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A COMPARATIVE STUDY OF FENTANYL WITH NALBUPHINE AS AN ADJUVANT TO HYPERBARIC BUPIVACAINE 0.5 % IN SUBARACHNOID BLOCK FOR LOWER LIMB ORTHOPEDIC SURGERIES.

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ABSTRACT **Background:** Subarachnoid block (SAB) possesses many benefits with a drawback of short duration of anesthetic action. Intrathecal opioids have been used to enhance the clinical efficiency and duration of action of local anesthetic drugs. The present study was aimed to compare the clinical efficiency of intrathecal fentanyl with nalbuphine as adjuvant to 0.5% hyperbaric bupivacaine for orthopedic surgery of lower limbs.

Material And Methods: 60 adult patients of American Society Of Anesthesiologists' physical status I and II of both gender aged 18 to 60 years were randomized into two groups of 30 each to receive either fentanyl 25 mcg (GROUP I) or nalbuphine 2 mg (GROUP II) with 3.0 ml 0.5 % hyperbaric bupivacaine making intrathecal drug volume 3.5 ml in each group. Sensory and motor block characteristics and time to first rescue analgesic were recorded as the primary end points. Drug related side effects of pruritis, nausea/vomiting and respiratory depression were recorded as secondary outcomes.

Results: Both groups were comparable regarding the onset and cephalic extension of block. The time to two dermatome regression and time for complete motor recovery were significantly prolonged in patients of group II with statistical significant difference ($P<0.05$). Duration of analgesia was also extended in patients of group II (378.0+/-35.72 mins) as compared to group I (234.0+/-24.10 mins) with highly significant difference ($P<0.001$). No drug related side effects were observed in either group.

Conclusion: Intrathecal nalbuphine 2mg as adjuvant to 0.5 % bupivacaine was clinically more efficient than fentanyl for enhancing the post-operative analgesia.

KEYWORDS : Fentanyl, Nalbuphine, Postoperative Analgesia, Subarachnoid Block

The rationale for the combination of opioids and local anesthetics is that these two types of drugs eliminate pain by acting at two different sites. Local anesthetics act at the nerve axon and the opioid at the receptor site in the spinal cord.[1] A pain-free and stress-free postoperative period definitely helps in early mobilization and recovery, thereby reducing morbidity and mortality. Intrathecal opioid is widely used in treating intraoperative, postoperative, traumatic, obstetric, and chronic cancer pain. Nalbuphine is a μ receptor antagonist and κ receptor agonist. Nalbuphine when added as adjunct to intrathecal local anesthetics has the potential to provide good intraoperative and postoperative analgesia.[2,3]

Recently, nalbuphine has been added to the anesthetic as an adjuvant to local anesthetics. Nalbuphine is opioids μ-receptor antagonist and κ-receptor agonist. It has the potential to provide good intra- and postoperative analgesia with decreased incidence and severity of μ-receptor side effects. In contrast to other centrally acting opioid analgesics, nalbuphine has a minimal respiratory depressant effect and low potential abuse[2].

The aim of this study was to compare postoperative analgesia and adverse effects of nalbuphine and fentanyl when used as an adjuvant to hyperbaric bupivacaine during spinal anesthesia in lower limb orthopedic surgery.

MATERIAL AND METHODS:

After getting approval of the Institutional Ethical Committee and written informed consent, this prospective randomized controlled trial study was conducted from Apr 2015 to Feb 2016 at the Department of Anaesthesiology and Critical Care, Sri Aurobindo Medical College, Indore (M.P.) on 60 adult patients of American Society of Anesthesiologist (ASA) physical status I and II of both genders aged 18–60 years, free from cardio-respiratory and autonomic dysfunction which are scheduled for elective orthopedic surgery of lower limbs under SAB with normal coagulation profile.

Patients excluded were ASA grade 3 and 4 patients, <18 and >60 years age, contraindication for regional anesthesia, known allergy, obesity, converted to General Anaesthesia, refusal to get enrolled for the study.

Detailed pre-anesthetic evaluation was done. Patients were randomized into two groups of 30 each-group N (inj. Bupivacaine (H) 3.0 ml + inj. Nalbuphine 0.2 ml (2mgs) with 0.3 ml normal saline), group F inj. Bupivacaine (H) 3.0 ml with inj. fentanyl 0.5 ml (25mcgs). Total amount of drug was 3.5 ml. Spinal anesthesia was administered in sitting position at L3-L4 or L4-L5 interspace, with 25G Quincke's needle using 3.5 ml. Patients were monitored with ECG, NIBP, SpO2 and respiration at regular intervals intra-operatively and continued the same for 3 hours. The assessment of sensory block, motor block, hemodynamic changes and post-operative analgesia was done.

Pre-anaesthetic Examination And Preparation

Pre-anesthetic check up was done one day prior to the surgery. Patient's weight, height were also recorded prior to surgery. All patients were kept nil orally for 6-8 hours. Patients were pre-medicated with Tab. Ranitidine 150mg and Tab. Alprazolam 0.5mg a night before & was preloaded with an I.V. infusion of 500 ml of Ringer Lactate solution, 30 min prior to surgery. CBC, RBS, BUN, S.creatinine, HIV/HBsAg, chest X ray and ECG was assessed.

Sensory Blockade Parameters:

Assessed by loss of sensation to alcohol cotton swab.

Time Of Onset Of Sensory Block: time between injection of the drug to loss of sensation at T10 level.

Time To Maximum Sensory Block: time to reach highest dermatomal level with loss of sensation.

Time To Two Segment Regression: time period to regain sensation at two dermatomes lower to the initial level of highest dermatome.

Time To Rescue Analgesia: time at which patient complained pain at the site of surgery intra-operatively or postoperatively.

Motor Blockade Parameters:

The degree of motor block was assessed using "Bromage scale". Motor blockade was assessed at 1, 4, 8, 12 and 15 minutes till grade IV block was achieved, then every 30 minutes until return of normal motor function.

Onset Time For Motor Block: time between injection and grade IV block.

Patients hypotensive if MAP <65 mmHg & treated with Inj. Ephedrine 6 mg I.V. If heart rate < 50 bpm (Inj. Atropine 0.3-0.6mg I.V).

Parameters Recorded Intra-operatively:
Blood pressure
Time of onset of sensory blockade.
Time to maximum level of sensory blockade.
Time to grade IV motor blockade.
Time to 2 segment regression.
Time to rescue analgesia.
Heart rate (HR).

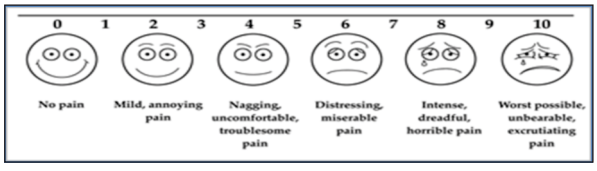
BROMAGE SCALE[4]
Grade Motor Activity:
1. Free movement of legs or feet.
2. Just able to flex knees with free movement of feet.
3. Unable to flex knees but with free movement of feet.
4. Unable to move legs or feet.

Complications such as nausea, vomiting and shivering were treated accordingly and the treatment given was recorded.

Campbell's Sedation Score[5]:

Score	Responsiveness
0	Wide awake
1	Sedated but easily arousal
2	Drowsy, difficult to arouse
3	Un-arousable

VAS Score[6]:
A Visual Analogue **Scale** (**VAS**) A 10 cm baseline is recommended for vas scale



RESULTS:
The demographic data of the study Patients of both groups were statistically comparable regarding mean age, weight, gender & ASA physical status.

The hemodynamic parameters SBP, DBP,SPO2 were comparable.

Comparison Of Side Effects:
Mean sedation score achieved by assessing campbell sedation score and found that More sedation was achieved from BN group as compared to BF group.

VAS score when assessed at the time of rescue analgesia in group 1 (BN) only 3.33% of the patients has suffered from severe pain where as in group 2 it is 13.3%. The difference between the two groups is clinically significant.

Duration Of Onset of motor block & Duration of motor block when compared between Group I (BN) and Group II (BF) and was comparable was significantly extended in patients of Group I as compared to patients of group II with statistically significant difference (P=0.009).

The time duration of 5 minutes, Intrathecal drug injection to reach bromage scale grade 3. More number of subjects in BN Group reaches to grade 3 of bromage scale as compare to subjects of BF group at 5 minutes. **At 10 minutes,** the differences between the two groups was not statistically significant (p value=1.000).

Sensory Block Parameters:
The onset of sensory block at T10 level of Group BN was 3.93±0.83 compared to patients of Group BF 4.4±0.48 with statistical significant (P = 0.014).

Time taken to achieve sensory blockade at most cephalic level in minutes for group BN was 6.70±1.489 and for group BF 7.57±1.612 which is statisticaly significant.

Time to reach maximal cephalic sensory level was also statistically comparable with median cephalic level of T6 in all patients.

Time to sensory regression of two dermatomes was significantly extended in patients of Group BN (126.03 ±11.109 min) as compared to patients of Group BF (116.27 ± 5.974 min) with statistically significant difference (P=0.041).

Time to adminster first rescue analgesia post-operatively to the subjects of group BN was comparatively longer 261.13±13.541 as compared to group BF where it was 221.30±16.920 which is statistically highly significant.

DISCUSSION:
The combination of adjuvants to local anesthetic is synergistic for producing the analgesia of prolonged duration without measurably increasing sympathetic or motor blockade, thus allows early ambulation of patients and reduction in dosages of local anesthetics, hence the decline of their systemic side effects. Opioids selectively decrease nociceptive input from A delta and C fibers without affecting dorsal root axons or somatosensory-evoked potentials. Various μ-agonists opioids such as morphine, tramadol, nalbuphine and fentanyl are used as adjuvant to hyperbaric bupivacaine to prolong its clinical efficacy and minimize the requirement of postoperative analgesics, but they are associated with side effects of pruritus, nausea, vomiting, respiratory depression, constipation, and urinary retention. Nalbuphine hydrochloride is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis. Receptor studies show that nalbuphine hydrochloride binds to mu, kappa and delta receptors, but not to sigma receptors. Nalbuphine hydrochloride is primarily a kappa agonist/partial mu antagonist analgesic. Kappa-opioid receptors are distributed throughout brain and spinal cord areas involved in nociception. The greatest concentrations of kappa-receptors in nociceptive regions are in lamina I and II of Rexed in the spinal cord dorsal horn as well as in the spinal nucleus of the trigeminal nerve (substantia gelatinosa). Taken together, these data suggest that nalbuphine acts primarily at the level of the first synapse in the nociceptive system in producing analgesia. The μ agonist, fentanyl exerts its action by opening K+ channels and reducing Ca++ influx, resulting in inhibition of transmitter release. The μ agonist also have a direct postsynaptic effect, causing hyperpolarization and a reduction in neuronal activity[7].

Gear et al[8] proves that Kappa agonist drugs like nalbuphine can be used to control the visceral pain caused by hysterectomy.

Our study is in accordance with **Gupta K (2017)[9] Yoon et al[10]** & **Gomaa et al[11]** The incidence of pruritus was significantly lower in the group N compared to other two groups, whereas the incidence of nausea and vomiting did not show any significant difference between groups.

Freye (1985)[12] Nalbuphine reversed total apnoea due to fentanyl anesthesia. The slope of the CO2-response curve (sensitivity of the respiratory center to CO2) was -8% below control at the 5th and +13.5% and +22.6% at the 30th respectively 45th minute post nalbuphine.[12]

Xavier et al[13] observed during spinal anesthesia, IT nalbuphine has an added advantage of providing intraoperative sedation thus reducing or even abolishing the need for any other sedative drug.

Verma D et al [14] also found similar results that The total duration of analgesia was 278.74 ± 29.67 min in patients of Group I and 318.64 ± 21.92 min in patients of Group II with statistically highly significant difference.

Parveen S (2015)[15] observed that the bupivacaine with nalbuphine as an adjuvant to see the duration of analgesia and found that onset of sensory and motor block was faster and time taken to attain complete sensory and motor block to occur was shorter in the N Group as compared to B Group. The mean onset of sensory block in Group N was 1.63 ± 0.57 min compared to 3.23 ± 1.03 min in Group B.

Gupta K et al[16] Time to sensory regression of two dermatomes was significantly extended in patients of Group II (127.86 ± 18.23 min) as compared to patients of Group I (116.75 ± 12.82 min) with statistically highly significant difference (P < 0.001)

Time to adminster first rescue analgesia post-operatively Verma et al (2013)[14] & Gupta k et (2017)[16] concluded that the duration of analgesia was significantly longer in Group N (378.0±35.72 min) as compared to Group C (234.0±24.10min) (p=0.000) and Group T (260.0±26.52 min) (p=0.00).

Verma et al[14] concluded that addition of nalbuphine to hyperbaric bupivacaine was effective in prolonging the duration of sensory motor block and enhancing the postoperative analgesia following lower limb orthopedic surgeries. The results of their study go well with the results of the present study.

Mukherjee et al (2011)[17] found that effective analgesia increased with increase in concentration, and the final observation of prolongation of analgesia was with 0.4 mg of nalbuphine with 0.5% hyperbaric bupivacaine without any side effects.

Shakooh et al (2014)[18] showed that the onset of sensory and motor block was faster and time taken to attain complete sensory and motor block to occur was shorter in the nalbuphine group as compared to bupivacaine group. The mean onset of sensory block in group N was 1.43±0.57 min and complete sensory block was attained in 4.73±1.31 min compared to 3.03±1.03 min and 8.60±2.36 min in group B respectively.

CONCLUSION:

Our study suggested that Group BN is a better drug combination in maintaining perioperative hemodynamics, fewer side effects and better post operative analgesia in patients undergoing Lower limb Orthopedic Surgeries.

Table 1:

Side Effects	GROUP 1 (BN)		GROUP 2 (BF)		Statistical Inference
	YES	NO	YES	NO	
Bradycardia	10	90	43.3	56.6	z = -2.661, p = 0.008 (S)
Vomiting	23.3	76.6	33.3	66.6	z = -0.852, p = 0.394 (NS)
Hypotension	23.3	76.6	33.3	66.6	z = -0.852, p = 0.394 (NS)
Shivering	36.6	63.3	30	70	z = -0.826, p = 0.409 (NS)

Table 2: Sedation Score

Groups	Sedation Score					
	1 min	15mins	30mins	60mins	90mins	120mins
Z VALUE	.000	.000	-2.053	-2.053	-2.053	-1.762
P VALUE	1.000	1.000	.040*	.040*	.040*	.078
p≤0.05= Significant*, p≤0.001= Highly Significant**						

Table 3: VAS Score

GROUPS	VAS SCORE (% IN SAMPLES)					
	At Two And Half Hour			At Rescue Anagesia		
	Grades (VAS)			Grades (VAS)		
	0	1	2	4	5	6
1	51.00	42.00	7.00	56.66	40	3.33
2	23.66	63.33	10	40	46.66	13.33

Table 4: Motor And Sensory Block Parameters

Parameters			Group 1	Group 2	Test Applied	P Value
Motor Block	Duration Of Onset Of Motor Block		8.43± 1.165	8.57± 1.104	T Test	0.651
	Total duration of motor block		163.82± 14.811	132.00± 9.266	T Test	0.009*
	Bromage Scale	5 Mins	(I-IV)	(I-IV)	Mann-Whitney	0.003*
		10 Mins	(IV)	(IV)	Mann-Whitneyt	1.000
Sensory Level Attained	Onset Time of sensory block At T10 Level		3.93± 0.83	4.4± 0.48	T Test	0.014
	Median Cephalic sensory Level		T6-T7	T6-T7	Mann-Whitney	0.999
	Time taken to achieve sensory blockade at most cephalic level (min)		6.70± 1.489	7.57± 1.612	T Test	.035*
	Time taken for two regressions of sensory block (min)		126.03± 11.109	118.37± 5.974	T Test	.041*
	Time to adminster First Rescue Analgesia (Min)		261.13± 13.541	221.30± 16.920	T Test	.000**
P≤0.05= Significant*, P≤0.001= Highly Significant**						

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