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COMPARISON OF BUTORPHANOL AND NALBUPHINE AS AN ADJUVANT TO ISOBARIC LEVOBUPIVACAINE IN SUBARACHNOID BLOCK FOR INFRAUMBILICAL SURGERY.

Dr. Sandip Sinha
Associate Professor, Department of Anaesthesiology, BSMC, Bankura, India.

Dr. Suman Chatterjee, Dr. Pranabesh Ganguly, Dr. Priyanka Kumari and Dr. Debanjana Roy

Junior Resident, Department of Anaesthesiology, BSMC, Bankura, India.

ABSTRACT

The aim of our study was to compare the efficacy of butorphanol and nalbuphine as an adjuvant to isobaric levobupivacaine in infraumbilical surgeries done under spinal anaesthesia.In a randomized double blind study, 96 cases of ASA grade I & II aged between 18-60 years of either sex undergoing elective infraumbilical surgeries were allocated into three groups of 32 each. Group L received intrathecal 0.5% isobaric levobupivacaine 2.8ml with 0.4 ml of normal saline (n=32).Group LB received intrathecal 0.5% isobaric levobupivacaine 2.8ml with butorphanol 25microgram (n=32). Group LN received intrathecal 0.5% isobaric levobupivacaine 2.8ml with nalbuphine 400microgram (n=32). The onset, level, duration and regression of sensory and motor block, duration of effective analgesia and vital parameters were recorded and compared.Statistical analysis was done by SPSS software (ver:23) using ANOVA, Tukey's post hoc test & Chi-square test. Regarding onset of sensory block, there were no significant differences noted between LBand LN group, but both groups had significantly faster onset

compared to L group. Onset of motor block and time to reach maximum sensory level were also significantly different in all groups and they were faster in LNgroup. Time for two segment regression of sensory block from highest sensory level and complete regression of motor block were also significantly higher in LN group than in other groups. Time to first request for analgesic was significantly prolonged in LN group than other groups. There was significant reduction in mean arterial pressure in LN group intraoperatively starting from 5 minutes onwards upto 20 minutes.Intrathecal nalbuphine and butorphanol as an adjuvant to isobaric levobupivacaine provides effective prolongation of anaesthesia.Nalbuphine –levobupivacaine combination provides earlier onset and longer duration of sensory and motor blockade and more prolonged analgesia than butorphanol- levobupivacaine combination.

KEYWORDS: Levobupivacaine, Butorphanol, Nalbuphine, SubarachnoidBlock,Post-Operative Analgesia.

INTRODUCTION

Spinal anaesthesia is the fastest, most predictable and reliable form of regional anaesthesia.[1] By adding a small dose of narcotics to local anaesthetic solution the duration of anaesthesia and analgesia can be significantly prolonged.[1] Using opioids intrathecally dates back to 1979 by Wang and his colleagues for acute pain management.[2] Levobupivacaine is the pure S(-)-enantiomer of racaemic bupivacaine but is less toxic to the heart and central nervous system. Intrathecal levobupivacaine is equal in efficacy to, but less toxic than, racemic bupivacaine.[3] In recent years levobupivacaine has emerged as a safer alternative for regional anaesthesia than its racaemic parent. It demonstrated less affinity and strength of depressant effects onto myocardial and central nervous vital centers in pharmacodynamic studies, and a superior pharmacokinetic profile. Clinically, levobupivacaine is well tolerated in a variety of regional anaesthesia techniques both after bolus administration and continuous postoperative infusion. Reports of toxicity with levobupivacaine are scarce and occasional toxic symptoms are usually reversible with minimal treatment with no fatal outcome.[4]The regression of motor block was significantly more rapid after levobupivacaine and ropivacaine than bupivacaine in a study by Casati and colleagues, which may be advantageous for early ambulation after day-case surgery.[5]Combining opioids with local anaesthetics has got a synergistic effect, improving the intra and post operative

analgesia. Both the opioids nalbuphine and butorphanol belong to phenanthrene group of agonist–antagonists, having agonist action on kappa receptor and antagonistic or partial agonist property at mu receptor.[6]

METHODS:

The study was approved by the Institutional Ethical Committee and written, informedconsent were obtained from all patients. Sample size was calculated by formula $\left\{\left[2 \times SD^2 \left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2\right] / d2\right.$ using data from previous studies. Considering 5% Type I error and power of study 80% ,value of $Z_{\alpha/2}$ (standard normal variate for level of significance) was 1.96 and value of Z_{β} (standard normal variate for power) was 0.842. By using this values and datas from previous studies , the required sample size of our study was 93.69. So rounding up we have selected total 96 sample size for our present study.

A randomised double blind study of 96 cases of ASA physical status I or II of either sex between the age group 18-60 years presenting for elective infraumbilical (lower abdominal and orthopaedic)surgical procedureswere randomly allocated to one of the three groups (n=32). Group L received intrathecal 0.5% isobaric levobupivacaine 2.8ml with 0.4 ml of normal saline (n=32). Group LB received intrathecal 0.5% isobaric levobupivacaine 2.8ml with butorphanol 25micrograms in 0.4 ml.(n=32). Group LN received intrathecal 0.5% isobaric levobupivacaine 2.8ml with nalbuphine 400microgram in 0.4 ml. (n=32). The baricity of the drugs were comparable. The drugs were prepared by an anaesthesiologist who did not take part in the study. An experienced anaesthesiologist who did not participate in the study performed the subarachnoid block and was blinded to the study drug used. Patients with history of adverse response to levobupivacaine, nalbuphine and butorphanol, pregnancy, or patients suffering from peripheral or central neurological, cardiac, respiratory, hepatic, renal disease or body weight more than 100 kg or lessthan 40 kg and height more than 180cm or less than 145 cm or with contraindicationto subarachnoid block were excluded from the study. All patients underwent pre-anaesthesia checkup encompassing complete general physical examination and systemic examination and were explained about the linear visual analogue scale scoring system (LVAS) for pain during the preanaesthetic 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, mean arterial pressure

(MAP), respiratory rate and peripheral arterial oxygen saturation were recorded for all subjects. All patients were preloaded with 10ml/kg of lactated ringer solution as within 20-30 minutes. Subarachnoid block was performed under strict aseptic conditions in the sitting position at the level of L3-4 intervertebral space using 26G Quincke 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 patients were placed in supine position. Intraoperative vitals were recorded at 5 minutes intervals for the first 20 minutes from the time of injection of spinal solution and thereafter 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 intravenous fluid boluses and 6mg intravenous boluses of mephentermine, while bradycardia (HR<50bpm) was treated with 0.6mg intravenous atropine. Sensory testing was performed by pinprick test using a 20 gauge hypodermic needle, and dermatomal levels were tested every 2 minutes until the level had stabilized for four consecutive tests. The highest level of sensory block was thereby determined in the midclavicular line bilaterally. Further sensory testing was then conducted every 10 minutes until the point of two segment regression of the block. Further testing was performed at 20 minutes intervals until the recovery of S2 dermatome. Data related to the highest dermatomal level of sensory blockade, the time to reach this level from the time of injection, modifiedBromage scale of motor blockade at the time of reaching peak sensory level, time to two segment regression, time to S2 sensory regression and incidence of side effects were collected. Motor block was assessed using the modified Bromage scale, till achievement of the 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 LVAS at 15min, 30min and thereafter every 30minutes, till 2 hourspostoperatively; and then every hour, till 4 hours postoperative duration. The time offirst request of rescue analgesia was recorded.

RESULTS:

Statistical analysis of the obtained data was done by SPSS software (ver:23) using ANOVA, Tukey's post hoc test & Chi-square test. A $p < 0.05$ was considered statistically significant. The three groups were comparable with regard to age, sex,height, weight, ASA physical status,

duration of surgery and preoperative haemodynamics.Sample size was calculated by formula $\left\{\left[2 \times SD^2 \left(Z_{\frac{\alpha}{2}} + Z_\beta\right)^2\right] / d^2\right\}$ using data from previous studies. Considering 5% Type I error and power of study 80% ,value of $Z_{\alpha/2}$ (standard normal variate for level of significance) was 1.96 and value of Z_β (standard normal variate for power) was 0.842. By using this values and datas from previous studies, the required sample size of our study was 93.69. So we have selected total 96 sample size for our present study.

Regarding onset of sensory block, there were no significant differences noted between LB (2.70±0.65 min) and LN groups (2.60±0.77 min) (p=0.892), but both the groups significantly differed from the L group (5.77±1.07 min) (p<0.05). Time to reach the maximum sensory level were significantly different in all groups (15.33±1.85 min ; 7.17±1.32 min ; 5.87±0.73min in L , LB and LN groups respectively) (p<0.05). Highest sensory level (T_5) was achieved earlier in LN group than in LB group (p=0.001). Time for two segment regression of sensory block from highest sensory level was also significantly higher in LN group than in other groups (111.77±6.03min ; 145.47±7.37min;175.03±7.93min in L , LB and LN groups respectively) (p<0.05).Regarding the onset of motor block (Bromage score Grade 3), significant differences were noted between all three groups (12.40±1.92min; 8.53±1.25min; 6.70±0.92min in L , LB and LN groups respectively) (p<0.05).Total duration of motor block were alsosignificantly different in between three groups (130.25±9.01min ; 189.19±9.45min ; 248.25±10.38min in L , LB and LN groups respectively) (p<0.05).Time to first request for analgesic was prolonged in LN group than other groups which is statistically significant (168.47±6.49min ;285.93±23.02min ; 316.13±15.62min in L , LB and LN groups respectively) (p<0.05). Intraoperative heart rates were comparable among the three groups (p>0.005). Reduction in MAP was noted in LN group intraoperatively starting from 5 minutes onwards upto 20 minutes , which is highly significant compared to the reduction of MAP in the other two groups(p<0.05). MAP were comparable among the groups from 25 minutes onwards. Regarding perioperative side effects, nausea was complained by 4 patients in LB group compared to 3 in LN group. Postoperative vomiting was complained by 3 patients in LB group compared to 2 in LN group. Only 4 patients developed shivering in LN group compared to 6 in LB group. Only 1 patient complained of pruritus in LB group compared to none in LN group. No episodes of respiratory depression , dry mouth , postoperative bradycardia or hypotension were noted in any of the groups. Postoperative side effects were comparable among the groups.

DISCUSSION:

Use of intrathecal opioids as adjuncts to intrathecal local anaesthetics has a definite place in present regional anaesthesia practice. Intrathecal opioids selectively decrease nociceptive input from A delta and C fibres without affecting dorsal root axons or somatosensory evoked potentials.[7]Intrathecal opioids are synergistic with local anaesthetics and intensify the sensory block without increasing the sympatheticblock. They are commonly added to local anaesthetics forpotentiating their effects, reducing their doses, and therebyreducing their complications and side effects and offer haemodynamic stability. They also prolong the duration of postoperative analgesia.[8] Local anaesthetics such as levobupivacaine act mainly by blockade of voltage gated Na+channels in the axonal membrane and presynaptic inhibiton of calcium channels.[9]Both butorphanol and nalbuphine exert their action by opening K+ channels and reducing the Ca++ influx, resulting in inhibition of transmitter release. A combination of theseeffects may explain the observed synergism between levobupivacaine and butorphanol/nalbuphine. The synergism is characterized by enhanced somatic analgesia without an effect on the degree of level of local anaesthetic induced sympathetic or motor blockade. We chose the dose 0.4 mg of nalbuphine as this dose provided better post operative analgesia with significantly lower side effects compared to other doses.[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. 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 hyperpolarization 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).[11] Nalbuphine is a semisynthetic opioid with mixed k-agonist-μ-antagonist opioid with a moderate analgesic effect when compared to morphine. Its affinity to k-opioid receptors results in analgesia, sedation, and cardiovascular stability with minimalrespiratory depression.[12] Nalbuphine was studied several times as an adjuvant to local anaesthetics in spinal, epidural and local, intravenousblock, and the result of all studies concludes that nalbuphine is effective when used as an adjuvant to local anaesthetics in spinal, epidural, and local intravenous block, as it

significantly prolongs the block duration. Nalbuphine has the potential to maintain or even enhance μ-opioidbased analgesic effect while simultaneously mitigating the μ-opioid side effects.[13] There is a great similarity between butorphanol and nalbuphine regarding the chemical nature (synthetic mixed k-agonist-μ-antagonists), also, both have the same mode of action on opioidreceptors, and inhibition of neuronal serotonin uptake which leads to augmentation of the spinal inhibitorypathways for pain.[12] Stimulation of opiate receptors on neurons of the central nervous system lead to an inhibitionof intracellular adenylyl cyclase, an opening of potassium channels, and closing the calcium channels.This leads to hyperpolarization of the cell membrane potential and inhibition of action potential transmission ofascending pain pathways.[14] Hala Mostafa Gomaa et al concluded that either intrathecal nalbuphine (0.8 mg) combinedwith (10 mg) bupivacaine or intrathecal fentanyl (25 μg) combined with (10 mg) bupivacaine improves intra-operative analgesia and prolongs early post-operative analgesia in Cesareansection.[15]N. Gopal Reddy et al in their study found that both fentanyl and butorphanol given intrathecally along with hyperbaric bupivacaine prolong the duration of effective analgesia.[16]Shehla Shakooh et al, who used nalbuphine 0.8 mg as an adjuvant to intrathecal hyperbaric bupivacaine (0.5%) for various lower abdominal and lower limb surgeries concluded that, nalbuphine as an adjuvant to spinal anaesthesia shortens the onset of sensory and motor block, prolongs duration of sensory and motor blockade, provides effective postoperative analgesia, provides desirable sedation intraoperatively and does not result in any major adverse effects.[17]Kumar et al concluded that both 25 μg fentanyl and 25 μg butorphanol given intrathecally along with 12.5 mg of hyperbaric bupivacaine provide effective anaesthesia for lower limb surgeries. Intrathecal bupivacaine-butorphanol mixture provides longer duration of sensory blockade and superior analgesia than intrathecal fentanyl-bupivacaine mixture.[18]Nag et al in their study found that butorphanol when used as an adjunct to bupivacaine in spinal anaesthesia helped in keeping the patient haemodynamically stable throughout the surgery in comparison to bupivacaine alone.[19]Sagar S et alconcluded that both nalbuphine or butorphanol in combination with low dosehyperbaric bupivacaine(14mg) are equally efficacious in patients undergoing lower limb orthopaedic surgeries instead of bupivacaine alone.[10]Mukherjee et al, who studied the effect of nalbuphine when used as an adjuvant to 0.5%hyperbaric bupivacaine in spinal anaesthesia, concluded that 0.4 mg of nalbuphine is the most effective dose that prolongs duration of analgesia early postoperatively without increasing the risk of side-effects in patients undergoing orthopaedic surgeries in lower limb.[20]The practice of intrathecal nalbuphine for over

ten years did not have any reports of neurotoxicity. The previous studies have been conducted on pregnant patients also but did not reveal any untoward effects. Chari et al concluded that intrathecal butorphanol potentiates bupivacaine-induced sensory spinal block and reduces the analgesic requirement in the early post-operative period without prolonging motor block recovery time and without any other major side effects to the mother as well as the neonate.[21]Kaur et al in their study concluded that combination of sufentanil and butorphanol with low-dose bupivacaine in spinal anaesthesia is equally acceptable clinically in terms of characteristics of sensory block, motor block, duration of analgesia and greater haemodynamic stability as compared with bupivacaine alone.Complications were reduced by the addition of butorphanol,which also has a lower tendency than sufentanil to produce pruritus. Thus, this combination of butorphanol with lowdose bupivacaine is especially beneficial in the geriatric group of patients, who have multiple co-morbid conditions.[22]T. Padma et al concluded that intrathecal nalbuphine added to hyperbaric bupivacaine provides better quality of block and prolongs the post-operative analgesia for almost 7 to 8 hours as compared to hyperbaric bupivacaine alone, without any significant side effects for patients undergoing lower limb surgeries under subarachnoid block.[23] In our study, there were no significant differences noted between LB and LN groups regarding onset of sensory block, but both the groups significantly differed from the L group. Time to reach the maximum sensory level were significantly different in all groups. Highest sensory level (T_5) was achieved earlier in LN group than in LB group. Time for two segment regression of sensory block from highest sensory level was also significantly higher in LN group than in other groups.Regarding the onset of motor block (Bromage score Grade 3), significant differences were noted between all three groups.Total duration of motor block was also significant higher in LN group than in LB group and Lgroup. Time to first request for analgesic was significantly prolonged in LN group than other groups.

CONCLUSION:

To conclude, both nalbuphine or butorphanol in combination with isobaric levobupivacaine provides safe and effective prolongation of subarachnoid block in patients undergoing infraumbilical surgeriesinstead of levobupivacaine alone.

As an adjuvant in subarachnoid blocknalbuphine is superior to butorphanol in terms of:

1) Earlier onset of highest level of sensory block & motor block.

2) Prolonged duration of two segment regression of sensory block & complete regression of motor block.

3) Prolonged duration of analgesia.

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