15,16].

Conclusion

The addition of Epidural Magnesium- 75 mg to Epidural Fentanyl-1 mcg/ kg results in prolonged duration of postoperative analgesia as compared to Epidural Fentanyl-1 mcg/ kg) alone. It also reduces the need for breakthrough analgesics without any side effects.

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