A comparison of epidural analgesia provided by Bupivacaine plus Pethidine, Bupivacaine plus Morphine, or Bupivacaine plus Morphine plus Midazolam for lower limb orthopaedic surgery.

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Abstract

Background: Epidural anaesthesia and analgesia in orthopaedic surgeries helps to prevent thromboembolic phenomenon by increasing venodynamics. Adequate post-operative analgesia with good patient satisfaction has been observed with this technique.

Objective: To assess the duration of postoperative analgesia and complications in patients receiving epidural anaesthesia with Morphine, Midazolam and Pethidine in combination with Bupivacaine.

Methods: We prospectively studied 75 patients who were scheduled for elective lower limb orthopaedic surgery with epidural anaesthesia at Lumbini Medical College, Palpa from 2010 March to 2012 March. They were randomly divided by lottery method into three equal groups. Group 'A' (BP) received 50 mg epidural Pethidine (3 ml) with 13 ml of 0.5% Bupivacaine. Group 'B' (BM) received 5 mg (3 ml) epidural Morphine with 13 ml of 0.5% Bupivacaine and Group 'C' (BMM) received 5 mg (1 ml) epidural Morphine with 13 ml 0.5% Bupivacaine and 2 mg (2 ml) epidural Midazolam. All the patients were observed for 24 hours for quality of analgesia and other side effects like nausea, vomiting and pruritus. Data were analysed by Statistical Package for Social Sciences (SPSS-16) software.

Results: The result of the study shows the duration of analgesia was prolonged in BM group than BP group and even more so in BMM group (p value <0.001). Incidence of nausea and vomiting in BMM group was lower than in BP and BM group but statistically the difference was not significant (p value: 0.489). Pruritus was absent in BP group, less in BMM group while significantly higher in BM group.

Conclusion: The use of epidural Morphine and Midazolam in combination with Bupivacaine is the satisfactory method of post operative analgesia. When Midazolam is added, duration of analgesia can be increased with decrease in incidence of nausea, vomiting and pruritus.

Key words: epidural analgesia, midazolam, morphine, pethidine.

INTRODUCTION

Perioperative pain is a potent trigger for stress response. Thus, effective analgesia may improve patient outcome[1]. Epidural morphine provides more complete analgesia than other route of administration[2].

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Studies show that the use of epidural opioids or combination of epidural opioids and local anaesthetics may improve outcome and decrease hospitalisation time[3]. Epidural anaesthesia provides not only good post-operative analgesia but also has good venodynamic effects so to prevent intraoperative as well as post-operative thromboembolic phenomena[4,5]. When Midazolam is added it acts through Gamma amino-butyric acid (GABA) receptors and enhances the affinity of GABA receptors[6]. Studies have revealed that use of epidural Midazolam provides effective analgesia in adults[7].

METHODS

We prospectively studied 75 Patients who were scheduled for elective lower limb orthopaedic surgery with epidural anaesthesia to determine post-operative analgesia and its side effects. The study was conducted from 2010 March to 2012 March in Lumbini Medical College (LMC), Palpa. Ethical clearance was taken from the research committee, LMC. Patients were randomly divided by lottery method into three equal groups. Group 'A' (BP) received 50 mg epidural Pethidine (3 ml) with 13 ml of 0.5% Bupivacaine. Group 'B' (BM) received 5 mg (3 ml) epidural Morphine with 13 ml of 0.5% Bupivacaine and Group 'C' (BMM) received 5 mg (1 ml) epidural Morphine with 13 ml of 0.5% Bupivacaine and 2 mg (2 ml) epidural Midazolam.

Informed consent was taken from all patients. Inclusion criteria were patients undergoing elective orthopaedic surgery of lower extremities with epidural anaesthesia and analgesia. Exclusion criteria included patients taking tranquilizers, history of substance abuse, allergy to morphine, pethidine, midazolam, cardiac compromise, respiratory compromise and coagulation abnormalities. All patients received an infusion of one to 1.5 L of Ringer's lactate solution intravenously prior to giving epidural anaesthesia. The epidural catheter was inserted at the L2-L3 or L3-L4 interspace. When surgery lasted more than two hours 10ml of 0.5% Bupivacaine was given and repeated every two hours. Postoperatively all three groups received 8 ml of 0.1% Pethidine and 0.1% Bupvacaine upon first complain of pain. Afterwards it was given every two hourly or as per patients' demand for next 72 hours. The incidence of nausea, vomiting and pruritus during the study period were recorded by the ward nurse for 24 hours. In addition, the respiratory rate was measured in every four hours. The use of Promethazine for treatment of nausea and vomiting and Pheniramine maleate for pruritus was also recorded. If pruritus was severe naloxone was administered. A questionnaire was filled at the end of the study detailing whether patients had adequate control of post-operative pain and side effects related to epidural medicines. Data were analysed by Statistical Package for Social Sciences (SPSS-16) software.

RESULTS

There were a total of 75 patients included in the study as shown in table 1. Out of them 48 (64%) were male and 27 (36%) were female. Mean age of patients was 49.8 years (SD 39.4 years). Age and gender distribution of patients was similar in three groups as shown in table 2. The average duration of analgesia was 4.2 hours, 13.2 hours and 23.04 hours in BP, BM, and BMM group respectively and the difference was statistically significant (p value <0.001) as shown in table 3. Incidence of nausea and vomiting in BMM group was lower than that in other two groups though it was not statistically significant (P value 0.489) as shown in table 4. Pruritus was absent in BP group and was significantly more with BM group (p = 0.002). Pruritus was comparable in BP and BMM group (P value 0.49) as shown in table 5.

Table 1: Age and sex composition of the study population.

Age (years)	Male	Female	Total
16–25	10	3	13
26-35	6	2	8
36-45	8	1	9
46-55	6	7	13
56-65	5	7	12
66-75	9	2	11
76-85	4	5	9
Total	**48**	**27**	**75**

Table 2: Age and sex distribution in the study groups.

	BP	BM	BMM	p value
Mean age in years (SD)	50.76 (20.835)	45 (17.879)	53.64 (20.087)	0.291*
Male:Female ratio	17:8	15:10	16:9	0.841†

p value calculated by one way ANOVA test* and chi-square test†.

BP: Bupivacaine + Pethidine; BM: Bupivacaine + Morphine; BMM: Bupivacaine + Morphine + Midazolam

Table 3: Analgesia duration in different study groups.

	BP	BM	BMM
Mean duration (in hours) of analgesia (SD)	4.6 (1.155)	13.2 (1.291)	23.04 (4.877)
p value	BP vs BM: <0.001; BP vs BMM: <0.001; BM vs BMM: <0.001		

p value calculated by t test.
BP: Bupivacaine + Pethidine; BM: Bupivacaine + Morphine; BMM: Bupivacaine + Morphine + Midazolam

Table 4: Incidence of nausea and vomiting in different study groups

Study groups	Nausea and vomiting		p value
	Present	Absent	
BP	11	14	
BM	12	13	0.489
BMM	8	17	

p value calculated by chi-square test.
BP: Bupivacaine + Pethidine; BM: Bupivacaine + Morphine; BMM: Bupivacaine + Morphine + Midazolam

Table 5: Incidence of pruritus in different study groups

Study groups	Pruritus		p value
	Present	Absent	
BP	0	25	BP vs BM: 0.002
BM	9	16	BM vs BMM: 0.037
BMM	2	23	BP vs BMM: 0.49

p value calculated by Fisher's Exact test.
BP: Bupivacaine + Pethidine; BM: Bupivacaine + Morphine; BMM: Bupivacaine + Morphine + Midazolam

DISCUSSION

Surgical stress consistently elicits a metabolic response by activation of the sympathetic and somatic nervous system and through local trauma[8]. Responses to surgical stress include release of neuroendocrine hormones and local release of cytokines. Serum concentrations of these factors correlate with severity of injury. Thus, the concept has arisen that inhibiting the stress response may improve surgical outcome[9]. The result in our study shows that epidural midazolam is more reliable and satisfactory for post-operative pain management when used in combination with Morphine and Bupivacaine in adults. Although the extensive preclinical testing may be seen burdensome, the risk-benefit relationship for epidural Midazolam justifies the need. There is convincing evidence that epidural Midazolam is superior for post operative pain management in combination with Morphine. Our study reveals that the use of Midazolam in combination with Morphine and Bupivacaine as in BMM group has reduced the incidence of Morphine induced side effects like nausea and vomiting than BM group, but statistically it was not significant (P = 0.489). The incidence of pruritus induced by Morphine was decreased significantly with the addition of Midazolam as in BMM group than BM group (P = 0.037). There was prolongation of analgesia duration with use of Midazolam which was highly significant compared to non Midazolam groups BP and BM (p value <0.001). Epidural Midazolam in combination with Morphine and Bupivacaine not only decreases the morphine induced pruritus but also increases the analgesia duration which was 23.04 hours in average than that of morphine 13.02 hours (p value <0.001). Statistically it was highly significant with the types of medicine and duration of analgesia (p value <0.001). Elhakim M et al have proved that the addition of Midazolam in combination with Morphine not only prolongs the duration of analgesia

but also has good antiemetic effect. In our study also the incidence of pruritus was significantly decreased by addition of Midazolam. Other similar studies also have revealed that the incidence of Morphine induced side effects like nausea; vomiting and pruritus were reduced with the use of Midazolam[11]. The most troublesome side effect of epidural Morphine is nausea and vomiting and pruritus. Some of the studies have revealed that the incidence of nausea and vomiting is up to 30% following epidural and intrathecal morphine[12]. Our study also reveals that nausea and vomiting was comparably higher in BM and BP group 48% and 44% respectively versus 32% in BMM group but statistically it was not significant (P value = 0.489). Four patients (16%) in BM group and two patients in BP group required single dose of Promethazine to control nausea and vomiting. No patient needed naloxone. It was been observed that with addition of midazolam in BMM group the incidence of nausea and vomiting was decreased to (32%) however statistically it is not significant (P = 0.489). The underlying mechanism of nausea and vomiting following epidural opioid is not related to systemic absorption of drug. The incidence may or may not be related to the dose of opioid administered and may be higher when epidural morphine is utilized[13]. Sensitization of the vestibular system to motion and decreased gastric emptying produced by opioids may also play a role in nausea and vomiting induced by intrathecal and epidural opioids[14].

Another common side effect of intrathecal and epidural opioids is pruritus. It may be generalized but is more likely to be localized to the face, neck, or upper thorax. It is higher in epidural or intrathecal route than in others. The incidence varies widely, from zero to 100 percent[15]. Pruritus induced by intrathecal and epidural opioids is likely due to cephalad migration of the drug in cerebrospinal fluid and subsequent interaction with the trigeminal nucleus located superficially in the medulla[6]. Our study reveals that there was no pruritus in BP group. It was higher in BM group than BMM group. Comparing the BP with BM group it was significantly different (P = 0.002). However when BP was compared with BMM there was no significant different (P = 0.49). The incidence of pruritus induced by Morphine can be reduced significantly with addition of Midazolam as our study has revealed (P =0.037). Among the pruritus patients in BP group two patients (8%) had a single dose of injection Pheniramine maleate. There was no use of Naloxone in any patients. Thus the addition of Midazolam in combination with Morphine and Bupivacaine during epidural analgesia and anaesthesia is satisfactory method of controlling post operative pain and side effects related to Morphine.

CONCLUSION

Combined use of epidural Midazolam with Morphine and Bupivacaine can reduce the incidence of morphine induced side effects as well as potentiates the analgesic effects of Morphine and Bupivacaine.

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