

# Study Protocol

## **Comparing the Effectiveness and Safety of Intrathecal Dexmedetomidine and Fentanyl as an Adjuvant to Isobaric Ropivacaine.0.75 % In Lower Abdominal Surgeries: A Study Protocol**

### **Abstract**

**Background:** Spinal anaesthesia is a form of local anaesthesia, wherein conduction block of nerve roots is done with the aid of injecting a small dose of local anaesthesia into the subarachnoid space via a lumbar puncture in left lateral position in midline at L3 L4 interface. Drug is given after confirming free flow of CSF. Local anaesthetics work for a short duration and adjuvants are used for prolongation of postoperative analgesia. Ropivacaine, a brand new amide local anaesthetic, accepted via FDA IN 1997 and using it extensively in India since 2009. Ropivacaine due to its excessive Pka and decreased lipid solubility has received popularity. This study has been planned to compare the effects of injection Dexmedetomidine & injection Fentanyl as an Adjuvant to Intrathecal isobaric Ropivacaine 0.75% for lower abdominal surgeries.

**Materials and Methods:** This will be a Comparative Experimental Prospective Study conducted at Anesthesiology department of AVBRH, Wardha. 80 patients will be randomized into two groups. One group will receive 3 ml of 0.75 percent isobaric ropivacaine with dexmedetomidine 10 mcg (Group RD). Another group will receive 20 mcg of fentanyl (Group RF) intrathecally for lower abdominal surgeries. Data on block characteristics, hemodynamic changes, and side effects will be collected and compared for the two groups.

**Expected Results:** Clinically significant results are expected in terms of mean time needed and Mean of total sensory block length in Group RD compared to Group RF.

**Conclusion:** Addition of 10µg dose of dexmedetomidine to 3ml of 0.75 percent isobaric ropivacaine produces earlier sensory blockade, prolonged sensory and motor blockade and improved sedation and post-operative analgesia.

**Keywords:** Dexmedetomidine, duration of block, fentanyl, isobaric ropivacaine, spinal anaesthesia

### **INTRODUCTION**

Spinal anaesthesia, a form of local anaesthesia, wherein conduction block of nerve roots is done with the aid of injecting a small dose of local anaesthesia into the subarachnoid space via a lumbar puncture in left lateral position in midline at L3 L4 interface. Drug is given after confirming free flow of CSF. (1) After Drug is given patient is placed in supine role immediately. Generally lignocaine, bupivacaine, and tetracaine belong to amide and ester linked local anaesthetics are generally used drugs for spinal anaesthesia. But, they have some side effects like central nervous system toxicity in addition to cardiovascular toxicity. Membrane associated proteins are voltage gated sodium (Na) channels that includes one

large subunit of alpha, through which Na ions move, and smaller  $\beta$  subunits, one or two. There are Na channels in three states: Resting nonconductive, open conductive and inactivated states. Local anaesthetics bind and inhibit a particular area of the alpha subunit, avoiding the activation of the Na channel **influx.**(2)

**Local clinical anesthetic potency correlates with octanol solubility. The capacity of the local anaesthetic molecule to penetrate lipids varies with membranes. Potency is enhanced by the addition of large groups of alkyl molecule. Local anaesthetic is not clinically measured.**(3)

**The onset of action depends on several** variables, including lipid solubility and water solubility. The nonionized, more lipid soluble free base form (B) and the more water soluble ionised form (BH<sup>+</sup>) expressed by pKa. The pKa is the pH at which there is an equivalent of fraction of a substance that is ionised and nonionized. Less potent, less lipid soluble agents like lidocaine or mepivacaine have a quicker onset than more potent, more lipid soluble agents like ropivacaine or bupivacaine.

The spinal canal comprises the spinal cord with its coatings (meninges), venous plexus and fatty tissue. The meninges consist of three layers: pia mater, arachnoid mater, and dura mater are all contiguous layers with their cranial equivalents. The pia mater is adhesive to spinal canal whereas the arachnoid material is adhesive to the thicker and denser dura mater. There is **Cerebrospinal fluid (CSF) between the pia mater and the arachnoid mater.**

**The lower nerve roots of the spinal cord usually end at L1, some distance before leaving the intervertebral foramina. The cauda equina forms these lower spinal nerves ("tail of a horse") Thus, carrying out a lumbar puncture in an adult below L1 normally avoids the possible Spinal cord trauma damage to the cauda equina since these nerves roots float below L1 in the dural sac and will be pulled away than pushing away.**(4)

Ropivacaine, a brand new amide local anaesthetic, accepted via FDA IN 1997 and using it extensively in India since 2009 .Ropivacaine due to its excessive Pka and decreased lipid solubility has received popularity.

Ropivacaine has less cardiovascular toxicity and central nervous system toxicity and has fast recovery. Ropivacaine additionally also belongs to pipercoloxylidide group. The efficacy and protection of intrathecal administration of plain and hyperbaric solutions of ropivacaine have been evaluated in different surgeries, including orthopedic and urologic surgeries. Ropivacaine blocks A $\delta$  & C (pain fibers) extra level compared to A $\beta$  (motor fibers) mainly to decrease postoperative motor blockade and for that reason early ambulation of the patients. Because of shorter length of sensory and motor block if the surgical procedure prolongs or the exceptional of motor **blockade is poor. Due to those drawbacks adjuvants are usually added to ropivacaine.**

**Alpha 2 adrenergic agonists** have each analgesic and sedative actions. In addition, they potentiate the effect of local anaesthetics when used as an adjuvant in local anaesthesia, and reduce the necessary doses.(5)

Dexmedetomidine is a more selective adrenoceptor alpha2 agonist that has hypnotic, sedative, anxiolytic, sympatholytic, opioid sparing and analgesic properties without producing significant respiratory depression. It works by inhibiting norepinephrine release at the locus coeruleus. Small doses of dexmedetomidine used in combination with spinal ropivacaine

result in shorter motor block and longer duration of sensory & motor block with retained hemodynamic stability and limited side effects.

Via direct N-glucuronidation and cytochrome P-450 (CYP 2A6) mediated aliphatic hydroxylation to inactive metabolites, dexmedetomidine undergoes almost complete biotransformation. In urine about 95 percent and in faeces 4 percent, metabolites are excreted. Dose changes are needed in patients with hepatic failure due to a lower rate of metabolism(6).

Fentanyl is a phenylpiperidine derivative synthetic opioid agonist has proven to enhance the analgesic efficacy of ropivacaine for spinal anesthesia. In spinal anaesthesia, fentanyl plus ropivacaine increases the duration of analgesia in the postoperative period Fentanyl is metabolized extensively by N-Demethylation, nor-fentanyl producing, hydroxy proprionyl fentanyl, and hydroxy proprionyl norfentanyl (7). Norfentanyl is similar structurally to Normeperidine and is the primary fentanyl metabolite in humans. That is excreted by the kidneys and can be observed for 72 hours after a period of time in the urine after single IV fentanyl dose. 10% fentanyl is excreted unchanged in the urine

It is believed that the pharmacologic function of fentanyl metabolites is Minimal. Fentanyl is a hepatic P450 enzyme (CYP3A) substrate and is Susceptible to interactions with drugs that indicate interference with the activity of enzymes.

The present study will be conducted for comparison of the effects of injection Dexmedetomidine & injection Fentanyl as an Adjuvant to Intrathecal isobaric Ropivacaine 0.75% for lower abdominal surgeries."

### **Aim and Objectives:**

#### **AIM**

The aim of the study is to compare the effectiveness and safety about Dexmedetomidine (10mcg) injection and fentanyl(20mcg) injection when given intrathecal as an adjuvant to isobaric ropivacaine.0.75 percent in patients undergoing lower abdominal surgery

#### **OBJECTIVES OF STUDY**

Primary outcome measures:

- Onset and duration of analgesia of sensory & motor blockade.

Secondary outcome measures:

- 2 segment Regression of sensory blockade
- Level of sedation
- Hemodynamic stability
- Postoperative analgesia as measured by VAS SCORE • Side effects ,if any

(Hypotension, Bradycardia, Nausea, Vomiting, Pruritus)

## **MATERIALS AND METHODS**

### **STUDY DESIGN:**

- Study period : 3 years
- Study area: Department of Anaesthesiology JNMC & AVBRH.
- Research design : Comparative Experimental Prospective Study
- Study population : Adult patients, 18 – 50 years of age

### **SETTING:**

The study will be conducted after approval of the ethics and screening committee of Jawaharlal Nehru Medical College, DMIMS (DU), Acharya Vinoba Bhave Rural Hospital (AVBRH), Datta Meghe Institute of Medical Sciences, Sawangi (M), Wardha. Written and informed consent will be taken by the patients prior to procedure.

### **PARTICIPANTS:**

#### **INCLUSION CRITERIA:**

- ASA I – II who will undergo lower abdominal surgeries
- Both males and females
- Age group 18yrs- 50yrs

#### **EXCLUSION CRITERIA:**

- Patients refusal
- Known allergy to Ropivacaine, Dexmedetomidine, Fentanyl.
- Local site infection
- ASA > grade III
- Hepatic or renal dysfunction
- Cardiac or respiratory problems,
- High abnormal prothrombin time (PT) or activated partial thromboplastin time (aPTT)
- Coagulopathy disorders
- Thromboembolic diseases
- Any malignant disease
- Patients aged below 18 years or above 50 years of age

#### **DATA SOURCE/ MEASUREMENTS**

Data source: AVBRH, Sawangi Meghe, Wardha.

Data measurement:

Hemodynamic parameters : HR, SpO<sub>2</sub>, Systolic bp, Diastolic bp, MAP

- Two segment Regression of sensory blockade
- Sedation level
- Hemodynamic variability
- Postoperative analgesia by VAS SCORE
- MATERIALS REQUIRED:

Drugs –Ropivacaine, dexmedetomidine fentanyl

SAMPLING SIZE & TECHNIQUE:

After the approval from the institutional ethics committee, the study will be conducted on 80 adult patients of both genders after fulfilling all inclusion and exclusion criteria.

Group RD(n=40) 3ml of Injection isobaric Ropivacaine 0.75% and injection Dexmedetomidine 10mcg plus 0.3ml Normal saline.

Group RF(n=40) 3ml of Injection isobaric Ropivacaine 0.75% and Injection Fentanyl 20 mcg .

#### **SAMPLE SIZE:**

Sample size is calculated using open EPI. com by keeping power 80 and alpha 0.05 and mean time for sensory block at t<sub>10</sub> as 156.46 +or- 33.78s and a mean difference of 15 percent . The sample size is 38 in each group which is rounded of to 40.

#### **STUDY PROCEDURE**

Pre-operative:

All patients will undergo a pre-anaesthetic checkup a day before the procedure. Basic patient details, history and presenting complaints of the illness, general and systemic examination and basic blood and lab investigations will be noted. Patients will be informed about study purpose, its merits and demerits. Prior written consent will be taken from each patient that will be included in the study. They will be asked to maintain a fasting status at least 8 hours prior to surgery.

Patients for the study will be randomly allocated in to 2 groups. 1 group of 40 patients will be receiving 3ml of Isobaric Ropivacaine 0.75% and injection Fentanyl 20mcg will be designated as group RF. The second group of 40 patients will be receiving 3ml of Isobaric Ropivacaine 0.75% with 10mcg Dexmedetomidine plus 0.3ml normal saline. This group will be designated as group RD.

#### **RESULTS AND DISCUSSION**

Intra-operative:

Standard monitoring will be done with ECG, pulse oximeter and automatic sphygmomanometer. The baseline parameters heart rate, respiratory rate, noninvasive BP and before the procedure, SpO<sub>2</sub> will be recorded. The 18G IV cannula will be used for peripheral venous cannulation and everyone will be preloaded with 10 ml/kg ringer lactate solution under all aseptic precautions.

Sub arachnoid block will be given with 25 G Quinke's needle by midline approach in midline in left lateral position at the L3-4 interspace after confirming free flow of CSF the drug will be given over approximately 10-15 seconds and patient will be given supine position immediately.

The following parameters will be recorded.

- 1) Sensory and motor blockage onset.
- 2) It will record the overall degree of sensory blockade achieved and the time taken for the same.
- 3) It will record the overall degree of motor blockade achieved and the time taken for the same.
- 4) Regression period of sensory blockade in two segments.
- 5) Total motor blockade time.
- 6) Level of RAMSAY SCALE sedation
- 7) (VAS SCORE) Quality of Analgesia
- 8) Time to first rescue analgesia
- 9) Adverse effects if any.

Using the pin prick method with a blunt tipped needle, sensory blockade will be tested every 2 minutes until surgical anaesthesia is achieved at the T10 dermatoma level.

The motor blockade quality will be evaluated by the modified Bromage scale.

### **Statistical Methods**

Statistical analysis may be conducted using descriptive statistics, i.e. mean, standard deviation, standard mean error, and unpaired t test students using inferential statistics such as chi-square test. All outcomes will be checked at a significance level of 5 percent.

### **EXPECTED OUTCOME/RESULTS**

At a dosage of 10 µg, dexmedetomidine is added to 3ml of 0.75% isobaric ropivacaine will provide Earlier sensory blockade, enhanced Sensory and Motor blockade for Patients with improved analgesia in spinal anaesthesia in Lower abdominal surgeries, dexmedetomidine 10 µg added to 3ml of 0.75% Isobaric Ropivacaine provided earlier Sensory Blockade, Prolonged

duration of Sensory and Motor Blockade for Patients with better analgesia under Spinal Anesthesia for Lower Abdominal Surgeries .

LIMITATIONS-Only ASA Class one and two patients were included., invasive monitoring of hemodynamic parameters to see the effect on Systemic vascular resistance and cardiac output is not done.

## DISCUSSION

The effect of intrathecal dexmedetomidine an adjuvant to Isobaric ropivacaine was studied by Gupta et al in two groups. The Groups are compared in age, height, weight, physical status. In the type and duration of surgery, there was no major difference. There was no difference in the overall block level (T5 and T6 respectively) or peak time ( $11.65 \pm 1.73$  and  $12.05 \pm 1.64$  minutes respectively) between groups D and R. With the addition of intrathecal dexmedetomidine, block regression was slightly slower compared to ropivacaine alone, since both groups were two section regressions. There was considerably more time for S2 regression with Intrathecal dexmedetomidine.

The VAS score in group D was lower till 24 hours postoperatively, relative to group R. With the addition of dexmedetomidine, the time of analgesia was substantially increased relative to Ropivacaine alone. In the 60 patients in the study, Nausea, Vomiting, Shivering, Itching, Pruritus, sedation, Respiratory Depression, and Hypo tension are not significant complications.

Elattar et. al. and Safari et al. has added additives to bupivacaine, compared intrathecal dexmedetomidine and fentanyl. They found that with respect to the initiation of motor blockade, intrathecal dexmedetomidine and fentanyl had statistically important significance. Their finding was that motor block has a quicker onset of intrathecal dexmedetomidine than fentanyl.

Mahendru ETAL intrathecal Dexmedetomidine, Clonidine, and Fentanyl were compared as adjuvants to Hyperbaric Bupivacaine for Lower Limb Surgery. They found that in both classes, the maximum height of the sensory block reached was T6 when dexmedetomidine and fentanyl were added as adjuvants.

Different doses and concentrations of intrathecal ropivacaine were compared in a study performed by McNamee et. al. and compared to intrathecal administration of 7.5 mg/ml (18.75 mg) of ropivacaine, the reduction time to T10 and the duration of the total motor block were longer with 10 mg/ml (25 mg) of intrathecal ropivacaine.

In a study conducted by McNamee et al.(4), different doses and concentrations of intrathecal ropivacaine are compared with 7.5 mg/ml the reduction time to T10 and duration of the total motor block are longer with intrathecal ropivacaine at 10 mg/ml (25 mg)(8). Some more studies related to similar anesthetic drugs were reported (9-14).

**Conclusion:**

The 10µg dose of dexmedetomidine added to 3ml of 0.75 percent isobaric ropivacaine produce earlier sensory blockade, prolongs sensory and motor blockade and improves sedation and post-operative analgesia under spinal analgesia in lower abdominal surgeries.

#### **COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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