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ORIGINAL ARTICLE

COMPARISON OF EFFICACY OF BUTORPHANOL AND FENTANYL AS INTRATHECAL ADJUVANT TO BUPIVACAINE

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ABSTRACT: OBJECTIVE: The objective of the study was to compare the efficacy of butorphanol and Fentanyl as an adjuvant to local anaesthetics in relation to onset, degree and recovery time of sensory and motor blockade in orthopaedic procedures done under spinal anaesthesia. **METHODS:** In a Randomized double blind study, 90 cases of ASA grade 1 & 2 between the ages of 18-60yrs of either sex undergoing elective lower limb orthopaedic procedures were allocated into three groups of 30 each. Group A received intrathecal 0.5% hyperbaric bupivacaine 3ml with 0.2 ml of normal saline (n=30). Group B received intrathecal 0.5% hyperbaric bupivacaine 3ml with Butorphanol 200microgram. (n=30) Group C received intrathecal 0.5% hyperbaric bupivacaine 3ml with fentanyl 20microgram. (n=30).Vital parameters, onset, level, duration and regression of sensory & motor block, duration of effective analgesia were recorded and compared. Analysis was done by of variance (ANOVA) test. **RESULTS:** Intrathecal administration of Bupivacaine + Butorphanol (141.6±7.2 min) Bupivacaine+Fentanyl (124.5±7.1min) prolongs 2 segment regression times compared to Bupivacaine with Normal saline (118.3±12.5min) without altering the duration of motor blockade. Duration of effective analgesia was 191.8±19,272.8±17.2 min and 270.0±27.4 min in Group A, Group B and Group C respectively. Post-operative side effects were comparable in all the three groups. **CONCLUSION:** Both fentanyl and butorphanol given intrathecally along with hyperbaric Bupivacaine prolong the duration of effective analgesia.

KEYWORDS: Hyperbaric Bupivacaine, Fentanyl, Butorphanol, Subarachnoid Block, Post-Operative Analgesia.

INTRODUCTION: Using opioids intrathecal dates back to 1979 by Wang and his colleagues for acute pain management.[1" Spinal anaesthesia is the fastest, most predictable and reliable form of regional anaesthesia".[2] By adding a small dose of narcotics to local anaesthetic solution the duration of anaesthesia and analgesia can be significantly prolonged.[2]

Fentanyl is a potent, synthetic opioid analgesic with a rapid onset and short duration of action.[3] Fentanyl provides some of the effects typical of other opioids through its agonism of the opioid receptors. Its strong potency in relation to that of morphine is largely due to its high lipophilicity, per the Meyer-Overton correlation. Because of this, it can more easily penetrate the CNS.[4] Intrathecal narcotics enhance the sensory blockade of local anaesthetics without affecting the sympathetic activity.[5] Intrathecal morphine provides prolonged postoperative analgesia but is associated with increased risk of nausea, vomiting, itching and respiratory depression.[6] The risk of respiratory depression may be further enhanced in the elderly.[7] Short acting narcotics like fentanyl and sufentanil have been used intrathecally in elderly population undergoing total hip replacement and provided adequate pain relief of short duration.[8] Buprenorphine a mu receptor agonist with low intrinsic activity can also be administered safely in the subarachnoid space. [9]

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It has a high molecular weight and lipophilicity which may prevent its rostral spread.

When used intrathecally in combination with bupivacaine it has improved the quality and duration of postoperative analgesia compared to bupivacaine alone.[10] Butorphanol exhibits partial agonist and antagonist activity at the μ opioid receptor, as well as competitive antagonist activity and partial agonist activity at the κ opioid receptor.[11] Stimulation of these receptors on central nervous system neurons causes an intracellular inhibition of adenylate cyclase, closing of influx membrane calcium channels, and opening of membrane potassium channels. This leads to hyper polarization of the cell membrane potential and suppression of action potential transmission of ascending pain pathways. Because of its κ-agonist activity, at analgesic doses butorphanol increases pulmonary arterial pressure and cardiac work. Additionally, κ-agonism can cause dysphoria at therapeutic or supertherapeutic doses; this gives butorphanol a lower potential for abuse than other opioid drugs. Butorphanol is also quite effective at reducing post-operative shivering (owing to its Kappa agonist activity). Butorphanol is more effective in reducing pain in women than in men.[11]

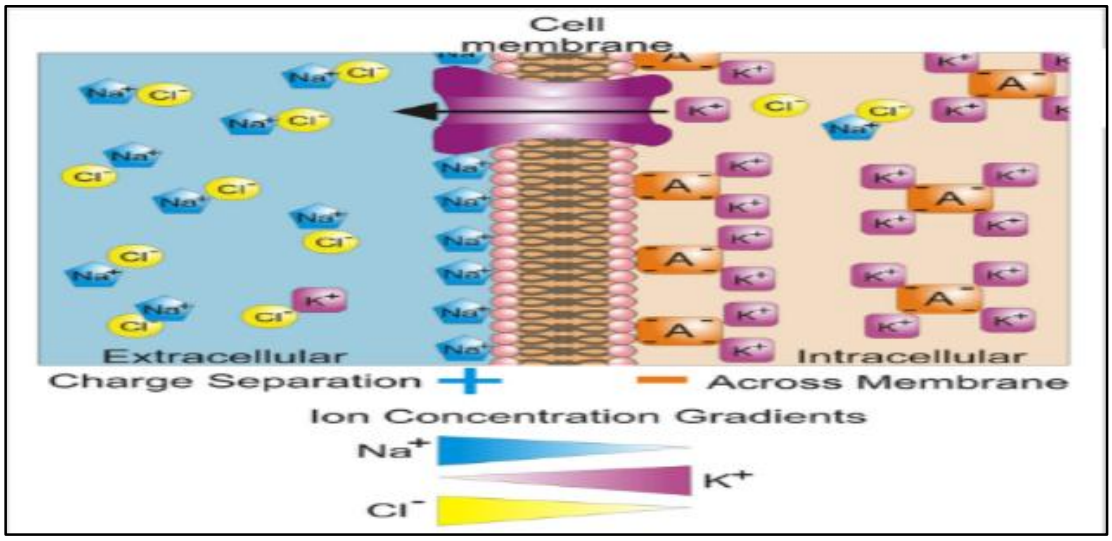

Diagram 1: Showing the ionic basis of the resting potential

There is paucity of literature comparing intrathecal butorphanol and its quality of analgesia to other narcotics used by intrathecal route. In current literature this use has not been addressed very less in prospective, double blind, randomized trial. On this basis we designed a double blind controlled study to evaluate and compare the characteristics of spinal block and its side effects in elderly patients undergoing orthopaedic operations who received a subarachnoid block with bupivacaine alone, or with the addition of butorphanol as it available without restrictions along with H schedule drug fentanyl.

Combining opioids with local anaesthetics has got a synergistic effect, improving the intra and post-operative analgesia. A combination of these agents reduces the side effects caused by either of them due to decrease in dose required to achieve the desirable effects especially in geriatric patients.[12,13] Both the opioids chosen, Fentanyl and Butorphanol belong to phenanthrene group of agonist–antagonists, having agonist action on kappa receptor and antagonistic or partial agonist property at mu receptor. They are synthetically prepared, having similar pharmacological properties.

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Many studies have shown that, they can be used as intrathecal opioids adjuvant with local anesthetics to provide quality intra and postoperative analgesia.[14] Butorphanol is widely available without restriction as compared to fentanyl and other potent opioids.

Orthopaedic procedures in geriatric patients require reduced dose of bupivacaine because of anatomical and physiological changes along with associated co-morbid conditions.[15] We therefore conducted this study to evaluate the efficacy of butorphanol and Fentanyl as adjuvant to bupivacaine in orthopaedic surgeries.

METHODS: The study was approved by the institutional ethical committee and written informed consent was obtained from all patients. A Randomised double blind study of 90 cases of ASA grade 1& 2, between the age group 18-60yrs undergoing elective lower limb orthopaedic procedures from January 2014 to January 2015 was undertaken. Patients were randomly allocated to one of the three groups (n=30).Group A received intrathecal 0.5% hyperbaric bupivacaine 3ml with 0.2 ml of normal saline (n=30).Group B received intrathecal 0.5% hyperbaric bupivacaine 3ml with Butorphanol 200 micrograms in 0.2 ml. (n=30) Group C received intrathecal 0.5% hyperbaric bupivacaine 3ml with Fentanyl 20microgram in 0.2 ml. (n=30) the baricity of the drugs were comparable. The drugs were prepared by one of the author who did not take part in the study. An experienced anaesthesiologist who did not participate in the study performed the SAB and was blinded to the study drug used. Patients with history of adverse response to bupivacaine, Fentanyl and butorphanol, pregnancy, or patients suffering from peripheral or central neurological, cardiac, respiratory, hepatic, renal disease or body weight more than 90 kg or less than 40 kg and height more than 175cm or less than 145 cm or with contraindication to SAB were excluded from the study.

All patients underwent complete general physical examination and systemic examination, after sign in taken in to OT room. All were explained about the linear visual analogue scale scoring system for pain during the pre-anesthetic check-up. In the operation theatre, an intravenous line was established. The intrathecal drugs were prepared beforehand to maintain the blinding process. Baseline heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate and peripheral arterial oxygen saturation were recorded for all subjects. All patients received 10ml/kg of lactated ringer solution as preload within 20-30 minutes. To be on safe side epidural catheter was kept for expected prolong surgery and difficult cases where extension of anaesthesia required in L2-L3epidural space. Subarachnoid block was performed under strict aseptic conditions in the sitting position at the level of L3-L4 Intervertebral space using 23GQuincke spinal needle. The midline approach was used to perform the spinal blocks after infiltrating the skin with 1ml of 2% Lidocaine. Following the subarachnoid block, the patient was put in supine position. Intraoperative, vitals and block data were recorded at 5 minutes intervals for the first 20 minutes from the time of injection of spinal solution and there after every 15 minutes for the complete period of surgery. This data were recorded by the primary investigator, who was unaware of the patient allocation. Hypotension more than 20% of base line was treated with fluid boluses and 6mg mephentiramine or 5mg of IV boluses of ephedrine, while bradycardia (HR<60bpm) was treated with 0.6mg IV atropine or 0.2mg of glycopyrrolate. The highest level of sensory block was determined in the midclavicular line bilaterally, by pinprick test using a 20-G hypodermic needle every 2miutes till the level was stabilized for four consecutive tests. Further sensory testing was performed at 15- min intervals till 2 segment regression. Motor block was assessed using the modified Bromage scale, till achievement of the

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highest motor level. Side effects such as hypotension, bradycardia, nausea, vomiting, sedation, Pruritus, shivering and respiratory depression were recorded. The quality of postoperative analgesia was assessed using VAS at 15min, 30min and thereafter every 30minutes, till 2 hours postoperatively; and then every hour, till 4 hours postoperative duration. The time of first request of rescue analgesia was recorded.

A sample of 30 in each group was derived taking an α value 5% and β value of 80%. We considered a sample size of 30 in each group to test the hypothesis. The data were compiled and analyzed using one way ANOVA with the help of SPSS. A $p<0.05$ was considered statistically significant.

RESULTS: The three groups were comparable with regards to age, height and duration of surgery. There were no difference in the demographical profile i.e. age, sex, height, ASA grade, duration of surgery between three groups were comparable and statistically not significant

Parameter	Group A	Group B	Group C
Age(year)	46.8±4.766	47.10±2.758	46.4±4.022
Height(cm)	162.6±4.287	161.0±6.58	162.0±3 4.197
Duration of Surgery(min)	130.0±6.	132.0±6.158	128.50 ±5.373

Table 1: Data is presented as Mean±SD

On intra group comparison after SAB, there was no statistically difference in the Intraoperative PR, BP, RR and Spo2 between the groups. Onset time for sensory and motor blockade in all the three groups was comparable and not statistically significant. Maximum sensory level achieved was T6; we were able to achieve sensory level up to T8-10 in all cases. Two segment regression time for sensory blockade and duration of analgesia was significantly prolonged in both butorphanol and Fentanyl groups compared to bupivacaine only group, $p<0.005$.

Parameters	Bupivacaine (A) Mean SD	Butorphanol (B) Mean SD	Fentanyl (C) Mean SD	P* Value
1.Onset Time To Sensory Blockade (Seconds) Segment	122.8 18.9	120.8 17.4	121.4 12.7	P<0.18
Regression time (minutes) VOLUME 1 I	118.3 12.5	141.6 7.2	144.5 7.1	P<0.001
Onset time to Complete motor Blockade(minutes)	20.0	20.5	21.2	
Duration of motor Blockade(minutes)	139.8 11.1	145.5 8.4	142.2 6.7	
Duration Of Effective Analgesia(Minutes) Hs I&II,I&III	191.8 19.3	272.8 17.2	270.0 27.4	P<0.001

Table 2

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* One-way ANOVA test, Post operatively side effects like PONV were comparable in all the groups. We did not come across any case of Pruritus, respiratory depression.

DISCUSSION: Low dose bupivacaine although reduces the cardiovascular effects, it was not enough to provide adequate level of sensory blockade and prolonged post-operative analgesia.[16] 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.

Local anesthetics such as bupivacaine act mainly by blockade of voltage gated Na+channels in the axonal membrane and presynaptic inhibition of calcium channels.[17] 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. We chose the doses of 200mcirogms butorphanol and 20 micro gms of Fentanyl as this dose provided better post-operative analgesia with significantly lower side effects compared to other doses.

In our study, there was not much of a difference for the onset of sensory and motor blockade in all the three groups (Table 2), which is in accordance with the previous studies of Mukherji et al. and Kumar et al.[18,19] The highest sensory level achieved across all groups were comparable (T 10). Two segment regression time was significantly prolonged in group B and group C compared to group A ($p<0.001$) which supports the results obtained from previous studies.[19,20] Duration of effective analgesia i.e. time for the first rescue analgesic when VAS≥4, was significantly prolonged in group B and group C compared to group A ($p<0.001$). Results obtained was comparable to previous studies in Fentanyl group.[19]

In Butorphanol group duration of analgesia was shorter compared to the study done by Kumar et al. This can be explained by the fact that in our study highest sensory level attained was T10 (median) compared to T7 (median) in previous study. No incidence of side effects like Pruritus, respiratory depression noted in group B and group C.

To conclude both Fentanyl or Butorphanol in combination with low dose hyperbaric bupivacaine (15mg) are equally efficacious in patients undergoing lower limb orthopedic surgeries instead of bupivacaine alone because:

1) Both opioids Fentanyl or Butorphanol are easily available in the market 1st one with license as schedule drug other without it when compared, hence useful in peripheral and rural hospital setups.
2) Haemodynamic stability with these combinations is good.
3) Effective Prolonged duration of sensory analgesia.
4) Lesser side effects compared to morphine.
5) Less addiction potential because of diaphoresis.
6) Comparing side-effects, butorphanol has the advantage of not having Pruritus as a side-effect.

Hence, this butorphanol with low-dose bupivacaine in spinal anesthesia is equally acceptable clinically in terms of characteristics of sensory block, motor block, duration of analgesia and greater hemodynamic stability as compared with bupivacaine alone. Complications were reduced by the addition of butorphanol, which also has a lower tendency to produce Pruritus. Thus, this combination

of butorphanol with low-dose bupivacaine is especially beneficial in the geriatric group of patients, who have multiple co-morbid conditions.

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