Comparison of Intrathecal Adjuvants with Bupivacaine Using Fentanyl 50μg and Butorphanol 25μg

Upasna Bhatia*, Nirav Patel, Nirzari Parikh*****

* Associate Professor, ** MD Anaesthesia , Ex SR, 1st Yr Resident , AMCMET Medical College , Ahmedabad Gujarat, india

Abstract: Background and objectives: Spinal opiates potentiate the effect of local anesthetic agent providing longer lasting post-operative analgesia. We compared injection butorphanol and Fentanyl as an adjuvant to Bupivacaine with respect to onset, duration of sensory and motor block and duration of analgesia. Method: Study was carried out on 60 patients aged between 18-55yrs of ASA grade I and II, 30 in each group under spinal anaesthesia. An adjuvant Injection of Butorphanol 25 g (Group-B) and fentanyl 50 g (Group-F) were added to Inj Bupivacaine 15 mg(0.5%). Onset of sensory and motor blockade, extent of analgesia and occurrence of any complications were studied in both groups. All patients were also observed for analgesia by VAS pain score post-operatively. Results: There was no significant difference in the onset of sensory and motor blockade in both the groups.The pulse rate in group butorphanol was 72.9 9.41 per min and fentanyl group 86.066.58 per min from 45-90 min after the subarachnoid block was given which was significantly lower. Duration of sensory block was 230.624.7 min and 197.815.4 min and the duration of motor block was 24632.6 min and18016.8min and post-operative analgesia was 303.640.4min and 269.415.4min in group Butorphanol and Group Fentanyl respectively which were significantly higher in gp Butorphanol. Conclusions: Adjuvance of 25g Butorphanol to intrathecal Bupivacaine significantly prolongs sensory and motor block as well as post-operative analgesia when compared to adjuvant 25g Fentanyl providing effective anesthesia for surgeries taken under spinal anesthesia. [Upasna B NJIRM 2017; 8(3):41-48]

Key Words: Analgesia, anesthesia, bupivacaine, Butorphanol, Fentanyl, spinal

Author for correspondence: Upasna Bhatia, B- 401, Samay apartments , near Azad society , Ambavadi , Ahmedabad Gujarat 380015 M: 9376163683 E-Mail: upasna90@gmail.com

Introduction: Opioid has been used as analgesics for century. It remains most commonly used drug for the treatment of postoperative pain. They exert their effect by mimicking the action of endogenous opioid receptors that are found in location throughout the central nervous system, including the periaquaductal and periventricular gray matter and the dorsal horn of the spinal cord[1].

Various combinations of intrathecal drugs have been tried to provide effective post-operative analgesia. The intrathecal administration of local anaesthetics and opioids is an excellent technique for managing postoperative pain. The patients often have better pulmonary function, are able to ambulate early and benefit from physical therapy. Moreover, the patients may be at lower risk for postoperative thrombosis[2].

Post operative pain is a complex physiological reaction to tissue injury or disease. The patients often perceive postoperative pain as one of the ominous expects of undergoing surgery. Opioids and Local Anaesthetics administration together intrathecally have a potent synergistic effect, improving the quality of intraoperative and post operative analgesia .A combination of these agents allows for a reduction in the dose of both the classed of drugs , lessening the likihood of side effects attributable to each , which is particularly beneficial in geriatric patients [3,4].

Neuraxial opioids also allow prolonged analgesia in the post operative period and faster recovery from spinal anaesthesia [5]. Butorphanol is a lipophilic opioid agonist-antagonist with a published affinity for opioid receptors in vitro of 1:4:25 (μ:δ :κ)[6], with a dose dependant increase in the duration of post operative analgesia[7].

Fentanyl , highly lipid soluble , a pure μ agonist opioid with rapid onset and shorter duration of action, has been used with various local anaesthetics for a wide variety of surgical procedures [8,9].

Opioids are central analgesics that act on the CNS (central nervous system) and PNS (peripheral nervous system. The mechanism of opioid and Local anaesthetics association has not been elucidated. It is known that local Anaesthetics act by blocking the influx of sodium in their channels, preventing increased permeability of the ion, needed for the potential action to occur[10].

Opioids act by mechanisms different from those of Local anaesthetics, i.e., through specific receptor opioid pathways, or through receptors coupled to ion

channels, and these receptors cause changes in cellular mechanisms and balance[11].

The combination of a centrally acting drug (opiod) with a peripherally acting drug (Local anaesthetics) supports the idea that drugs with actions that involve uniting central and peripheral pathways generate onset times, activity durations and various sites of drug action that could increase the analgesic capacity; moreover, these additive and synergistic effects could occur at lower doses[12].

Both Opioid and Local anaesthetics have hydroxyl groups on a molecular chain attached to the benzene ring. This is an important factor for the nervous system. The influx of Ca^{2+} and induction of K^{+} in the nerve terminal is considered the trigger for release in synaptic cleft neurotransmitters. Considering the possible blockade of Ca^{2+} and K^{+} channels induced by opioid codeine and tramadol, together with the blockade of Na^{+} channels by Local anaesthetics, which keep the cell hyperpolarized, a synergistic effect would occur, resulting in nerve conduction impairment [12,13].

The study was designed to compare the effect of intrathecally bupivacaine 0.5%Heavy with 25µg Butorphanol and 50 µg Fentanyl in different surgeries. We compared the onset of sensory and motor block, duration of block and postoperative analgesia, hemodynamic changes, and per op and post operative side effects.

Methods: Sixty patients were randomly selected after taking approval from the institutional ethic board for the comparative study of Fentanyl and Butorphanol as an adjuvants to Bupivacaine in spinal anaesthesia considering the level, duration and quality of block with hemodynamic effects in elective surgeries.

Patients who belonged to ASA grade I and II posted for elective surgeries were chosen for the study. Patients comprised of age group of 18 to 55 years, body mass index of <30kg/m^2 , height 150-170cm.

Patients who were comprised of skin infection at the site of anaesthesia, coagulopathy, taking anticoagulant drugs, neurological disorder and deformity of spine were excluded from the study.

Patients were divided in 2 groups having 30 patients each.

Group B	Inj Bupivacaine heavy 0.5%heavy 3cc + 25 µg Butorphanol
Group F	Inj Bupivacaine heavy 0.5%heavy 3cc + 50 µg Fentanyl

All patients were thoroughly examined on the previous day of the operation and again in pre anesthetic room in the morning on the day of surgery. A history of any present or past illness and detailed general as well as systemic examination was done and investigations were checked. Visual analogue scale was shown to the patient and the procedure of post operative pain measurement was explained in detail.

Base line vitals were noted and informed written consent was taken from patient and his or her relatives. On the day of surgery, intravenous line was taken and after attaching ECG monitor, Pulse oximeter, non invasive BP monitor/ cuff, vitals like Pulse, BP,RR, Spo_2 were noted. Each patient was preloaded with 20 ml/kg of Ringer lactate solution about 15 min prior to intrathecal drug administration.

Patients were positioned in the left lateral or sitting position and after aseptic precautions lumber puncture was performed at L_3-L_4 intervertebral space using midline approach with 23G quinke's spinal needle. After ensuring free flow of CSF, patients in the group F received a single dose of 15 mg Bupivacaine 0.5% heavy+ inj Fentanyl 50µg.The patients in group B received 15 mg of bupivacaine 0.5% heavy + inj Butorphanol 25µg. Following injection of the drugs patients were returned to supine position. All the patients were monitored in the form of BP, Pulse, RR, ECG and Spo_2 at 1, 5, 10 ,15 minute and then at every 15 minute interval.

Onset of sensory blockade was taken as the time required in seconds to produce loss of pin prick sensation bilaterally around anterior superior iliac spine.(T_{12} dermatome)

Bromage criteria was taken for onset of motor blockade (Table 1), Ramsay sedation scale was used for sedation (Table2), side effects were noted as nausea, vomiting , Bradycardia was taken >30% of base line Fall in basal pulse rate, >30% of base line Fall in BP recording was noted as hypotension , Respiratory depression <10 breaths/min and pruritis.

On completion of surgery, patients were shifted to the recovery room. Temperature, pulse rate, blood pressure, respiratory rate, Spo_2 and visual analogues score (VAS) fig 1 were measured every 1 hour for 12 hrs. Time for regression of analgesia to pin prick below L_2 dermatome was considered as duration of anesthesia. Rescue analgesia was administered in the form of inj. Diclofenac sodium 75 mg IM when VAS score was >5 and it was considered as duration of post operative analgesia.

Duration, intensity and number of episodes of nausea, vomiting, bradycardia, hypotension, respiratory depression were assessed.

All the observations were recorded and the results were analyzed. Statistically data are presented as mean ± SD. For comparing data ANOVA test (Analysis of variance is used and p values<0.05 were interpreted as clinically significant.

Results: Both the groups were comparable with respect to age, height, weight, BMI and ASA grading The mean duration of surgery in Group B (Bupivacaine + Butorphanol) was 119±25 minutes and 119±24.6 in Group F (Bupivacaine + Fentanyl) which was comparable and not significant, p>0.05 (Table 3 and Table 4).

The mean time to achieve T8 level and modified bromage scale 3 were comparable in both the groups and statistically not significant. The mean duration of sensory and motor blockage was statistically significant. Motor block (246±32.6) and sensory block (230.6 ±24.7) was longer in Group B (Butorphanol + bupivacaine) than Group F (Bupivacaine + Fentanyl). Duration of analgesia was observed to be longer in Group B (303.6±40.4) (Butorphanol + bupivacaine) than Group F (269.4±15.4) (Bupivacaine+ Fentanyl) (Table 5).

The base line pulse rate was comparable in both the groups. The pulse rate in Group B (Bupivacaine + Butorphanol) was significantly lower as compared to Group F (Bupivacaine + Fentanyl) from 45 to 90 minutes after subarachnoid block. There was no statistically significant change in pulse rate between 90 min to 12 hrs post-op among both the groups (Table 6).

Similarly, the mean base line blood pressure was comparable in both the groups but the mean arterial blood pressure was significantly lower in Group B (Bupivacaine + Butorphanol)compared to Group F (Bupivacaine + Fentanyl) from 45mins to 90 mins after the subarachnoid block. There was no statistically significant difference in blood pressure from 120 minutes till 12 hrs post operatively (Table 7).

Perioperative side effects Two patients from gp B and 3 patients from gp F had hypotension and same patients experienced bradycardia which were treated with injection 0 .3mg of Atropine and 6 mg of mephentermine intravenously (Table 8).

Intrathecal adjuvants were used to lower the dose of Bupivacaine as they provided adequate perioperative analgesia with reduced cardiovascular effects. Intrathecal opioids used as adjuncts are capable of producing analgesia of prolonged duration but allow early ambulation of patients because of their sympathetic and motor nerve sparing activities.

Table 1 : Bromage Criteria

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0 %)
II	Just able to flex knees with free movement of feet	Partial(33 %)
III	Unable to flex knees, but with Free movement of feet	Almost complete(66%)
IV	Unable to move legs or feet	Complete (100 %)

Table 2 : Ramsay Sedation Score

Score	Response
1	Anxious or restless or both
2	Cooperative, oriented, and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

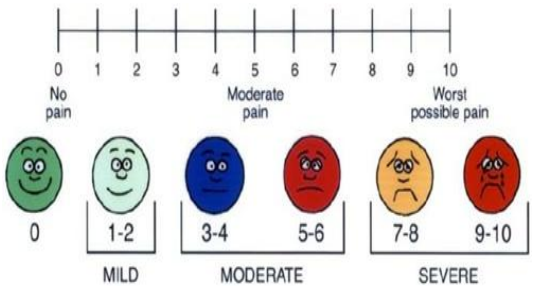

Table 3 : Demographic variables

Variables Mean ±sd	Group B n=30	Group F n=30	P value
Mean Age (years)	37.73 ±10.59	39.9 ±10.03	>0.05
Mean Height (mt)	1.59 ±4.98	1.59 ± 4.64	
Mean weight (Kg)	55.6 ± 6.49	56.16 ± 5.93	
Mean BMI (Kg/m^2)	21.72	21.95	
ASA grading (I /II)	19 / 11	18/12	
Duration of surgery	119±25	119±24.6	

Table 4 : Types of Surgery

	Group B	Group F
Hydrocele	1	2
Hernia	12	14
Umblical hernia	2	4
Fistula in ano	1	1
Acute Appendicitis	2	5
# femur	4	2
#tibia fibula	6	2
# calcaneum	2	0

Tables 5 : Characteristics of block

Duration (minutes)	Group B Mean ± SD	Group F Mean ± SD	P value
Time to T8 sensory level	6.39±0.61	6.59±0.60	0.21
Time to modified Bromage Scale 3	4.93±0.77	5.15±0.63	0.23
Duration of Sensory Block	230.6 ±24.7	197.8±15.4	0.038
Duration of motor Block	246±32.6	180±16.8	.003
Duration Of analgesia	303.6±40.4	269.4±15.4	.001

Table 6 : Changes in pulse Rate

Time (Minutes)	Group B (Mean+SD)	Group F (Mean+SD)	P Value
Pre op	87.56±4.46	88.88±2.61	0.19
After SAB	84.53±6.23	88.13±3.03	0.006
2 Min	85.46±5.35	88.66±4.05	0.09
5	87.56±2.45	88.43±2.06	0.15
10	86.13±4.53	87.5±1.97	0.24
15	86.26±3.31	86.8±1.98	0.27
30	85.23±6.40	84.2±9.21	0.11
45	73.53±10.53	86.06±2.44	0.00
60	72.9±9.41	86.46±6.58	0.00
75	72.46±8.33	86.96±2.47	0.003
90	72.46±6.92	85.46±1.96	0.027
120	84.3±5.49	85.4±1.97	0.3
180	84.46±4.58	85.1±1.91	0.4
360	86.1±3.02	85.46±1.94	0.33
540	85.83±4.30	87.46±2.89	0.09
720	83.03±6.29	86.3±5.94	0.06

Table 7 : Changes in mean Arterial blood pressure

Time (Minutes)	Group B (Mean+SD)	Group F (Mean+SD)	P Value
Pre OP	95.16±4.80	95.36±3.58	0.8
After SAB	93.16±4.06	93.2±2.99	0.9
2 min	92.46±3.41	92.03±4.20	0.6
5	89.9±2.49	90.46±4.05	0.5
10	87.2±2.73	87.7±3.60	0.5
15	88.5±2.47	88.66±2.18	0.7
30	86.13±2.56	86.16±2.10	0.9
45	79.5±4.50	79.2±5.23	0.02
60	79.3±4.83	78.03±4.99	0.03
75	78.1±4.16	76.66±3.53	0.015
90	84.7±5.20	84.53±3.85	0.04
120	84.93±2.82	84.73±3.93	0.8
180	85.13±2.94	84.9±4.64	0.8
360	88.46±1.96	88.96±4.31	0.5
540	87.73±4.22	87.3±2.85	0.6
720	86.5±4.22	87.3±2.57	0.7

Table 8 Perioperative side effects

Side effects	Group B	Group F
Hypotension Bradycardia >30% of Fall in basal BP recording	2	3
Bradycardia >30% of Fall in basal pulse rate	2	3
Nausea	0	0
Vomiting	0	0
Respiratory depression	0	0
Pruritus	0	0
Sedation	0	0

Discussion: Local anesthetics such as bupivacaine act mainly by blockade of voltage gated Na+ channels in the axonal membrane and presynaptic inhibition of calcium channels[14]. Both butorphanol and Fentanyl exert their action by opening K+ channels and reducing the Ca++ influx, resulting in inhibition of

transmitter release. A combination of these effects may explain the observed synergism between bupivacaine and butorphanol / Fentanyl. The synergism is characterized by enhanced somatic analgesia without an effect on the degree of level of local anesthetic induced sympathetic or motor blockade[15-17]. We chose the doses of 25µg butorphanol and 25 µg of Fentanyl, as this dose provided better post-operative analgesia.

Pain is typically associated with neuroendocrine stress response that is proportional to pain intensity. Moderate to severe pain, regardless of site, can affect nearly every organ function and may adversely influence postoperative morbidity and mortality. The effective postoperative pain management is a very important aspect of postoperative care. The visual analogue scale is the widely used measure to evaluate and quantify the intensity of pain. In this study the pain was assessed subjectively by a 10 cm visual analogue scale.

The demographic data in terms of age, weight, height and ASA grade were comparable in both the groups of our study (Table4A-B). Binay et.al[18] 2012, used butorphanol-bupivacaine mixture in lower limb orthopedic surgeries and stated that the wide variability in the age of the patients (18-75yrs) in their study was a confounding factor in relation to perception of pain as pain perception varies with age. However this was not observed in our study as the demographic data (age: 18-55yrs) did not have extreme variability and was comparable to other studies.

Sensory and motor blockade: Onset: In the our study there was no significant difference in the onset of motor blockade in both the groups 4.93 ± 0.77 and 5.15±0.63 min and onset of sensory to T_8 level 6.39± 0.61 and 6.59± 0.60 gp in Butorphanol and Fentanyl gp respectively which is in accordance with the previous studies of Kumar et.al[18,19]where onset of motor 3.47± 1.01 and 4.47 ± 1.46 min sensory block T_8 was at 1.43 ± 0.57 and 3.03 ± 1.03 min in Gp Fentanyl and Butorphanol respectively. Though not significant difference in both the groups but findings contradicted with in Binay et. al[18] where onset of motor 9.5± 1.8 and 10.1 ± 1.7 min sensory block T_8 was at 8.0± 1.7 and 8.6 ±1.4 min in Gp Fentanyl and Butorphanol respectively.

Duration of sensory and motor block: was longer in Group Butorphanol than Group Fentanyl. Similar findings were observed by Binay et.al[18], Manpreet et.al[19]and Gopal Reddy et.al[20].

Binay et.al[18], 2011, observed total duration of sensory blockade 156± 18.4 and 167.0 ± 23.8 min in gp Fentanyl and butorphanol gp which was much lower than our study group.

Manpreet et. al[19], 2011, studied addition of butorphanol & sufentanil to bupivacaine for subarachnoid block and reiterated that the addition of butorphanol significantly prolonged the duration of sensory block. They also found that 90% of patients achieved a bromage scale of 3 in butorphanol group & the duration of motor block was prolonged. However, as compared to our study, the duration of both sensory block and motor block was 230.6 ±24.7min and 246±32.6 min which was lower (in sensory block) 170.87 ±22.21 and (in motor blockade) 132.20 ± 20.8 min in group butorphanol in their study.

Vaghadia et.al[21] observed that opioids like butorphanol increases the sensory block and delays the time of two-segment regression of the sensory level.

Gopal Reddy et.al[20]also observed that addition of Butorphanol to intrathecal Bupivacaine prolonged the duration of motor block 145.5 ± 8.than addition of Fentanyl, 142.2 ± 6.7 though not significant which is again comparable to our study .

Vinita et. al[22], also added butorphanol to hyperbaric bupivacaine and concluded that butorphanol intensifies the sensory blockage and increases the duration of sensory blockade without increasing the intensity of motor blockade & requirement of rescue analgesia which was similar to study.

In Butorphanol group duration of analgesia was shorter compared to the study done by Binay et. al[18]. This can be explained by the fact that in our study highest sensory level attained was T_{10} (median) compared to T_7 (median) in previous study.

Duration of analgesia: The use of opioids in conjunction with local anaesthetic for spinal anaesthesia has been associated with decreased pain scores and reduced analgesic requirement in the post-

operative period. Results of previous studies have demonstrated that intrathecal opioids not only enhance analgesia when added to sub therapeutic doses of local anaesthetics but also do not prolong recovery. In our study, butorphanol with bupivacaine not only provided adequate anaesthesia & analgesia but also significantly prolonged its duration which was observed to be longer in Group Butorphanol (303.6±40.4 min) than Group Fentanyl (269.4±15.4 min).

Binay et.al[18] observed that patients receiving butorphanol had lower VAS pain scores at all observed times than patients who received fentanyl, although this difference in VAS scores reached a statistical significance only at 1-hour post operative duration. A higher number of patients in the fentanyl group requested for rescue analgesia earlier than patients in the butorphanol group as the average times to 1st rescue analgesia were 308.6±14.9 and 365±12.3 respectively in the post operative period which correlated with our observation .

Similarly N.Gopal Reddy et.al[20], also observed that the duration of analgesia was more prolonged with intrathecal butorphanol than fentanyl. They found that the duration of analgesia was 272.8±17.2 with butorphanol and 270±27.4 min which is comparable with our study. The duration of analgesia was 311.2 ±58.7 min (SN singh et.al[23]), 299 ±73.9min (Manpreet et.al[19]) and the patients in the fentanyl gp requested rescue analgesia earlier than patients in the butorphanol gp to first request were 308.6±14.9 and 365.9±12.3 minutes, respectively.

Haemodynamic parameters & side effects / complications: In this study all the haemodynamic parameters (Pulse, Blood pressure, Respiratory rate & SpO2) of both the groups were comparable at all the time intervals and were clinically & statistically insignificant except from 45-90 minutes pulse rate and mean arterial BP were lower in Group-B than Group-F which were statistically significant(Table 4). The pulse rate in group butorphanol was (72.9± 9.41 per min) which was was significantly lower as compared to fentanyl group (86 .06± 6.58 per min) from 45 – 90 min after the subarachnoid block was given..

A low incidence of side effects was observed in our study. Two patient had hypotension and two patient had bradycardia in Group B .In Group F 3 patients had hypotension, 3 patients had bradycardia and one patient had sedation. Patients with hypotension required a small dose (6 mg) of mephentermine in addition to crystalloid bolus (150 ml).

Prof.Dr.Subrata Nag et.al[24]concluded that Butorphanol when used as an adjunct to bupivacaine in spinal anesthesia helped in keeping the patient hemodynamically stable throughout the surgery in comparison to bupivacaine alone.

Binay et.al(18), observed hypotension in two patients (5%) in the butorphanol treated group requiring treatment with a single bolus dose of 6mg ephiderine in addition to crystalloid bolus.

Patients with bradycardia required inj.atropine 0.4mg . Most common side effect of spinal opioids is pruritus which is related to cephalad migration of opioids in the CSF. None of our patients in either group had complained of pruritus. In correlation with our study both Bhawna and Gupta et.al[25] noted no incidence of nausea, vomiting, headache and urinary retention. Sedation is a reported side effect of neuraxially administered butorphanol. In our study none of the patient had Ramsey score above 2 though one patient in Group F experienced sedation which required no treatment.

Respiratory depression (Spo_2 <95, RR>20) was not observed in our study this finding is consistent with the previous studies by, Binay et.al[18] and Nag,N.Gopal Reddy et.al[20].

Conclusions: Post-operative pain is a complex physiological reaction to tissue injury or disease. The patients often perceive postoperative pain as one of the ominous expects of undergoing surgery. Spinal opiates have been of much interest in recent times as they potentiate the effect of local anesthetic agent and provide longer lasting post-operative analgesia. We compared injection butorphanol and Fentanyl as an adjuvant to local anesthetic agent in subarachnoid block with respect to onset, duration of sensory and motor block and duration of analgesia

The results of our study are consistent with experimental evidence of synergistic interaction between spinal opioids and local anesthetics, which were characterized by enhanced somatic analgesia

without effect on the degree or level of the local anesthetic induced sympathetic or motor blockade.
The synergism between intrathecal opioids in addition to local anesthetics is due to the drugs' separate mechanism of action; blockade of Na^+ channel by local anesthetics and voltage-gated Ca^+ channels with opioids.

The combination of opioids with LA allows for a reduction in doses of the LA, thus lessening the likelihood of side effects.

Thus the result of our study showed that supplementation of intrathecal Bupivacaine with Butorphanol (25µg) significantly prolonged sensory and motor block as well as post-operative analgesia when compared with Fentanyl (25µg) as the adjuvant to Bupivacaine. Results also showed effect of Fentanyl as an adjuvant also increased post-operative analgesic effect but the duration was little less when compared to Butorphanol. Both 25-µg fentanyl and 25-µg butorphanol given intrathecally with 15 mg of hyperbaric bupivacaine provide effective and safe anesthesia for surgeries taken under spinal anesthesia. Intrathecal bupivacaine – butorphanol mixture provides longer duration of sensory blockade and better quality of analgesia than intrathecal fentanyl – bupivacaine mixture.

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