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Effect of Epidural Nalbuphine versus Butorphanol for Postoperative Analgesia in Combined Spinal Epidural Anaesthesia (CSEA) Technique in Abdominal Hysterectomy- A Comparative Study

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Abstract
Background*:-Postoperative pain management is important for early mobilization and post-operative discharge. The aim of the study was to evaluate the efficacy of 1 mg of epidural butorphanol with 5mg of epidural nalbuphine for postoperative analgesia following CSEA in patients undergoing abdominal hysterectomy.* ***Methods:*** *Sixty patients undergoing total abdominal hysterectomy were allocated into two groups: Group 1(n=30):received 12.5 mg of 0.5% of bupivacaine(heavy) in L3-4 intrathecally plus butorphanol 1 mg diluted in 10 ml normal saline in L2-3 epidurally. Group 2(n=30): received 12.5 mg of 0.5% of bupivacaine(heavy) in L3-4 intrathecally plus nalbuphine 5 mg diluted in 10 ml normal saline L2-3 epidurally. The duration of analgesia was recorded as the interval from the completion of anaesthetic procedure to the time of the first complaint of pain or visual analogue pain >4.*
Results: *Higher sensory block level was attained with the nalbuphine group- T4 in 80% patients. It also showed prolonged post–operative analgesia (279.4 ± 68.43 min) compared to butorphanol group, where the time to first rescue analgesic was 201.9 ± 62.31 min.($p<0.001$).The total amount of rescue analgesic consumed in the first 24 hours was significantly more in butorphanol group than the nalbuphine group($p<0.001$).* ***Conclusion:*** *Epidural nalbuphine provided good intraoperative analgesia, prolonged postoperative analgesia, superior sedation level and stable cardio-respiratory parameters without significant adverse effects.*
Key words: *Epidural, nalbuphine, butorphanol, CSEA, postoperative analgesia*

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I. Introduction

Postoperative pain gives rise to various physiological and psychological problems and is vital for early mobilization and post-operative discharge.[1]The use of neuraxial blockade are well established regional anaesthesia techniques and the use of combined spinal-epidural technique anaesthesia (CSEA) is becoming more popular. The combination of the two techniques brings about the advantages of each technique, minimizes the disadvantage and combines the efficacy of both the anaesthetic techniques.[2]

Various neuroaxial adjuvants such as opioids, sodium bicarbonate, adrenaline, α2 adrenoceptor agonists, N-methyl D-aspartate antagonists, and GABA receptor agonists are used to improve, hasten, or prolong analgesia and decrease the adverse effects associated with high doses of the local anesthetic agent.[3]

Nalbuphine, a synthetic μ receptor antagonist and κ receptor agonist opioid is structurally related to oxymorphone and naloxone and epidural nalbuphine provides moderate analgesia.[4]Similarly, butorphanol another μ-antagonist and κ agonist, was found to produce lesser respiratory depression, larger margin of safety and lesser incidence of nausea, vomiting, urinary retention and pruritus.[5]The equianalgesic doses of butorphanol and nalbuphine are 2 mg and 10 mg compared to 10 mg morphine.[6]

Hence, the aim of the study was to evaluate the efficacy of 1 mg of epidural butorphanol with 5mg of epidural nalbuphine for postoperative analgesia following CSEA in patients undergoing abdominal hysterectomy.

II. Materials and methods

After obtaining institutional ethics committee approval and written informed consents, sixty female adult patients aged 18-60yrs of American Society of Anaesthesiology (ASA)[7]physical status I &II, undergoing total abdominal hysterectomy were recruited in this randomized double blinded prospective study conducted in the department of Anaesthesiology of a tertiary care teaching hospital in Imphal over a period of two years.

The study drug was prepared by a colleague not directly involved in the study in a 10 ml syringe in equal volume. The sample size was calculated based on a previous study[8] for α value of 0.05 and power of 0.80(i.e.80%) assuming the mean duration of analgesia between two study drugs to be 5.4hrs and 6.3hrs and a common standard deviation of 1.2, and it was 28 in each group. Assuming a 5% dropout, in our study, we enrolled 30 patients in each group. Using computer generated randomization; the patients were allocated into two groups:

- **Group 1(n=30):**received 12.5 mg of 0.5% of bupivacaine(heavy) in L3-4 intrathecally plus butorphanol 1 mg diluted in 10 ml normal saline epidurally in L2-3.
- **Group 2(n=30):** received 12.5 mg of 0.5% of bupivacaine(heavy) in L3-4 intrathecally plus nalbuphine 5 mg diluted in 10 ml normal saline epidurally in L2-3.

Patients with any contraindication to neuraxial anaesthesia – spinal deformities, previous spinal surgery, local site infection, hypotension, coagulation abnormalities, cardiopulmonary problems, neurological diseases, uncooperative patients, patients on opioids, antiarrythmics, tricyclic antidepressants, α and β blockers and hypersensitive to the study drugs- were excluded from the study.

After pre-operative assessment a day before surgery, standard monitors were instituted on arrival at the operation theatre, namely – non-invasive blood pressure (NIBP), pulse rate, electrocardiography and pulse oximetry (SpO2) readings were recorded and preloaded with Ringers lactate solution at 10 ml per kg.

Under strict aseptic and antiseptic precautions, with the patient in the left lateral decubitus position, the injection site in the lumbar region was infiltrated with local anaesthetic and the epidural space between L2-3 was located using 18-gauge Tuohy needle (Perifix 401, B Braun Medical Melsungen, Germany) using midline approach and loss of resistance technique and a 20-gauge epidural catheter was placed in situ. After negative aspiration of blood and cerebrospinal fluid, a test dose of 3 ml of lignocaine with adrenaline 1:200,000 was injected through the catheter to exclude intrathecal or intravascular placement of the catheter. In the same position, dural puncture was performed in L3-4 interspace with 25-gauge Quincke needle (Spinocan, B Braun Medical Melsungen, Germany) and 2.5 ml of 0.5 % hyperbaric bupivacaine was deposited intrathecally. All durations were calculated considering the time of intrathecal injection as time "0" (zero). After securing the epidural catheter and making the patients supine, epidural adjuvants were administered depending on the group assigned.

Hypotension, defined as a systolic blood pressure (SBP) <100 mmHg or a decrease in SBP<20% of the baseline blood pressure, which was corrected with additional rapid infusion of ringer's lactate administered at the time of hypotension or injection mephenteramine in aliquots of 3 mg. Bradycardia (heart rate<50bpm) was treated with injection atropine 0.3-0.6 mg intravenously. The incidence of adverse effects such as nausea, vomiting, shivering, pruritus, respiratory depression, sedation, hypotension and bradycardia was recorded.

Sensory testing was assessed by loss of pinprick sensation along the midclavicular line bilaterally every minute until the highest level has been stabilized for four consecutive tests. Further testing was performed until the recovery of S2 dermatome was achieved.

Time of analgesic block at T_{10} dermatome i.e. time interval between the end of administration of anaesthetic drug and the onset of cutaneous analgesia at T_{10} was evaluated using midline bilateral pin prick every min till complete loss of cutaneous sensation at T_6-T_8 at which point surgery was started.

The degree of motor block was assessed when cutaneous sensation was lost at T10 using Modified Bromage Scale,[9] and sedation scores were assessed using Modified Ramsay Sedation Scale.[10]

The duration of analgesia was recorded as the interval from the completion of anaesthetic procedure to the time of the first complaint of pain or visual analogue pain >4. Rescue analgesia was provided by injection diclofenac 75 mg. The data collected were analyzed using Statistical package for social sciences for windows (SPSS) version21.0 (Armonk, NY: IBM corp.) and compared using Student t test for continuous data and Chi square test for categorical data and $P < 0.05$ was considered statistically significant.

III. Results

The demographic profile was comparable between the two groups as shown in table1 ($p>0.05$). As shown in table 2, the time to onset of analgesia to reach T10 sensory level was 2.5 ± 1.18 min. in group 1 and 1.4± 0.65 min in group ($p=0.00$); further , the time to reach maximum sensory block level in group 1 versus group 2 was 8.5 ± 3.50 min versus 8.8 ± 2.86 min, which was statistically insignificant($p= 0.693$). Similarly, there was no significant difference in the time to achieve complete motor block between the two groups ($p=0.245$).The time to two segment dermatome regression between group I versus group 2 was 77.09 ± 28.65

versus 85.89 ± 18.78 min. , which was statistically insignificant(p=0.168). Also the time to S2 level sensory regression was more prolonged in group 2 (276.6 ± 49.01 min.) than in group I (221.39 ± 47.7 min.) and statistically significant (p< 0.001;Table 2).The difference between the maximum dermatome level achieved in the two groups were statistically significant(p=0.05). Higher sensory block level was attained with the nalbuphine group- T4 in 80% patients. The nalbuphine group showed prolonged post–operative analgesia (279.4 ± 68.43 min) compared to butorphanol group, where the time to first rescue analgesic was 201.9 ± 62.31 min.(p<0.001).The total amount of rescue analgesic consumed in the first 24 hours was significantly more in butorphanol group than the nalbuphine group(p=0.000) and the amount of mephenteramine used was more in group 2, which was statistically significant(=0.000).

The mean arterial pressure (MAP) at various time intervals was comparable between the two groups, with a fall in the MAP at the 10^{th} and 20^{th} minute, along with a statistically significance in the heart rate at the 40^{th} minute, but remained within the physiological range. (Fig. 1)

The changes in the SBP was more in the nalbuphine group at varied time intervals compared with the butorphanol group and statically significant (p<0.05), but within the physiological range; but, the diastolic blood pressure were comparable between the two groups and statistically not significant (p>0.05).

The incidence of hypotension in group 1 versus group 2 were 7/30(23%) vs. 21/30(70%) respectively and statistically significant (p=0.002). There was no incidence of bradycardia, pruritus, shivering in any of the cases in the study. The incidence of sedation was 5/30(16.7%) versus 7/30(23.3%) in group 1 versus group 2 respectively.

IV. Discussion

Combined spinal epidural anaesthesia provides superior post-operative analgesia, leading to early mobilisation.[11]In order tokeep the post-operative pain intensity almost constant thereby avoiding bias due to the operative procedure, the surgical procedure that lasted more than one hour were excluded from the study. The patients in both groups were comparable as regards the age, body weight, ASA physical status and the duration of surgery with no significant statistical differences(p>0.05).

The rationale for comparing the two selected doses of butorphanol (1mg) and nalbuphine (5 mg) was derived from previous studies [12,13], where the drug doses were found to provide prolonged analgesia without significant side effects.

Since the discovery of opioid receptors in the spinal cord, the action of narcotics through opioid receptors has become more clearly understood. The kappa opioid receptor is mainly involved with the mediation of visceral pain and achieving satisfactory postoperative analgesia with either epidural or intrathecal narcotics or a combination. The use of epidural opioids had become an increasingly popular technique for management of acute postoperative pain in recent times. Recent studies would indicate that it is possible to achieve better analgesia with lower doses of opioid medication when these drugs are administered in extradural space as compared to intramuscular or intravenous routes of administration. However, there are disadvantages associated with narcotics as they may be associated with some unpleasant adverse effects. Stimulation of spinal opiate receptors (kappa, κ) can also produce spinal analgesia but with fewer side effects. The high lipid solubility and high affinity for opioid receptors are additional factors that contribute to the paucity of side effects.[14]

The findings of the present study shows that the addition of nalbuphine as epidural adjuvant following intrathecal bupivacaine significantly affects the onset time sensory block at T10(p=0.000). The mean onset time of sensory block at T10 in nalbuphine group was 1.4±0.65 min whereas in butorphanol group was 2.5±1.18 min which is consistent with the study of Ankita et al[15] (p<0.001) and Kumar PS et al[16] (p<0.001).The differences observed in time domains in the various studies might be due to variation in anaesthetic technique and drug doses.

In our study, the time to reach maximum sensory block level (p=0.693) and time for complete motor block (p=0.245) were consistent with those of previous studies.[15,17] Maximum sensory dermatomal level was T4 in 24/30 (80%) patients in nalbuphine group while it was 17/30 (56.7%) in butorphanol group (p=0.052), which was statistically insignificant and this is similar to the findings of Kar P[18].

The time to two segment dermatome regression was more prolonged in the nalbuphine group but was statistically insignificant; however, the sensory block regression to S2 was significant (p<0.001). Sharma R et al[19] in their study observed that time for two segmental regression was more with nalbuphine than fentanyl (p=0.004) and regression to S1 was prolonged in nalbuphine group in another study[20].

The result of our study shows that the analgesic effect of epidural nalbuphine was significantly prolonged when compared with butorphanol group (p<0.001) as indicated by the time of first rescue analgesia. The duration of analgesia with nalbuphine group was 279.4±68.43 min. and that of butorphanol group was 201.9±62.31 min. which is consistent with those of previous studies.[15] In another study,[21] the combination of intrathecal bupivacaine with different nalbuphine doses significantly prolonged postoperative analgesia compared to the control group.

The cardiovascular parameters suggested that there was significant decrease in mean arterial pressure in nalbuphine group than butorphanol group (p=0.001 at 10 min and p=0.003 at 20 min). However, it was stabilized with vasopressor. Other studies[19, 20] reported insignificant haemodynamic alteration with nalbuphine. Palacios et al[12] found that no patients in their study group receiving epidural butorphanol developed clinically important change in haemodynamic parameters, which may be favourably compared with our findings.

Narcotic analgesics are well-known for the potential side effects such as pruritus, nausea, vomiting, urinary retention and respiratory depression.[22]Delayed respiratory depression is the most troublesome of these side effects. This phenomenon is thought to be due to transport of drug in cerebrospinal fluid from the lumbar region to the fourth ventricle, with consequent depression of the medullary centre. Bromage[23] suggested that lipid soluble, highly protein bound narcotic analgesics might be less likely to exhibit this phenomenon and this appears to be true for both butorphanol and nalbuphine. No case of respiratory depression was observed in any group in our study, which was consistent with other studies.[12,17] The incidence of sedation and nausea/vomiting was high in nalbuphine group compared to butorphanol group in our study. Seven cases in nalbuphine group and five cases in butorphanol group had sedation. Two patients, one each, in nalbuphine and butorphanol had nausea (intraoperative) and vomiting (postoperative). In a study by Revar B et al[10], epidural butorphanol had lesser side effects like nausea and vomiting and had sedation in milder degree which was an additional advantage in the postoperative period.

The mean total dose of rescue analgesia required in 24 hours was 135.0±45.7 mg and 82.5±36 mg of injection diclofenac in the butorphanol and nalbuphine respectively in our study, which was consistent with a previous study[15], where nalbuphine group required minimum dose of rescue analgesia than butorphanol group.

V. Conclusion

Epidural nalbuphine provided good intraoperative analgesia, prolonged postoperative analgesia, superior sedation level and stable cardio-respiratory parameters without significant adverse effects. It also required lesser dose of rescue analgesic in the postoperative period. Hence, epidural nalbuphine was a better alternative to epidural butorphanol when used as adjuvant to intrathecal bupivacaine in patients undergoing abdominal hysterectomy. However, further studies maybe advocated to come to a concrete conclusion.

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VI. Tables & Figures

Table 1: Demographic profile between the two study groups

Parameters	Mean±SD		Statistical Value 't'test	P value
	Group 1	Group 2		
Age(years)	48.1± 8.2	46.4 ± 6.8	0.885	0.380
Weight(Kg)	54.43 ± 4.5	56.56 ±7.6	1.31	0.19
ASA I:II	29:1	28:2	Fischer exact test 0.351	1.00

Table 2: Block Characteristic between the two study groups

Parameter	Mean ± SD (n =30)		Statistical Value 't' test	P value
	Group I	Group 2		
Time to Sensory block to reach T10 (min.)	2.5 ± 1.18	1.4± 0.65	4.232	0.00
TPSBL (min.)	8.5 ± 3.50	8.8 ± 2.86	0.397	0.693
Time to complete motor blockade (min)	5.5 ± 12.04	2.8 ± 1.75	1.173	0.245
TTSR (min)	77.09 ± 28.65	85.89 ± 18.78	- 1.396	0.168
TTS 2R (min)	221.39 ± 47.7	276.6 ± 49.01	- 4.419	< 0.001
MSBL	T4-17 ; T6 - 13	T4 – 24; T6 – 6	Fischers exact test 3.77	0.052
TFAR (min)	201.9 ± 62.31	279.4 ± 68.43	't' test – 4.594	<0.001
Total amount of rescue analgesic in 24 hrs(mg)	135.0±45.7	82.5±36.0	t test- -4.241	0.000
Amount of intraoperative mephenteramine consumed(mg)	1.1±2.0	3.4±2.1	-4.241	0.000

TPSBL–time to peak sensory block level ; TTSR – time to two segment regression; TTS2R- time to S2 regression; MSBL – maximum sensory block level; TFAR- time to first analgesic rescue.

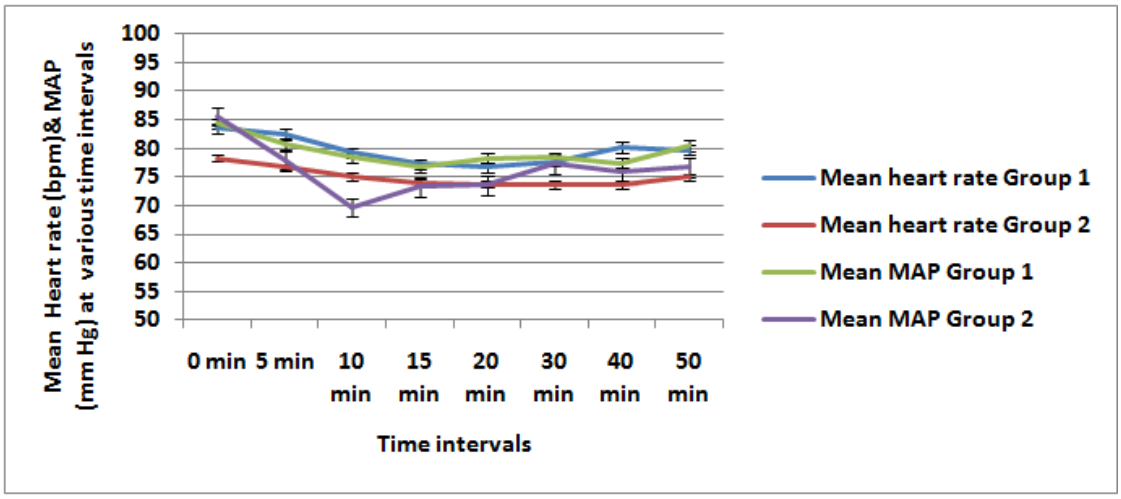

Fig. 1. The mean arterial pressure ± standard deviation and heart rate at different time points between the two study groups

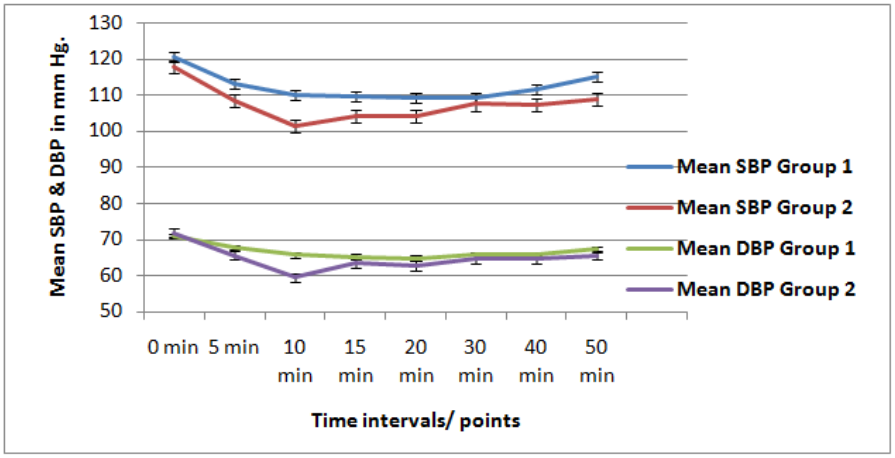

Fig 2. The mean systolic blood pressure ± standard deviation and diastolic blood pressure(DBP) ± standard deviation at different time points between the two study groups

Table 3 : The side effects between the two study groups

Parameters	Group 1	Group 2	Statistical value X^2 /'t' test	P value
Hypotension	7/30(23%)	21/30(70%)	9.6	0.002
Bradycardia	0	0	x	x
Pruritus	0	0	x	x
Nausea and vomiting	0	2 /30(6.7%)	1.491	0.11
Shivering	0	0	x	x
Sedation	5/30 (16.7%)	7/30 (23.3%)	x	x

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