Review Form 1.6

Journal Name:	**Journal of Pharmaceutical Research International**
Manuscript Number:	**Ms_JPRI_80803**
Title of the Manuscript:	**Comparing the Effectiveness and Safety of Intrathecal Dexmeditomidine and Fentanyl as an Adjuvant to Isobaric Ropivacaine.0.75 % In Lower Abdominal Surgeries: A Study Protocol**
Type of the Article	**Study Protocol**

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PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments	- Where improvements are needed, a recommendation for major revision is typical. - I am ready to do the post-revision review too. -Review title as first. -Add name of author, affiliation, qualifications abbreviations after title -the English is understandable but the paper has some typographical and grammatical errors -Add any conflict of interest -Add any acknowledgements -Add any sponsorship or financial support - Keep images, graphs and data tables in clear view at end of article - You need to check referencing for accuracy, adequacy and balance. -limit research article to maximum 1000 words. -add more keywords.	
Minor REVISION comments	- Good research, worthy for study - the Abstract highlights the important findings of the review of fertilizers. -the tables or figures, aid understanding and superfluous - the research Is relevant and interesting - good sampling in analytical papers -clarify the validity of questions, the use of a detailed methodology and the data analysis being done systematically (in qualitative research) - good reviews of all types and modalities of fertilizers used for agriculture in India - the paper's premise is interesting and important - the methods used are appropriate - the data support the conclusions	
Optional/General comments	**ARTICLE AFTER Grammar corrections: -** 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 anesthesia is a form of local anesthesia, wherein conduction block of nerve roots is done with the aid of injecting a small dose of local anesthesia into the	

	subarachnoid space via a lumbar puncture in the left lateral position in the midline at the L3 L4 interface. The drug is given after confirming the free flow of CSF. Local anesthetics work for a short duration and adjuvants are used for the prolongation of postoperative analgesia. Ropivacaine, a brand new amide local anesthetic, was 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 the 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: The addition of a 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 the block, fentanyl, isobaric ropivacaine, spinal anesthesia INTRODUCTION Spinal anesthesia, a form of local anesthesia, wherein conduction block of nerve roots is done with the aid of injecting a small dose of local anesthesia into the subarachnoid space via a lumbar puncture in the left lateral position in the midline at the L3 L4 interface. The drug is given after confirming the free flow of CSF. (1) After the Drug is given patient is placed in a supine role immediately. Generally, lignocaine, bupivacaine, and tetracaine belong to amide and ester-linked local anesthetics are generally used drugs for spinal anesthesia. 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 include one large subunit of alpha, through which Na ions move, and smaller β subunits, one or two. There are Na channels in three states: Resting nonconductive, open conductive, and inactivated states. Local anesthetics 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 anesthetic molecule to penetrate lipids varies with membranes. Potency is enhanced by the addition of large groups of alkyl molecules. Local anesthetic 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 ionized form (BH+) expressed by pKa. The pKa is the pH at which there is an equivalent of a fraction of a substance that is ionized 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 the 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 anesthetic, was accepted via FDA IN 1997 and used 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 a	

	fast recovery. Ropivacaine additionally also belongs to pipecoloxylidide 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 Aδ & C (pain fibers) extra level compared to Aβ (motor fibers) mainly to decrease postoperative motor blockade and for that reason early ambulation of the patients. Because of the shorter length of sensory and motor block if the surgical procedure prolongs or the exceptional of the 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 anesthetics when used as an adjuvant in local anesthesia, 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 a 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 feces 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 that has proven to enhance the analgesic efficacy of ropivacaine for spinal anesthesia. In spinal anesthesia, 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 nor fentanyl (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 some time in the urine after a 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 study aims to compare the effectiveness and safety of Dexmedetomidine (10mcg) injection and fentanyl(20mcg) injection when given intrathecally 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 before the 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, SPo2, 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 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 Ropivacaine0.75%and injection Dexmeditomidine 10mcg plus 0.3ml Normal saline. Group RF(n=40) 3ml of Injection isobaric Ropivacaine 0.75% and Injection Fentanyl 20 mcg. SAMPLE SIZE: The sample size is calculated using open EPI. com by keeping power 80 and alpha 0.05 and meantime for the sensory block at t10 as 156.46 +or- 33.78s and a mean difference of 15 percent. The sample size is 38 in each group which is rounded to 40. STUDY PROCEDURE Pre-operative: All patients will undergo a pre-anesthetic 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 the study purpose, its merits, and its 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 before surgery. Patients for the study will be randomly allocated into two 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 Dexmdeitomidine 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, SpO2 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.
The subarachnoid block will be given with 25 G Quincke's needle by midline approach in the 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 the 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 pinprick method with a blunt-tipped needle, the sensory blockade will be tested every 2 minutes until surgical anesthesia is achieved at the T10 dermatome 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 the chi-square test. All outcomes will be checked at a significance level of 5 percent.

EXPECTEDOUTCOME/RESULTS
At a dosage of 10 µg, dexmedetomidine is added to 3ml of0.75% isobaric ropivacaine will provide Earlier sensory blockade, enhanced Sensory and Motor blockade for Patients with improved analgesia in spinal anesthesia 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±1.73 and 12.05±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 Hypotension are no significant complications. Elattar et. al. and Safari et al. have added additives to bupivacaine, compared intrathecal

dexmedetomidine and fentanyl. They found that concerning 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 intrathecalropivacainearecomparedwith7.5mg/ml reduction time to T10 and the 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 used products in our area of research and country. There is 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 the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

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PART 2:

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Are there ethical issues in this manuscript?	*(If yes, Kindly please write down the ethical issues here in details)*	

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