

A comparative study of intrathecal 0.5% isobaric levobupivacaine with fentanyl and 0.5% isobaric levobupivacaine with nalbuphine in infraumbilical surgeries: A randomized double blind clinical trial

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Abstract

Introduction: Spinal anaesthesia is most commonly used technique for lower abdominal surgeries. Its main disadvantage remains the short duration of action, hence different additives have been used. Opioids have been used to enhance the clinical efficacy and duration of action of local anesthetic drugs. The present study was aimed to compare the clinical efficiency of fentanyl and nalbuphine as an adjuvant to 0.5% Isobaric levobupivacaine for lower abdominal surgeries.

Materials and Methods: After obtaining ethical committee clearance and written consent from patient. ASA grade I&II patients aged between 20-60 years undergoing infra umbilical surgeries were selected divided into two groups of 45 each by computerized randomization. Group A received intrathecal fentanyl 25µg(0.5ml) with 3ml(15mg)of 0.5% Isobaric Levobupivacaine, and group B received intrathecal nalbuphine 0.8mg(0.5ml) with 0.5% Isobaric levobupivacaine 3ml(15mg). Statistical analysis performed by STATA 11.2. Students t test prior to find the significance difference between the study parameters.

Results: The duration of first rescue analgesia required prolonged in group B (430.3±11.13min) compared to group A is 285.97±8.8min with p value of 0.001(<0.05) (Table 1). There were no significant hemodynamic changes and intra, postoperative complications in both groups.

Conclusion: Both the groups were equally efficacious with good intraoperative conditions with haemodynamic stability however group B improves the quality of intraoperative and postoperative analgesia with minimal side effects.

Keywords: Spinal anaesthesia, Nalbuphine, Levobupivacaine, Fentanyl, Postoperative analgesia.

Introduction

Spinal anaesthesia consists of the temporary interruption of nerve transmission within the subarachnoid space produced by injection of local anaesthetic solution into CSF. Used widely, safely and successfully spinal anaesthesia has many potential advantages over general anaesthesia, especially for operations involving the lower abdomen, the perineum and the lower extremities.¹ Spinal anaesthesia is the most commonly used technique for infra umbilical surgeries because of its unmatched reliability, cost effectiveness, effective analgesia, muscle relaxation and prolonged postoperative analgesia. Recent advances in anaesthesia has allowed more surgeries to be performed on day case basis.²

The popularity of spinal block is that, the block has well defined end points and anaesthesiologist can produce the blocks relatively with a single injection. The versatility of spinal anaesthesia is afforded by a wide range of local anaesthetics and additives that allow control over the level, the time of onset and the duration of spinal anaesthesia. The distribution of local anaesthetic solutions within the subarachnoid space determines the extent of the neural blockade produced by spinal anaesthesia.

Levobupivacaine has been widely used in ambulatory surgeries after the development of low dose spinal anaesthesia technique. To improve the block characteristics of intrathecally administered low dose local anaesthetics, addition of adjuvant is must.³ Various types of medications

can be used to overcome pain but opioids provide the most effective pain relief and standard of care. Intrathecal opioids are synergistic with local anaesthetics and intensify the sensory block without affecting the sympathetic block.⁴

Opioids are an important modality of postoperative pain management. They blunt the neuroendocrine stress response to pain. The technique of Opioid administration along with local anaesthetic has been exclusively studied to provide superior quality of analgesia in a variety of surgical procedures.^{5,6} The rationale for the combination of opioids and local anaesthetics is that two types of drugs eliminate pain by acting at two different sites. Local anaesthetics act at the nerve axon and the opioid at the receptor site in the spinal cord.^{4,7}

Thus this study is designed to quantitatively examine the effects of adding nalbuphine and fentanyl to 0.5% isobaric levobupivacaine hydrochloride spinal anaesthesia, to evaluate the efficacy, to know the duration of postoperative analgesia and to know the complications if any.

Materials and Methods

A prospective randomized, double blind clinical study was approved by our institutional ethical committee for a period of one year. Written informed consent was obtained from patients. 90 (45 in group A and other 45 in group B) patients of physical status American society of anaesthesiologist (ASA) grade 1 and 2, aged between 20 to 60

years undergoing elective infra umbilical surgeries under spinal anaesthesia were included in the study. Patients with history of known drug hypersensitivity to local anaesthetics and sensitivity to opioids, blood coagulation disorders, unwilling patients, spinal deformities, raised intracranial tension, local sepsis were excluded from the study.

A total sample size of 90, sample size calculation done by using open epi software version 2.3.1. At 95% confidence limit and 80% power of the study. According to study conducted by Nimisha P Brahmhatt et al to evaluate the effects of fentanyl added to low dose levobupivacaine on sensory, motor blockade characteristics, postoperative analgesia & complications, if any lower abdominal and perineal surgeries SD of motor block in Levobupivacaine plus Fentanyl group is found to be 16.05. Expecting / Assuming 10% difference in motor block between two groups, sample size calculated is 41~45 in each group, hence the total sample size is 90 that is 45 in Group A and 45 in Group B.

Materials and Methods

A total of 90 patients undergoing elective infraumbilical surgeries under subarachnoid block were included in the study. Patients randomly divided into two groups by using computer generated table.

Group A - will receive 15mg isobaric Levobupivacaine 0.5% (3ml), plus 25mcg Fentanyl.

Group B - will receive 15mg isobaric Levobupivacaine 0.5% (3ml) plus 0.8mg Nalbuphine.

A detailed pre-anaesthetic evaluation will be carried out for each patient with relevant laboratory and radiological investigations. All patients will be visited a day prior to the surgery and explained in detail regarding the anaesthetic procedure and an informed written consent will be obtained.

All patients will receive tablet Ranitidine 150 mg orally as pre-medication in the night. Patient will be kept nil per orally from 12 midnight prior to the day of surgery. On the day of surgery, patient will be preloaded with ringer lactate solution at the rate of 15ml/kg. Monitoring of vital parameters like heart rate, noninvasive arterial blood pressure, SPO2 and ECG will be done using automated multiparameter monitor. Basal line readings will be recorded.

Under aseptic precautions, spinal anaesthesia at L3-L4 interspace using 25 G Quincke spinal needle with patient in sitting position would be performed. The studied drug would be injected into the subarachnoid space according to group, after noting the clear free flow of CSF with the operation table kept flat. Patients are turned supine immediately. Hypotension will be treated with intravenous incremental doses of Ephedrine 6 mg. Bradycardia will be treated with IV Atropine 0.6 mg (0.02mg/kg body weight).

Sensory testing will be assessed by loss of pinprick sensation to 23 G hypodermic needle for onset and dermatomal levels were tested every two minutes until, the highest level had stabilised for 4 consecutive tests. Testing will then be conducted every ten minutes until, the point of 2 segment regression of the block. Data regarding the time

to reach highest dermatomal level of sensory blockade from the time of injection, time for 2 segment sensory regressions will be recorded. Sedation will be assessed intraoperatively by Ramsay sedation scale and recorded.

Group A - will receive 15mg isobaric Levobupivacaine 0.5% (3ml), 25mcg Fentanyl

Group B - will receive 15mg isobaric Levobupivacaine 0.5% (3ml) plus 0.8mg Nalbuphine.

After surgery, patient will be shifted to post anaesthesia care and recovery unit where they will remain until there is complete recovery of sensory and motor blockade. Postoperatively vital parameters will be recorded every hour and also any adverse events like nausea, vomiting, pruritus, shivering etc. will be noted. The time for rescue analgesia when patient complains of pain at surgical site will be recorded and treated with suitable analgesics. Time to gain back the motor functions of lower limb defined as time to reach modified Bromage 0 will also be noted.

Parameters to be evaluated:

1. Haemodynamic changes – HR, SBP, DBP, MAP, RR, SPO2, ECG will be monitored at every 5 minutes for 15 minutes and at every 10 min till the end of surgery. Then hourly in the postoperative period.
2. Assessment of motor blockade – Tested by modified Bromage scale.

Grade 0 : No motor block.

Grade 1: Inability to raise extended leg; able to move knees and feet.

Grade 2: Inability to raise extended leg and move knee; able to move feet.

Grade 3: Complete block of motor limb.

- a. Duration of complete analgesia and effective analgesia would be assessed using visual analogue scale (VAS).
- b. Side-effects and complications would be noted – adverse effects like bradycardia, hypotension, respiratory depression, nausea, vomiting, shivering and pruritus will be noted.

Statistical Analysis

Data were entered in MS – Excel and analysed in SPSS V22. Descriptive statistics for qualitative data were represented with frequencies and percentages, whereas for quantitative data descriptive statistics were represented with Mean and Standard Deviation. Chi-square and t-test were applied for finding significance between the groups in qualitative and quantitative data respectively. $P < 0.05$ was considered as statistically significant.

Results

Demographic data did not show any significant difference in age, weight, and sex ratio among the two groups and thus the two groups were comparable (Table 1). In our study the two groups were comparable with respect to their mean heart rate and the difference between the two groups were not statistically significant ($p > 0.05$) (Graph 1) and also the groups were comparable with respect to their mean arterial pressure (MAP) because there was no

statistically significance difference among the two groups with the p value of 0.641(p>0.05) (Graph 2).

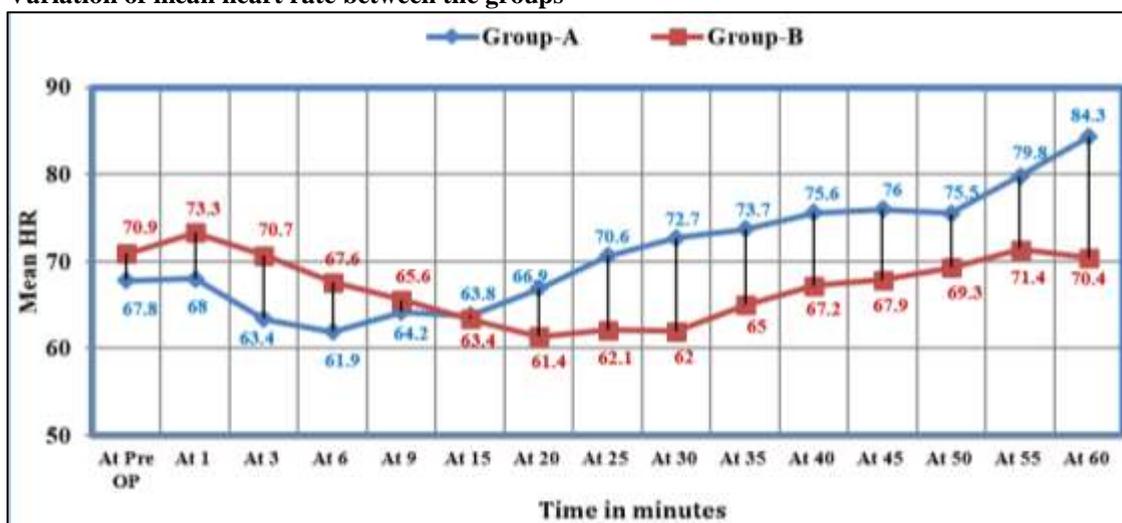
The mean duration of analgesia between the groups were statistically significant. There is significant difference among two groups in the maximum duration of analgesia with p value of 0.001 (p<0.05). (Table 2), and mean duration at which First Rescue Analgesic requirement between groups were statistically significant that is group A

having at 277.6+_11.4 min compared to group B requiring at 431.0+_13.5 min with p value of 0.001(<0.05). (Table 3). There is significant difference among two groups in maximum duration of motor block with p value of 0.001(p<0.05). There was no statistically significant difference found between the groups for side effects. (Graph 3).

Table 1: Demographic data

Variables	Group A (N=45)	Group B (N=45)
Age (Years)	52.96± 13.06	49.40± 11.19
Weight	64.58± 9.46	67.76± 7.60
Gender (Male/Female)	39/6	41/4

Graph 1: Variation of mean heart rate between the groups



Graph 2: Graph showing variation of MAP between the groups

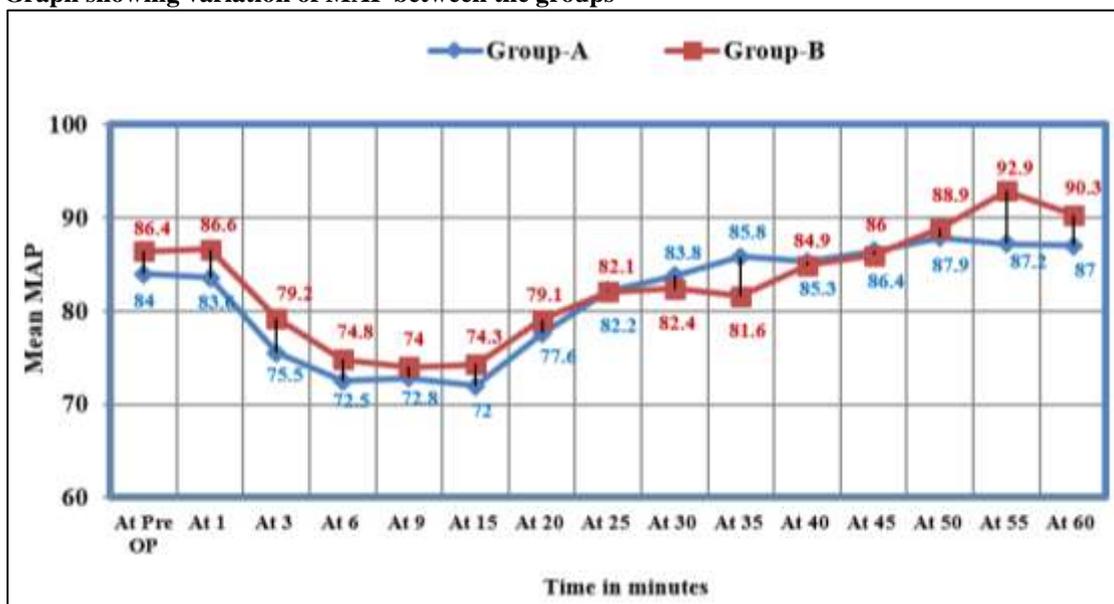


Table 2: Table showing duration of analgesia between groups:

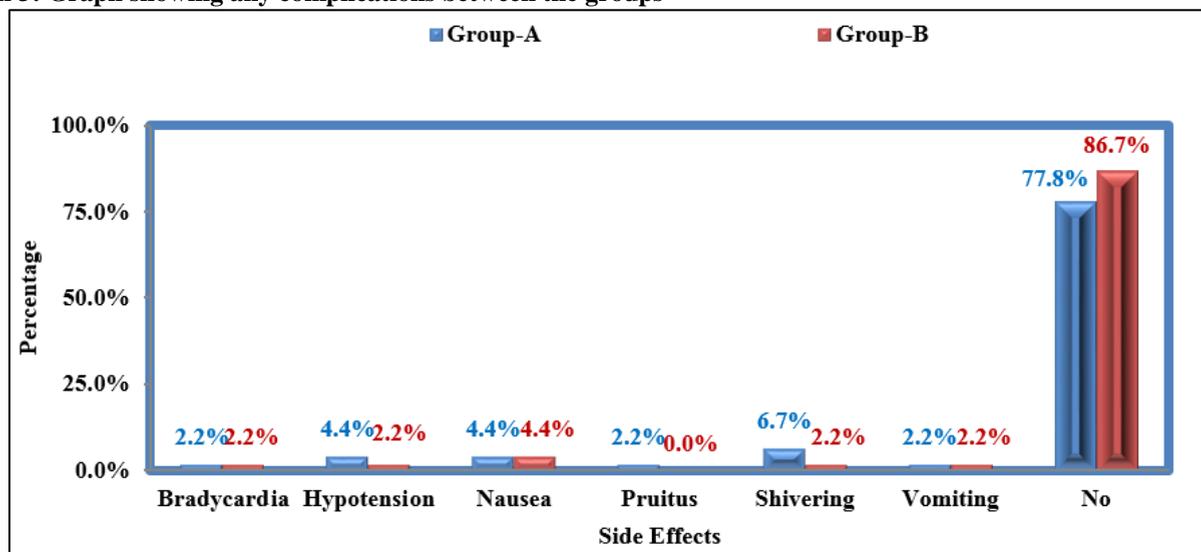
Variable	Group	Mean	SD	P-value
Duration of analgesia (min).	A	282.6	11.3	<0.001
	B	436.9	13.0	

Table 3: Table showing time of rescue analgesia between the groups

Variable	Group	Mean	SD	P-value
Rescue Analgesic (min) post test	A	277.6	11.4	<0.001
	B	431.0	13.5	

Table 4: Table showing duration of motor block between the groups:

Variable	Group	Mean	SD	P-value
Duration of Motor Block(min)	A	145.0	4.0	<0.001
	B	138.8	9.9	

Graph 3: Graph showing any complications between the groups

Discussion

Spinal anaesthesia is the most commonly used technique for infra umbilical surgeries because of its unmatched reliability, cost effectiveness, effective analgesia, muscle relaxation and prolonged postoperative analgesia. Recent advances in anesthesia has allowed more surgeries to be performed on day case basis. Levobupivacaine has been widely used in ambulatory surgeries after the development of low dose spinal anaesthesia technique. To improve the block characteristics of intrathecally administered low dose local anaesthetics, addition of adjuvant is must. Intrathecal opioids enhance sensory block without prolonging motor and sympathetic block. Local anaesthetics work by inhibiting voltage-gated sodium channels in the spinal cord by interfering with afferent and efferent sensory and motor impulses while intrathecal opioids activate opioid receptors in the dorsal gray matter of the spinal cord (substantia gelatinosa) to modulate the function of afferent pain fibers.⁸ A number of adjuvants have been added to the intrathecal local anaesthetics for supplementation of intraoperative

anaesthesia and postoperative analgesia. They have advantages as they reduce the dose of local anaesthetic; provide long lasting postoperative analgesia with reduced incidence of central nervous system depression, motor effects or hypotension.⁷

Opioid analogues have been used as additive to bupivacaine in spinal anaesthesia to improve the onset of action, quality of intraoperative and postoperative analgesia and to prolong the duration of block. Fentanyl is a potent synthetic opioid agonist and nalbuphine is a synthetic opioid agonist-antagonist analgesic. Some of intrathecal opioid absorbs back in the blood stream and produces analgesia by stimulating opioid receptors at brain level. Degree of this absorption is mainly determined by lipophilicity of the drug. Highly lipid soluble opioids like fentanyl or sufentanyl diffuse into blood stream quickly compared to less lipophilic morphine therefore producing short duration of analgesia.⁹ Highly hydrophilic opioids such as morphine, though provides very good intra and postoperative analgesia, its use becomes limited because of delayed

respiratory depression that it causes due to rostral spread in intrathecal space.¹⁰

The present study was a randomized, prospective and double blind clinical study, done in 90 patients belonging to the age group of 20-60 year female patients of ASA grade I and II undergoing for infra umbilical surgeries. It was designed to compare the effects of adding intrathecal nalbuphine and fentanyl as an adjunct to levobupivacaine in spinal anaesthesia by assessing the motor blockade characteristics and duration of postoperative analgesia. There are limited data on comparison of spinal effects of nalbuphine and fentanyl.⁹

Fentanyl acts by binding with opioid receptors in the dorsal horn of spinal cord and may also have its action via supra spinal spread when given intrathecally and has been used as an adjuvant to local anaesthetics in subarachnoid block. It reduces both visceral and somatic pain but its use is now limited due to dose dependent adverse effects associated with it.^{11,12}

Singh H, et al¹³ in 1995, Biswas BN, et al¹⁴ in 2002, Khanna MS, et al¹⁵ in 2002 have chosen 25 micrograms of fentanyl as an additive to intrathecal hyperbaric bupivacaine in their studies. Hence in our study, we chose 25 micrograms of fentanyl as an additive to levobupivacaine.

Nalbuphine is a synthetic lipophilic opioid with agonist action at the kappa opioid receptor and antagonist at the mu receptor. Unlike morphine, it has a short duration of action due to its liposolubility and rapid plasma clearance⁹. Mechanism of analgesia is by its agonistic action on this receptor. It also stimulates kappa receptors. This inhibits release of neurotransmitter that mediates pain such as substance P. In addition it acts as post synaptic inhibitor on the interneuron and output neuron of spinothalamic tract which transports nociceptive information. It improves quality of block and offers prolonged and long lasting postoperative analgesia. It has low incidence of adverse effects known for other opioids (respiratory depression, nausea, vomiting, pruritus). It is also cost effective.¹⁶ There are only few studies available of central neuraxial administration of nalbuphine as intrathecal adjuvant, which concluded that nalbuphine significantly enhanced the sensory analgesia with minimal pruritus and respiratory depression.¹⁷

In our study mean duration of first rescue analgesic requirement in group A is at 285.97+₋8.8min & in group B is at 430.3+₋11.13min with p value of 0.001 (<0.05) which is statistically significant. And this is similar to study done by Gupta K, et al⁸ in which they compared intrathecal 0.5% hyperbaric bupivacaine 17.5 mg (3.5ml) with fentanyl 25 mcg and 0.5% hyperbaric bupivacaine 17.5mg (3.5ml) with nalbuphine 2mg in lower limb orthopaedic surgeries showing mean time for first analgesic requirement is at 278.74+₋29.67 min in FB group and in group NB is at 318.64+₋21.92 min with p value of 0.000(<0.05) which is statistically significant. And also similar to study done by Bisth, et al⁹ in which they compared the intrathecal 0.5% hyperbaric bupivacaine 15mg with fentanyl 25mcg (0.5ml) and 0.5% hyperbaric bupivacaine 15mg with nalbuphine

1mg in total abdominal hysterectomy surgeries in which they concluded that mean time for first rescue analgesic requirement in FB group is at 283.44+₋78.97 min and in NB group is at 460.78+₋77.98 min with p value of <0.001(<0.05) which is statistically significant

In our study mean duration of motor block in group A 145.0+₋4min & in group B 138.8+₋9.9 with p value of 0.001(<0.05) statistically significant which is similar to the study done by Gupta K, et al⁸ in which they compared the intrathecal bupivacaine with fentanyl (25mcg), nalbuphine 2mg, showing mean duration of motor blockade in FB group 141.63+₋18.05min and in BN group 183.26+₋21.92 min (p value 0.003), statistically significant.

The present study revealed no statistically significant difference in the cardiovascular parameters like mean heart rate, mean systolic blood pressure, mean diastolic blood pressure, mean arterial pressure, spO₂ and haemodynamic status and our study was comparable to Gupta K et al⁸ and Culebras X et al¹⁸ for haemodynamic parameters.

In the present study, two patients developed hypotension in group A and one patient in group B, this could be due to 0.5% isobaric levobupivacaine (15mg) in subarachnoid space producing hypotension rather than opioids. Nausea developed in 2 patients in each group, shivering developed in 3 patients in group A and one patient in group B, there was no significant statistical difference in the adverse events between the two groups.

Similar finding was seen in study done by Culebras X, et al¹⁸ comparing the 0.5% hyperbaric bupivacaine 15 mg with fentanyl 25mcg and 0.5% hyperbaric bupivacaine 15 mg with nalbuphine 1mg in lower abdominal surgeries. In fentanyl Group two patients developed hypotension and one had pruritus. Nausea was seen in two patients in either group. None developed respiratory distress. As far as side effects of intrathecal opioids were concerned in our study, patients in both groups had minimal side effects. No pruritus, respiratory depression, euphoria dysphoria, desaturation in both the groups.

Conclusion

Both the groups were equally efficacious with good intra operative conditions with haemodynamic stability however group B improves the quality of intra operative and postoperative analgesia with minimal side effects.

Conflict of Interest: None.

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