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# A Comparative Study of Intrathecal Clonidine and Intrathecal Buprenorphine as Adjuvant to 0.5% Bupivacaine for Spinal Anaesthesia in Infraumbilical Surgeries

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**Abstract:**
The most widely used local anesthetic for spinal anesthesia are hyperbaric bupivacaine and tetracaine. The most important determinants of level of block are baricity of local anesthetic, position of patient during and immediately after injection and drug dosage. However the duration of anesthetic action of bupivaine is short so adjuvant is required to prolong the effect.Neuroaxially administered opioids and α2 agonists exihibit synergism. They prolong the regression of sensory block, prolong the time to first request of an analgesic and prolong the duration of complete motor block.Total 60 patients were divided by simple randomization technique using computer generated random number list into two groups of 30 each. Patients in group C received 3ml of 0.5% hyperbaric Bupivacaine + 45 µg of clonidine in 0.2 ml normal saline, total volume is 3.5 ml. Patients in group B received 3ml of 0.5% hyperbaric Bupivacaine + 90 µgm of buprenorphine in 0.2 ml normal saline, total volume is 3.5 ml.Intrathecal buprenorphine 90 µg gives adequate analgesia as the mean time required for first rescue analgesia in Group B was 5.87 ± 1.14 min, which is significantly longer than that of intrathecal clonidine 45 µg, i.e., 4.47 ± 0.86 minutes.. Quality of analgesia was acceptable to patients. Administration of buprenorphine and clonidine intrathecally does potentiate the duration of analgesia, sensory and motor block. The study suggests that combination of two or more drugs from different group (e.g., opioid and α2 agonist) can give better analgesia and less chance of side effects.

## INTRODUCTION

Spinal anesthesia is safe and effective technique alternative to general anesthesia when the surgical site is located in lower extremities, perineum or lower abdominal wall. Spinal anesthesia can be used as sole source of anesthesia. It produces intense sensory and motor blockade as well as sympathetic blockade. It also provides additional benefits like reduction in incidence of venous thrombosis, pulmonary embolism, cardiac complications in high risk patients, respiratory depression, bleeding and transfusion requirement
The first spinal analgesia was administered in 1885 by James Leonard Corning (1855–1923), a neurologist in New York [1]. He was experimenting with cocaine on the spinal nerves of a dog when he accidentally pierced the dura mater. The first planned spinal anaesthesia for surgery in human was administered by August Bier (1861–1949) on 16 August 1898, in Kiel, when he injected 3 ml of 0.5% cocaine solution

into a 34-year-old laborer. After using it on 6 patients, he and his assistant each injected cocaine into the other's spine[2]. They recommended it for surgeries of legs, but gave it up due to the toxicity of cocaine. Since then there have been many changes in spinal anesthesia. After discovery of amide local anaestheyics , spinal anaesthesia has been revolutionized as they are long acting and safer drug. Since 1949, lignocaine had been the main agent but after reporting of Cauda equina syndrome it became less popular.

The most widely used local anesthetic for spinal anesthesia are hyperbaric bupivacaine and tetracaine. The most important determinants of level of block are baricity of local anesthetic, position of patient during and immediately after injection and drug dosage. However the duration of anesthetic action of bupivaine is short so adjuvant is required to prolong the effect.

A wide variety of drugs have been used for both neuraxial and peripheral nerve blocks. It is broadly divided into non-opioids and opioids, with non-opioids being epinephrine, $\alpha_2$-adrenoceptor agonists (clonidine and dexmedetomidine), acetylcholine esterase inhibitors (neostigmine), adenosine, ketorolac, midazolam, magnesium, sodium bicarbonate and hyaluronidase, and opioids being lipophilic (fentanyl and sufentanyl) and hydrophilic (morphine).

Buprenorphine is semisynthetic opioid. It is thebaine derivative with powerful mu agonist action and partial antagonist action .Its intrathecal doses are smaller. Because of it highly lipophilic nature it produces prolonged and profound analgesia .It doesn't cause addiction or physical dependence . Adverse effects associated with fully agonist (morphine) like nausea , vomiting and constipation are less with buprenorphine.

Clonidine is selective partial α2 receptor agonist which acts by reducing norepinephrine release from sympathetic preganglionic neuron. Thus overall effects are analgesia, hypotension, bradycardia and sedation. Spinal clonidine causes 30% prolongation of sensory and motor block of local anaesthetic. Its intrathecal dose ranges from 10 to 50 µg. Abrupt withdrawal of clonidine after surgery causes rebound hypertension due to release of catecholamines, so it should be withdrawn slowly.

Neuroaxially administered opioids and α2 agonists exihibit synergism. They prolong the regression of sensory block, prolong the time to first request of an analgesic and prolong the duration of complete motor block . The stable hemodynamic and the decreased oxygen demand due to enhanced sympathoadrenal stability make them very useful pharmacologic agents.

## AIMS AND OBJECTIVES

### AIM

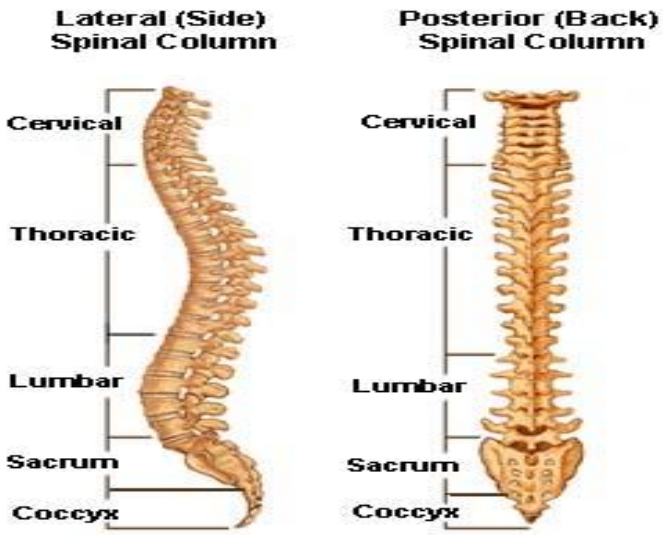
To compare the efficacy and safety of intrathecal buprenorphine vs intrathecal clonidine as an adjuvant to 0.5%bupivacaine in infraumbilical surgeries.

### OBJECTIVES

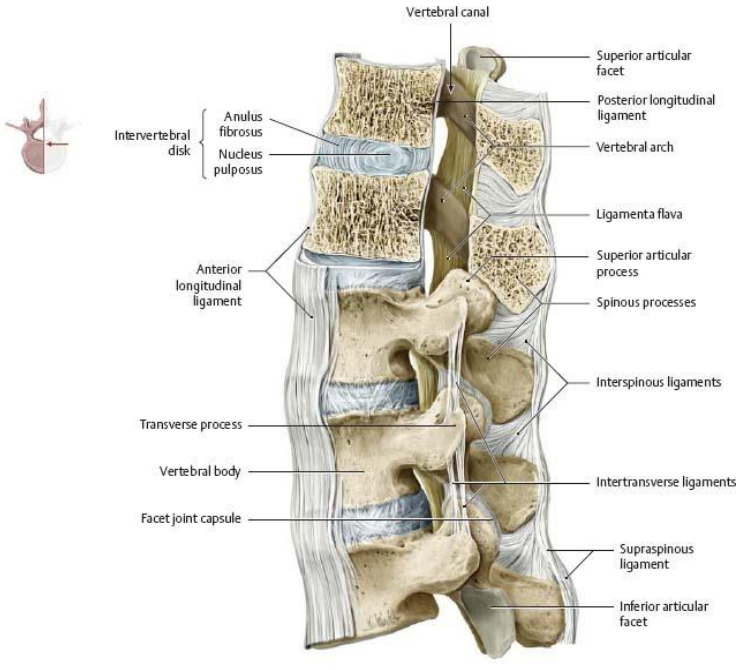
1. Onset and duration of analgesia.
2. Onset and duration of sensory blockade.
3. First feeling of pain/rescue analgesia.
4. Onset and duration of motor blockade.
5. Hemodynamic parameters- heart rate, blood pressure and $spO_2$.
6. Time to two segmental dermatomal regression.
7. Complications

## FUNCTIONAL ANATOMY OF SPINAL BLOCKADE

The vertebral column consists of 33 vertebrae and three curves. The vertebraes are - 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal segments. The cervical and lumbar curves are convex anteriorly, and the thoracic curve is convex posteriorly. The vertebral column curves, along with gravity, baricity of local anesthetic, and patient position, influence the spread of local anesthetics in the subarachnoid space.




There are 5 ligaments which hold the spinal cord together which are supraspinous ligament, interspinous ligament, ligamentum flavum, anterior and posterior longitudinal ligament. The supraspinous ligaments connect the apices of the spinous processes from the seventh cervical vertebra (C7) to the sacrum. The supraspinous ligament is known as the ligamentum nuchae in the area above C7. The interspinous ligaments connect the spinous processes together. The ligamentum flavum, or yellow ligament, connects the laminae above and below together. Finally, the posterior and anterior longitudinal ligaments bind the vertebral bodies together.



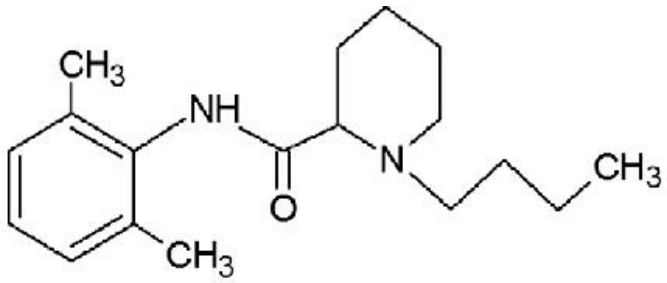
Spinal cord is protected by three membranes which are dura mater, arachnoid mater and pia mater. The dura mater is the outermost layer. The dural sac extends to the second sacral vertebra (S2). The arachnoid mater is the middle layer, and the subdural space lies between the dural mater and arachnoid mater. The arachnoid mater ends at S2. The pia mater ends in the filum terminale, which helps to hold the spinal cord to the sacrum. The space between the arachnoid and pia mater is known as the subarachnoid space, and spinal nerves run in this space, as does CSF.

The length of the spinal cord varies according to age. In the first trimester, the spinal cord extends to the end of the spinal column, but as the fetus ages, the vertebral column lengthens more than the spinal cord. At birth, the spinal cord ends at approximately L3. In the adult, the terminal end of the cord lies at approximately L1.

While giving subarachnoid block by midline approach the anatomical layers that are pierced are skin, subcutaneous fat, supraspinous ligament, interspinous ligament, ligamentum flavum, dura mater, subdural space, arachnoid mater, and finally the subarachnoid space. When the paramedian technique is applied, the spinal needle should traverse the skin, subcutaneous fat, paraspinous muscle, ligamentum flavum, dura mater, subdural space, and arachnoid mater and then pass into the subarachnoid space.

**PHARMACOLOGY**

**BUPIVACAINE-**




Bupivacaine hydrochloride is 2-Piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-,monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. Bupivacaine hydrochloride is related chemically and pharmacologically to the aminoacyl local anesthetics[3]. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Each mL of Bupivacaine Hydrochloride in Dextrose Injection contains 7.5 mg bupivacaine hydrochloride (anhydrous) and 82.5 mg dextrose (anhydrous). The pH of this solution is adjusted to between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The specific gravity is between 1.030 and 1.035 at 25°C and 1.03 at 37°C and it does not contain any preservatives.

Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. Clinically, the order of loss of nerve function is pain, temperature, touch, proprioception and skeletal muscle tone.[4]

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems . At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic

blood concentrations may lead to atrioventricular block, ventricular arrhythmias and cardiac arrest. Local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

**PHARMACOKINETICS**

The rate of systemic absorption of bupivacaine depends on the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. The onset of sensory blockade following spinal block with Bupivacaine Hydrochloride in Dextrose Injection is very rapid (within one minute); maximum motor blockade and maximum dermatome level are achieved within 15 minutes in most cases. Bupivacaine Hydrochloride with a high protein binding capacity has a low fetal/maternal ratio(0.2 to 0.4)[5,6]

Pharmacokinetic studies on the plasma profiles of Bupivacaine Hydrochloride after direct intravenous injection suggest a three-compartment open model[7]. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

Amide-type local anesthetics such as Bupivacaine Hydrochloride are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecolylxylidine is the major metabolite of Bupivacaine Hydrochloride.

**ADVERSE REACTIONS-**

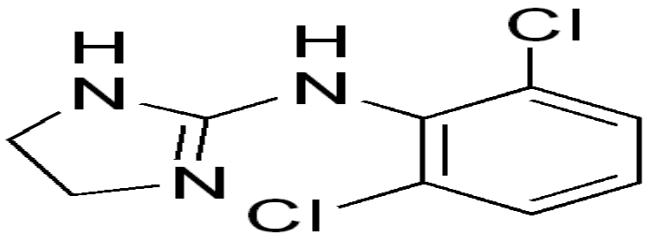
Systemic and localised adverse effects of local anaesthetic drugs usually occur because of excessive dosage, rapid absorption or inadvertent intravascular injection. All local anaesthetics can cause central nervous system toxicity and cardiovascular toxicity if their plasma concentrations are increased by accidental intravenous injection or an absolute overdose.

**CENTRAL NERVOUS SYSTEM TOXICITY-** Excitation of the CNS may be manifested by numbness of the tongue and perioral area, and restlessness, which may progress to seizures, respiratory failure and coma. Bupivacaine is the local anaesthetic most frequently associated with seizures. Treatment of CNS toxicity includes maintaining adequate ventilation and oxygenation, and controlling seizures with the administration of thiopental sodium or benzodiazepines.

**CARDIOVASCULAR TOXICITY-** It begins after signs of CNS toxicity have occurred. Bupivacaine and etidocaine appear to be more cardiotoxic than most other commonly used local anaesthetics. Sudden onset of profound bradycardia and asystole during neuraxial blockade is of great concern and the mechanism remains largely unknown. Treatment of cardiovascular toxicity depends on the severity of effects. Cardiac arrest caused by local anaesthetics should be treated with cardiopulmonary resuscitation procedures, but bupivacaine-induced dysrhythmias may be refractory to treatment.

The AAGBI( Association of Anaesthetists of Great Britain ) recommended Intravenous lipid emulsion or Intralipid regimen following cardiac arrest from local Anesthetics systemic toxicity involves a large initial intravenous bolus injection of 20% lipid emulsion at 1.5 mL/kg over 1 minute; followed by an infusion of 15 mL/kg/h. Cardiopulmonary resuscitation should be continued throughout. In the absence of return of spontaneous circulation or deterioration after 5 minutes, two further boluses (1.5 mL/kg) may be given at 5-minute intervals. The intravenous infusion rate should also be doubled to 30 mL/kg/hr. A maximum of three boluses can be given, and a cumulative dose of 12 mL/kg should not be exceeded. The ASRA (American Society of **Regional Anesthesia** and Pain Medicine )guidelines differ in that only one additional bolus is recommended, and the infusion should continue for 10 minutes after haemodynamic stability is reached, with a maximum dose of 10 mL/kg over 30 minutes [8].

**CLONIDINE-**



Clonidine is an imidazole compound, alpha-adrenergic agonist with selectivity for alpha-2 receptors[9] . Although it is known for long time, clonidine, an alpha-2-agonist drug, was used for the first time in human for anesthetics aims only in 1984, epidurally [10]. Since then, several clinical trials, reviews and clinical practice have demonstrated many benefits from the association of clonidine to other anesthetic drugs systemically, spinally or epidurally, with relative safety [11-21]. 50% of it is metabolized in liver in inactive form and other 50% is eliminated in unchanged form by kidney. The elimination half-life when administrated by intravenously is from 6 to 23 hours, depending on kidney function. It has great lipossolubility and crosses the blood brain barrier with no difficulties[22] . The elimination half-life for the spinal administration is 1-5 hours [11] .

**MECHANISM OF ACTION-**

Alpha-2-agonists receptors are present in the terminal primary afferent (spinal and peripheral), in spinal superficial lamina neurons and in the supra-spinal nuclei (locus ceruleus)[23] .Thus clonidine and other alpha-2-agonists have analgesic actions on the three sites of sensitive afferents: peripheral, spinal and brain. Clonidine may increase the effect of local anesthetics in peripheral nerve blocks, by action on C and Aδ fibers, decreasing the conduction on those fibers, because of increase of trans-membrane potassium conductance, and through vasoconstrictor effect (alpha1-adrenergic effect), which reduces local anesthetics wash-out from perineural tissues[23-25]. It acts on alpha-2 receptors and inhibits the adenylcyclase enzyme, reducing intracellular AMPc, leading to a hyperpolarization membrane state[26]. Inhibition of calcium voltage-dependent channels is another secondary action mechanism of clonidine[22] . Clonidine has a selective affinity to alpha-2 receptor 220 higher than its affinity to alpha-1 receptor[11].

**SYSTEMIC EFFECTS-**

**CARDIOVASCULAR SYSTEM-**

Clonidine has central and peripheral mechanisms for cardiovascular effects. On solitary tract nuclei and on locus ceruleus, the alpha-2 receptors activation reduces the sympathetic tonus, with inhibition of

noradrenaline release on the synaptic junctions, leading to bradycardia and low blood pressure effects[27]. The alpha-2 pre-synaptic receptors on peripheral nerves reduces the noradrenaline exocytosis. In the other hand, post-synaptic alpha-2 receptors stimulation, on endothelium, leads to vasoconstriction, and may cause transitory high blood pressure right after intravenous injection of clonidine[28] . As clonidine is a non-specific selective alpha-2 agonist, in high doses (450µg, spinal, for example), it may increase blood pressure. This is due to the fact that this drug, in less proportion, also is an alpha-1 agonist[29].

**RESPIRATORY SYSTEM-**

Alpha-2 agonist do not induce deep respiratory depression, even in high doses, nor potentiate respiratory depression caused by opioids[30]. It can reverse the muscle stiffness induced by fentanyl, alfentanil, sufentanil and remifentanil[31].

**CENTRAL NERVOUS SYSTEM-**

Sedation is frequent with clonidine use, in accordance with the sedative and anesthetic-sparing properties that alpha-2- agonists present, mainly due to the action of these drugs on the receptors of the locus ceruleus[20].

**RENAL SYSTEM-**

Alpha-2-adrenergic receptors induce diuretic and natriuretic effects in the renal system. Alpha-2 agonist drugs also inhibit the release of the antidiuretic hormone and antagonize its action in the renal tubule. Unlike opioids, they do not present a urinary retention effect[32,33].

**ENDOCRINE SYSTEM-**

Clonidine is a powerful sympatholytic agent. It reduces the secretion of noradrenaline, adrenaline, ACTH, cortisol. It stimulates the release of growth hormone[34]. As a direct effect on the alpha-2 receptors of the pancreatic Langerhans cells, they inhibit insulin secretion, which may increase glycaemia, but without relevant clinical consequences [11].

**USES OF CLONIDINE-**

**SYSTEMIC USE-**

Clonidine, either orally pre-anesthetic or intraoperative venous administered clonidine, showed that the use of this drug reduces opioid consumption and postoperative pain scores in the first 24 hours, and incidence of nausea in the first 8 hours, but at the expense of lower intraoperative blood pressure levels (not clinically impacting) [13]. Clonidine has been used to attenuate symptoms resulting from withdrawal of opioids, alcohol and benzodiazepines, with encouraging results. Clonidine also has benefit in the treatment of postoperative tremors. As a premedication, a dose of 2 to 4µg/kg orally provides sedation, hypnosis and antisialogogue effect[35].

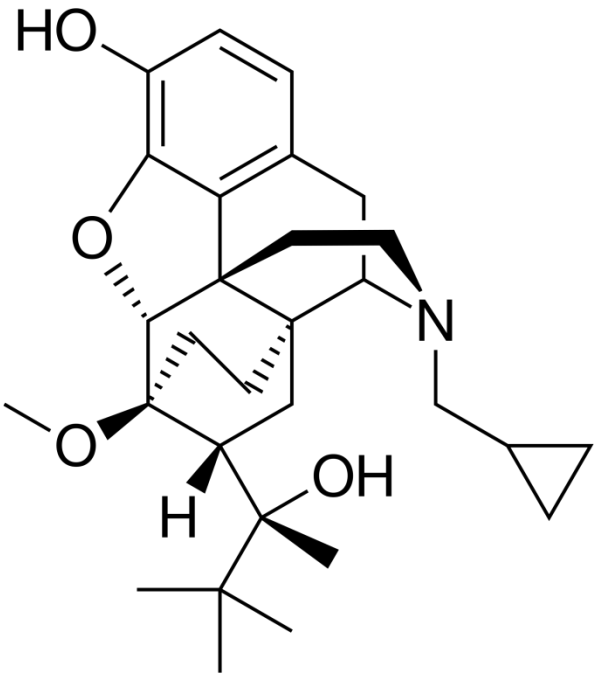
**EPIDURAL USE-**

Epidural clonidine may be used at a dose of 2 to 4µg/kg and it prolongs the time and improves the quality of analgesia and motor blockade of the associated local anesthetic, with a sedative effect. It can be used continuously at the dose of 30µg/h[11] . In children, it can be used in sacral epidural block at a dose of 1 to 2µg/kg[36].

**INTRATHECAL USE-**

Clonidine at the dose of 1-2 µg/kg has most pronounced effects when administered intrathecally [11] . As an adjunct to local anesthetics, the drug prolongs sensory and motor blockade without resulting in the typical adverse effects of opioids (urinary retention and respiratory depression). The main adverse effect observed is intraoperative hypotension[37,38].

**BUPRENORPHINE-**




Buprenorphine is a new synthetic analgesic agent, of high potency and prolonged action, derived from thebaine and closely related in structure to morphine. Buprenorphine, a partial agonist, has an affinity higher than that of a full agonist at the mu receptor. It has lower efficacy, slow offset, as well as a ceiling effect, making surgical analgesia difficult to control for those on a maintenance therapy[39].

Buprenorphine is a partial agonist of the mu receptor[40] and potent kappa receptor antagonist[41]. Mu receptor stimulation produces supraspinal analgesia, euphoria, respiratory depression, bradycardia, and dependence. Kappa stimulation produces spinal analgesia, sedation, miosis, and dysphoria; these latter effects are antagonized with buprenorphine.

The receptor theory, as discussed in Barash (2009), states that drugs have two independent characteristics at receptor sites, affinity and efficacy. Affinity is the ability to bind to a receptor to produce a stable complex. Efficacy is a dose effect curve resulting from the drug-receptor combination. A partial agonist has a dose-effect ceiling that is lower than that of a full agonist. Barash (2009) goes on to state, “even at a very large doses the efficacy, or maximum effect achieved by the partial agonist will be less than the maximum possible effect of a full agonist”. Buprenorphine is described as “having a high affinity for the mu receptor, 1000-fold higher than morphine, with an extremely slow dissociation from the receptor”. Although it binds tightly, it only partially activates the receptor, reducing the efficacy. This satisfies the classification of a partial agonist. Its affinity for the mu receptor is greater than that of naloxone as well as other mu agonists and it will displace a full agonist from the mu receptor. Buprenorphine is a partial agonist with high mu receptor affinity, slow dissociation and long duration of action.

Buprenorphine has an increased safety profile because of the partial agonism compared to methadone, a full agonist. Less respiratory depression is noted as well as a decrease in the euphoric high associated with a full agonist. This is attributed to the ceiling effect of respiratory depression and euphoria. Buprenorphine is both lipophilic and highly protein bound. It is distributed to adipose tissue and slowly redistributed to plasma, extending the half-life. The half-life is route and dose dependent.

Buprenorphine is excreted in the feces through the bile, which undergoes glucuronidation in the liver, so the renal excretion rate is about 1%[42]. Therefore, buprenorphine can be used in patients with renal

dysfunction and even in those on dialysis due to renal failure; these patients can receive the same dose of buprenorphine administered to those with normal renal function.

As the response from the μ receptor is slower to buprenorphine than to other opioids, withdrawal symptoms of buprenorphine are usually not seen, as there is a ceiling effect. Therefore, there is little risk of dependency, and tolerance is inhibited. The rewarding effect caused by opioids is also mild compared to that of morphine, as the rewarding effects are only observed at higher doses . Therefore, buprenorphine is considered an opioid with a low risk of abuse or addiction .

**ADVERSE EFFECTS –**

Regarding adverse effects, constipation, nausea, and vomiting are seen at a high rate. Therefore, it is necessary to combine buprenorphine with antiemetics and laxatives. Often the incidence of constipation caused by buprenorphine is less than that due to morphine. In patients taking oral P-glycoprotein inhibitors, there is a possibility that norbuprenorphine may easily pass through the blood brain barrier and thus enhance the analgesic effect . Therefore, patients who are taking drugs such as verapamil, amiodarone, quinidine, an immunosuppressive agent, and HIV therapeutic agents that have the ability to inhibit P-glycoprotein may enhance the analgesic effect of buprenorphine.

**REVIEW OF LITERATURE**

**Anil et al(2013)** performed a double blind randomized study with intrathecal clonidine as an adjuvant to hyperbaric bupivacaine. The aim of the study was to evaluate and compare the effects of addition of two different doses of clonidine (15 and 30 mcg) to 11 mg hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy surgery under spinal anesthesia. For the study 75 patients were enrolled and randomly divided into 3 groups of 25 each. Group I patients received 11 mg hyperbaric bupivacaine, whereas groups II and III received 15 mcg and 30 mcg clonidine, respectively, as an adjuvant to 11 mg hyperbaric bupivacaine. The volume of solution was kept constant to 2.4 ml by adding saline wherever needed. The result of the study was that highest level of sensory block, time to achieve this level, and highest Bromage scale recorded were comparable among the groups. The mean time to two-segment regression, regression of sensory block to L3 dermatome, and mean duration of motor block were the greatest in group III followed by group II and group I. There was significant fall in mean arterial pressure (MAP) in groups II and III as compared to group I ($P$ = 0.04). Episodes of hypotension were more in group III than in group II. **The** final conclusion was that 30 μg clonidine was associated with more incidence and duration of hypotension than 15 μg of clonidine. 15 μg clonidine added to 11 mg hyperbaric bupivacaine provides better sensory and motor blockade for inguinal herniorrhaphy.

**Sandhya Gujar et al(2014)** did a comparative study between intrathecal buprenorphine and clonidine as aduvant to local anesthetics in spinal anesthesia. For the study 60 patients of A.S.A grades I and II scheduled for gynecological and orthopedic surgery were selected and divided into 3 groups. Group I plain sensorcaine, Group II sensorcaine with 75μg of clonidine and Group III sensorcaine with 150μg of buprenorphine. The result showed definite prolongation of both sensory and motor blockade with both the adjuvants but the duration of postoperative analgesia with buprinorphine was 12 to 24 hrs which was almost double than clonidine group which was upto 6 to 8 hrs. Patient with clonidine had more incidences of hypotension and bradycardia. The VAS score at 6 and 10 hours was lower for patients of buprenorphine group as compared to groupI and II .

**R B Singh et al (2014)** conducted a double blind randomized study to establish efficacy and safety of intrathecal clonidine as adjuvant to bupivacaine. 100 of patients undergoing lower abdominal surgery were selected and randomly allocated in two groups, A and B. Group A received bupivacaine 0.5%, 3 ml with placebo (normal saline 0.33 ml) and Group B, bupivacaine 0.5%, 3 ml with clonidine 50 µg (0.33 ml). Duration of sensory, motor blockade and analgesia were compared between the two groups. The result was that mean duration of motor block was significantly higher in Group B (280.80 ± 66.88 min) as compared with Group A (183.60 ± 77.06 min). Significant difference in duration of sensory block was noted between Group B (295.20 ± 81.17 min) and Group A (190.80 ± 86.94 min). Duration of postoperative analgesia was significantly higher in Group B as compared to Group A (551.06 ± 133.64 min and 254.80 ± 84.19 min respectively). Mean visual analog scale scores at different time intervals were significantly lower in the study group (except for 4-h time interval), but the control group had better hemodynamic stability as compared with study groupThe findings in this study suggested that use of clonidine 50 µg added to bupivacaine for spinal anesthesia effectively increased the duration of sensory block, duration of motor block, and duration of analgesia..

**Seyed Mozaffar et al (2014)** conducted a double blind randomized clinical trial study in patients for cesarean section under spinal anesthesia. The patients were randomly divided into case and control groups. The mean age of case and control groups was 24.4±5.38 and 26.84±5.42 years, respectively .Case group (208 patients) received 65-70 mg of 5% lidocaine plus 0.2 ml of buprenorphine while the same amount of 5% lidocaine diluted with 0.2 ml of normal saline was given to 234 cases in the control group. Hemodynamic changes and neonatal APGAR scores (Appearance, Pulse, Grimace, Activity, Respiration) were recorded. Pain score was recorded according to the visual analog scale. The result of the study was that systolic blood pressure was not significantly different until the 45th minute but diastolic blood pressure showed a significant difference at the 15th and the 60th minutes (P<0.001). Heart rate changes were significantly different between cases and controls at the initial 5th, 15th and after 60th minutes (P<0.001). Pain-free period was significantly different between two groups (1.25 h versus 18.73 h) (P<0.001).***:*** The final conclusion drawn was that prescription of intratechal buprenorphine prolongs the duration of analgesia without any significant considerable side effects.

**Mahima et al (2014)** performed a study to compare and evaluate the characteristics of subarachnoid block of intrathecal buprinorphine and intrathecal dexmedetomidine as an adjuvant to 0.5%hyperbaric bupivacaine for lower abdominal surgeries. For the study 60 patients aged between 18-60 years scheduled for elective lower abdominal surgeries were selected and randomly allotted into 2 groups of 30 each. Group B was given 3 ml of 0.5%bupivacaine with 60 µg of buprenorphine and Group D was given 3 ml of 0.5%bupivacaine with dexmedetomidine. The onset and duration of sensory blockade, motor blockade and analgesia were noted alongwith hemodynamic variables and adverse effect. The result was that the motor, sensory blockade and time of rescue analgesia were prolonged in Group D compared to Group B. The sedation level was higher in Group D as compared to group B.

**Rashmi Pal et al (2015)** conducted a prospective comparative study on intrathecal buprenorphine, clonidine and fentanyl as adjuvants to 0.5%hyperbaric bupivacaine in lower abdominal surgeries. The study included 90 ASA class 1 and 2 patients undergoing lower abdominal and lower limb surgery . Patients were randomly allocated into 3 groups of 30 each and received 50 µg of clonidine, 25µg of fentanyl and 75 µg of buprenorphine respectively in group BC, BF and BB as adjuvants to 3 ml of 0.5% hyperbaric bupivacaine. Onset and duration of sensory and motor block, duration of analgesia, hemodynamic changes and complications were recorded. The result was that the onset time of motor block

and the duration of motor, sensory blockade and analgesia were prolonged in group BC as compared to group BF and BB(P<.001). No significant difference was noted in onset of sensory blockade in three groups(P>.05). In group BC there was lower heart rate and blood pressure and higher sedation score.

**Krishnakumar et al(2016)** performed a randomized , prospective and comparative study between intrathecal buprenorphine , clonidine and fentanyl as an adjuvant to 0.5 % hyperbaric bupivacaine in spinal anesthesia in patients undergoing lower abdominal surgery. For the study 90 ASA class 1 & 2 patients aged between 20 – 60 years undergoing lower abdominal surgeries under spinal anesthesia were selected after approval from hospital ethics committee with written informed consent of patients. Patients were then randomly allocated into three groups of 30 each. Group BC received 50µg of clonidine, Group BF recieved 25µg of fentanyl and Group BB received 75µg of buprenorphine as adjuvants to 15mg of 0.5% hyperbaric bupivacaine (3.0ml). The onset and duration of sensory and motor blockade, duration of analgesia, haemodynamic changes and side effects were recorded. The result obtained was that the onset time of motor block and durations of sensory, motor blockade and analgesia were prolonged in group BC as compared to group BF and BB (P<.001). However no significant difference in the onset time of sensory block in three groups (P>.05) was noted. Group BC had lower heart rate and mean blood pressure and higher sedation score. The conclusion drawn was that intrathecal clonidine in a dose of 50µg is an effective adjuvant to local anesthetics in spinal anesthesia.

**MV Arora et al (2016)** performed a double blind comparative study between intrathecal clonidine-bupivaicaine, buprenorphine-bupivaicaine and bupivaicaine alone in patients undergoing lower limb surgery under spinal anesthesia. 75 ASA Grade I and II patients undergoing lower limb surgery under spinal anesthesia were selected after approval from ethics committee and written informed consent taken. Patients were randomly allocated into three Groups A, B, and C. Control Group A received injection bupivacaine 0.5% (heavy) 2.5 ml + saline 0.5 ml whereas Group B received injection bupivacaine 0.5% (heavy) 2.5 ml + injection buprenorphine 50 µg and Group C received injection bupivacaine 0.5% (heavy) 2.5 ml + preservative free injection clonidine 50 µg intrathecally. Then the onset, duration of sensory and motor block, hemodynamic changes, level of sedation, duration of postoperative analgesia, and any adverse effects of clonidine and buprenorphine were compared. Statistically highly significant differences in mean time of sensory regression to L1, mean time to attain the Bromage Score of 1, and mean time of first rescue analgesic request were observed between the three groups. The patients did not suffer any serious side effects. The conclusion drawn was that use of buprenorphine and clonidine intrathecally does potentiate the duration of analgesia, sensory and motor block, with buprenorphine having a long-lasting effect.

**Kiran et al (2016)** did a comparative study between intrathecal buprenorphine and intrathecal fentanyl as adjuvant to bupivacaine in spinal anesthesia. For the study 60 patients of ASA Grade I and II aged 20-75 years posted for lower limb surgery were selected after clearance from the ethical committee. Patients were randomly allocated into 2 groups of 30 each. Group A was given 3.5ml of heavy Bupivacaine with 100micrograms of Buprenorphine (made up to 4 ml with NS) and Group B was given 3.5ml of heavy Bupivacaine with 50micrograms of Fentanyl(made up to 4 ml). The onset of sensory, motor block; highest level of sensory block, motor block; hemodynamic changes, time to 2 segment regression; VAS scores during the postoperative period were noted. The result was that onset of sensory and motor blockade was earlier in Fentanyl group(with Mean ± SD 301.30±11.25 and 407.43±26.77 respectively) compared to Buprenorphine group. But duration of analgesia (Mean ± SD of 108.67±3.50 and P<0.001) and duration of motor blockade (Mean ± SD of 351.53±9.18 ) was comparatively more with Buprenorphine group.

They also observed that number of rescue analgesia required were comparatively less with Buprenorphine group i.e, only 9 out of 30 patients required only one rescue analgesia in 24 hrs. VAS scores were less with buprenorphine group (Mean ± SD of 4.20±0.81) compared to Fentanyl group (Mean ± SD of 4.97±0.72). Side effects were not much significant, only 4 out of 30 in buprenorphine group and 7 out of 30 in Fentanyl group experienced side effects.

**Deepti Agarwal et al(2014)** performed prospective, randomized, double-blind study to test the hypothesis that addition of small doses of clonidine augments the spinal block levels produced by hyperbaric bupivacaine in elderly without affecting the side-effects if any of clonidine in these patients.. Above 60 years male patients were allocated to three equal groups. Group C received 9 mg hyperbaric bupivacaine without clonidine while Group $C_{15}$ and Group $C_{30}$ received 15 µg and 30 µg clonidine with hyperbaric bupivacaine respectively for spinal anesthesia. Effect of clonidine on sensory block levels was the primary study outcome measure. Motor blockade and hemodynamic parameters were also studied. The result of study was that a significantly higher median block levels were achieved in Group $C_{15}$ ($P < 0.001$) and Group $C_{30}$ ($P = 0.015$) than Group C. Highest median sensory block level, the mean times for sensory regression to $T_{12}$level and motor block regression were statistically significant between Groups $C_{15}$ and C and between Groups $C_{30}$ and C. On comparison of fall in systolic blood pressure trends, there was no significant difference in the clonidine groups as compared with the control group. The conclusion obtained was that in elderly patients, clonidine when used intrathecally in doses of 15 µg or 30 µg with bupivacaine, significantly potentiated the sensory block levels and duration of analgesia without affecting the trend of systolic blood pressure as compared to bupivacaine alone. Clonidine in doses of 30 µg however facilitated the ascent of sensory level block to unexpectedly higher dermatomes for a longer time.

**Prachee Sachan et al(2014)** did a single-blind prospective randomised controlled study at a tertiary care centre from 2010 to 12, 60 full-term parturients scheduled for elective CSs were divided into two groups on the basis of technique of intrathecal drug administration. Group M received mixture of clonidine (75 mcg) and hyperbaric bupivacaine 0.5% (10 mg) intrathecally, whereas Group B received clonidine (75 mcg) followed by hyperbaric bupivacaine 0.5% (10 mg) through separate syringes. Observational descriptive statistics, analysis of variance test, Wilcoxon test and Chi-square test were used as applicable. The result drawn was that the duration of analgesia was significantly longer in Group B (474.33 ± 20.79 min) in which the drug was given sequentially than in Group M (337 ± 18.22 min). Furthermore, the time to achieve highest sensory block and complete motor block was significantly less in Group B without any major haemodynamic instability and neonatal outcome. Hence it was concluded that when clonidine and hyperbaric bupivacaine were administered in a sequential manner, block characteristics improved significantly compared to the administration of the mixture of the two drugs.

**Debjyoti Dutta(2013)** performed a randomized controlled study to compare two different doses of intrathecal clonidine with hyperbaric bupivacaine fentanyl combination in women undergoing abdominal hysterectomy to get best beneficial effects with minimal incidence of side effects/complications. 90 patients undergoing abdominal hysterectomy under spinal anesthesia, were randomized to 3 groups, BFC0: received 3 ml hyperbaric bupivacaine 0.5% + 25µg fentanyl, BFC30: received 3 ml hyperbaric bupivacaine 0.5% + 25µg fentanyl + 30µgm clonidine and BFC60: received 3 ml hyperbaric bupivacaine 0.5% + 25µg fentanyl + 60µgm clonidine. Time to reach peak sensory levels, sensory and motor regression times, intraoperative pain score and time for first analgesic requirement, hemodynamic changes, fluid and vasopressor requirement were recorded. The result obtained was that addition of clonidine has not increased the rapidity of spread of sensory block to T4. Duration of motor block and time to regression to

L1 is significantly less in BFC0, (167.78±25.09min and 213.59±22.99min respectively) compared to BFC30 (248.33±26.07 min and 297.33±25.96 min respectively) and BFC60 (260.18 ± 47.64min and 306.43±44.76min respectively). In patients of BFC0 intraoperative vas score (1.3±1.2) was significantly higher and demanded analgesics earlier (241.3 ± 27.76 min) compared to others. Fall in BP was observed in a dose dependent manner. Hence it was concluded that adding small doses of clonidine to bupivacaine-fentanyl combination improves the quality of perioperative analgesia in a dose dependent manner. However, 60µg clonidine shows significant hemodynamic changes. Hence, 30µg of intrathecal clonidine added to bupivacaine (15mg) fentanyl (25µg) combination is the preferred choice.

**Sidharth S Routray et al (2017)** did a prospective randomized study to compare the effect of intrathecal clonidine and fentanyl as adjuvant to bupivacaine in the subarachnoid block for lower limb orthopedic surgery. 80 patients posted for lower limb orthopedic surgery were divided into two groups of forty each. Group C – Received intrathecal hyperbaric bupivacaine (2.5 ml) +50 µg clonidine (diluted to 0.5 ml). Group F – Received intrathecal hyperbaric bupivacaine (2.5 ml) + fentanyl 25 µg (diluted to 0.5 ml). Duration of postoperative analgesia, sensory and motor block characteristics, hemodynamic parameters, and side effects were recorded and analyzed. The result obtained was that time for first dose of rescue analgesic was delayed in Group C (510.84 ± 24.10 min) in comparison to Group F (434.95 ± 19.16 min) which was statistically significant ($P < 0.001$). Duration of sensory and motor block was significantly prolonged in Group C compared to Group F ($P < 0.001$). Sedation was more in Group C than Group F ($P < 0.001$). Other block characteristics, hemodynamic, and side effects were comparable in both groups. The conclusion obtained was that intrathecal clonidine as adjuvant to hyperbaric bupivacaine provided prolonged postoperative analgesia with more sedation in comparison to intrathecal fentanyl.

**Rashmi Ravindram et al (2017)** performed prospective randomized double-blind controlled study to compare the efficacy of two doses of buprenorphine (45 µg and 60 µg) as an adjuvant to hyperbaric bupivacaine for postoperative analgesia in cesarean section. 90 parturients posted for elective cesarean section under subarachnoid block were divided into three groups. Group A ($n = 30$) received 1.8 ml of 0.5% hyperbaric bupivacaine with 45 µg buprenorphine, Group B ($n = 30$) received 1.8 ml 0.5% hyperbaric bupivacaine with 60 µg buprenorphine, Group C ($n = 30$) received 1.8 ml of 0.5% hyperbaric bupivacaine with 0.2 ml normal saline, respectively. Following parameters were observed: onset and duration of sensory block, postoperative pain scores based on visual analog scale (VAS), rescue analgesic requirement, and maternal and neonatal side effects if any. The result obtained was that duration of postoperative analgesia was significantly prolonged in Groups A and B in comparison to Group C and it was longest in Group B. Rescue analgesic requirement and VAS score were significantly lower in the buprenorphine groups. No major side effects were observed. It was concluded that addition of buprenorphine to intrathecal bupivacaine prolonged the duration and quality of postoperative analgesia after cesarean section. Increasing the dose of buprenorphine from 45 µg to 60 µg provided longer duration of analgesia without increase in adverse effects.

**Navdeep Kaur et al (2017)** performed a randomized prospective study to compare the sensorimotor effects of addition of buprenorphine or dexmedetomidine to low-dose bupivacaine. Sixty patients were randomly allocated to three different groups. All received 1.8 mL 0.5% hyperbaric bupivacaine intrathecally. Sterile water (0.2 mL) or buprenorphine (60 µg) or dexmedetomidine (5 µg) was added to control group (Group C), buprenorphine group (Group B), and dexmedetomidine group (Group D), respectively. Time to the first analgesic request was the primary objective, and other objectives included the level of sensory-motor block, time to two-segment regression, time to $S_1$ sensory regression and time

to complete motor recovery. All sixty patients completed the study. Postoperative analgesia was not required in the first 24 h in a total of 10 (50%), 12 (60%) and 15 (75%) patients in groups C, B, and D, respectively. Time to $S_1$regression was 130 ± 46 min (Group C), 144 ± 51.3 min (Group B) and 164 ± 55.99 min (Group D), $P = 0.117$.Time to complete motor recovery was 177 ± 56.9 min (Group C), 236 ± 60 min (Group B) and 234 ± 61.71 min (Group D), $P < 0.001$. Conclusion drawn was that addition of buprenorphine (60 μg) or dexmedetomidine (5 μg) to intrathecal bupivacaine for transurethral resection prolongs the time to the first analgesic request with comparable recovery profile.

**Arvind Pal Singh (2016)** did prospective double-blind study to compare the anesthesia characteristics between buprenorphine and fentanyl when added as an adjuvant to intrathecal ropivaciane in an attempt to prolong the duration of spinal anesthesia. 90 American Society of Anesthesiologist I and II patients between 18 and 60 years of age undergoing subarachnoid block for lower limb surgery were selected. Group I ($n = 30$) patients were administered 3 ml of intrathecal solution (2.8 ml of 0.75% ropivacaine + 0.2 ml of isotonic sodium chloride), while Groups II and III patients ($n = 30$ each) received 2.8 ml 0.75% ropivacaine + 0.2 ml buprenorphine (60 μg) and 2.8 ml 0.75% ropivacaine + 0.2 ml fentanyl (10 μg), respectively. Parameters observed were onset times and duration of sensory and motor block, time to first analgesic use, total dose of rescue analgesia, intra- and post-operative pain scores based on visual analog scale, sedation scores, hemodynamic parameters, and side effects if any. Data were analyzed by appropriate statistical tests and $P < 0.05$ were considered significant. The result obtained was time to onset of sensory and motor block in all the three groups was comparable. However, duration of sensory block was significantly prolonged in Groups II and III in comparison to Group I ($P < 0.05$) and it was the longest in Group II ($P < 0.05$). The duration of motor blockade was similar in all the three groups. The time to first analgesic dose was also significantly prolonged in Groups II and III as compared to Group I ($P < 0.05$) but was comparable between Groups II and III. Intra- and post-operative hemodynamic parameters, as well as side effects, were comparable. The conclusion drawn was that addition of buprenorphine and fentanyl as adjuvants to intrathecal 0.75% ropivacaine prolongs postoperative pain relief without causing any increase in the duration of motor blockade but buprenorphine is better as compared to fentanyl in prolonging the duration of sensory block and achieving a better outcome in terms of pain relief.

**Sakhpal Pravin et al(2013)** performed randomized controlled study to evaluate and compare the efficacy, duration of post-operative analgesia and untoward effects of intrathecal Clonidine 60μg and intrathecal Buprenorphine 60μg used as additive adjuvants in spinal anesthesia for lower limb orthopaedic surgeries. Total 80 patients, aged 20-60 yrs, belonging to ASA grade I and II undergoing elective or emergency lower limb orthopedic surgery scheduled to last less than 180 minutes and fit to receive spinal analgesia were randomly allocated into two groups. Group C received intrathecal 0.5% heavy Bupivacaine 3.0 ml with Clonidine 60μg and Group B received intrathecal 0.5%. Heavy Bupivacaine 3.0 ml with Buprenorphine 60μg. Duration of subarachnoid block, total analgesia, effective analgesia, number of rescue analgesics and any untoward effects were assessed and compared in both groups. The result obtained was that both groups were comparable in demographic data. The difference in the duration of subarachnoid block in both groups is statistically significant. The duration of total analgesia in both groups is statistically comparable. Effective analgesia in Clonidine group was statistically longer than Buprenorphine group. The nausea was noted in 17.5% of patients in Buprenorphine group and 7.5% patients in Clonidine group. Vomiting was present in 5% of patients in Buprenorphine group while none of the patient in Clonidine group had vomiting.

The conclusion drawn was that this study concludes that intrathecal Clonidine 60µg significantly prolongs the duration of spinal anesthesia and quality of analgesia was acceptable to patients in both groups though VAS assessment was better in Buprenorphine group. Hence we suggest that combination of low dose intrathecal Î±2 agonist and opioid would give better analgesia & might reduce incidence of untoward effects.

**Sukhwinder J S Bajwa et al( 2012)** performed a randomized clinical study to establish the dose of intrathecal clonidine that would allow reduction of the dose of local anesthetic (thereby reducing the incidence and magnitude of hypotension) while at the same time providing clinically relevant prolongation of spinal anesthesia without significant side effects. 100 pregnant females who underwent emergency caesarean section were selected. The participants were divided randomly into four groups: A, B, C, and D, each comprising 25 parturients. Subarachnoid block was performed using a 26G Quincke needle, with 12 mg of hyperbaric bupivacaine (LA) in group A, 9 mg of LA + 30 µg of clonidine in group B, LA + 37.5 µg of clonidine in group C, and LA + 45 µg of clonidine in group D. The solution was uniformly made up to 2.2 mL with normal saline in all the groups. Onset of analgesia at $T_{10}$ level, sensory and motor blockade levels, maternal heart rate and blood pressure, neonatal Apgar scores, postoperative block characteristics, and adverse events were looked for and recorded. The result obtained was that the four groups were comparable with regard to demographic data and neonatal Apgar scores. Onset and establishment of sensory and motor analgesia was significantly shorter in groups C and D, while hypotension (and the use of vasopressors) was significantly higher in groups A and D. Perioperative shivering, nausea, and vomiting were significantly higher in groups A and D, while incidence of dry mouth was significantly higher in group D.

The conclusion drawn was that the addition of 45 µg, 37.5 µg, and 30 µg of clonidine to hyperbaric bupivacaine results in more prolonged complete and effective analgesia, allowing reduction of up to 18% of the total dose of hyperbaric bupivacaine. From the results of this study, 37.5 µg of clonidine seems to be the optimal dose.

**A G Gashi et al(2012)** performed double-blinded study to investigate the effects of clonidine in co-administration with bupivacaine during subarachnoid block. 66 male patients (age 35 to 70), from the American Society of Anesthesiologists (ASA) class I–II scheduled for transurethral surgical procedures were randomly selected. These patients were randomly allocated into two groups of 33 patients each: group B (bupivacaine) only received 0.5% isobaric bupivacaine 7.5 mg intrathecally and group BC (bupivacaine + clonidine) received bupivacaine 7.5 mg and clonidine 25 µg intrathecally. Spinal anesthesia was performed at a level of L3–L4 with a 25-gauge needle. The sensory block with a pin-prick, the motor block using the Bromage scale, analgesia with the visual analog scale and sedation with the modified Wilson scale were assessed along with the recording of the hemodynamic and respiratory parameters.The result obtained was that the mean time of achievement of motor block (Bromage 3) and sensory block at level T9 was significantly shorter in the BC group compared with B group ($p = 0.002$, $p = 0.000$, respeectively). The motor block regression time was not significantly different between the two groups ($p = 0.237$). The postoperative analgesia requirement was significantly longer in group BC compared with group B ($p = 0.000$). No neurological deficit, sedation or other significant adverse effects were recorded. Hence it was concluded that the intrathecal application of clonidine in combination with bupivacaine improves the duration and quality of spinal anesthesia; it also provides longer duration of postoperative analgesia, without significant side effects.

**Ranju Singh et al(2013)** did a randomized control trial to evaluate the effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section. A total of 105 parturients carrying a singleton fetus at term, scheduled to undergo elective LSCS under spinal anesthesia were randomized in a double blind fashion to one of the three groups. Group BF (*n*=35) received 2 ml of 0.5% hyperbaric bupivacaine+25 µg fentanyl, Group $BC_{50}$ (*n*=35) received 2 ml of 0.5% hyperbaric bupivacaine+50 µg clonidine, Group $BC_{75}$ (*n*=35) received 2 ml of 0.5% hyperbaric bupivacaine+75 µg clonidine. The result obtained was that the duration of postoperative analgesia was 184.73±68.64 min in group BF, 360.71±86.51 min in group $BC_{50}$ and 760.50±284.03 min in group $BC_{75}$ , *P*0<0.001. The incidence of hypotension was comparable, *P* =0.932, whereas the incidence of nausea and pruritis was significantly lower in groups $BC_{50}$ and $BC_{75}$ as compared to group BF, *P* <0.001. No other side effects of intrathecal clonidine were detected. Neonatal outcome was similar in all the three groups. Thus it was concluded that addition of 75 µg clonidine to hyperbaric bupivacaine in spinal anesthesia for LSCS significantly prolongs the duration of postoperative analgesia without any increase in maternal side effects. There was no difference in neonatal outcome.

## MATERIAL & METHODS

The present study entitled **"A COMPARATIVE STUDY OF INTRATHECAL CLONIDINE AND INTRATHECAL BUPRENORPHINE AS AN ADJUVANT TO 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANESTHESIA FOR INFRAUMBILICAL SURGERY."** will be carried out in the Department of Anesthesiology, Bombay Hospital, Indore [M.P.] after approval of ethical committee.

## PLACE OF STUDY

Department of Anesthesiology, Bombay Hospital, Indore [M.P.]

## STUDY POPULATION

Patients coming to the Bombay Hospital, Indore during the study period with ASA grade I & II scheduled for infraumbilical surgeries.

## STUDY DESIGN

Prospective, randomized controlled study.

## SAMPLE SIZE-

Sample size calculation revealed that 25 patients per group will be required to detect a difference of 40 Minutes in mean value of duration of Sensory Block between two groups, at an alpha of 0.05 with power of 80%.

p values < 0.05 were considered to indicate statistical significance. Hence, we intend to take 30 patients per group.

Formula

This calculator uses the following formula for the sample size n:

$n = (Z\ \alpha/2 + Z\ \beta)^2 * 2 * \sigma^2 / d^2$ ,

where $Z\ \alpha/2 = 1.96$ is the critical value of the Normal distribution at $\alpha/2$ for a confidence level of 95%, $Z\ \beta = 0.84$ is the critical value of the Normal distribution at $\beta$ for power of 80%, $\beta$ is 0.2,

σ = 50 is the population Standard Deviation and d =40 is the difference we would like to detect**.**

**TIME FRAME OF STUDY**

The study will be carried out from ethical committee approval to April 2019.

**INCLUSION CRITERIA**

1. Patients of ASA grade I and II undergoing infraumbilical surgeries.
2. Patients aged 20-60 years without any Renal, Hepatic, Metabolic and Neuromuscular disease.
3. Patients and/or his/her legally acceptable representative willing to provide their voluntary written informed consent to participate in the study

**EXCLUSION CRITERIA**

1. Patients refusal
2. Morbidly obese patients
3. Patient aged less than 20 years and more than 60 years.
4. Coexisting severe systemic illness.
5. Contraindications of subarachnoid block.
6. Past history of allergy to local anesthetics, clonidine or buprenorphine.
7. Patient on chronic analgesic therapy.
8. Patients on adrenoreceptors antagonists/beta blockers/ACE inhibitors.

**METHODOLOGY**

A careful pre operative assessment of all patients will be done prior to surgery. Spinal anesthesia technique will be explained in detail and a written informed consent will be obtained from all patients before conducting the study.

**GROUPING**

Total patients will be divided by simple randomization technique using computer generated random number list into following groups:

1. Group C-Patients in group C will receive 3ml of 0.5% hyperbaric Bupivacaine + 45 µg of clonidine in 0.2 ml normal saline, total volume is 3.5 ml.
2. Group B- Patients in group B will receive 3ml of 0.5% hyperbaric Bupivacaine + 90 µgm of buprenorphine in 0.2 ml normal saline, total volume is 3.5 ml.

**MATERIALS USED**

- Disposable plastic syringes 2cc, 5cc
- Povidone iodine solution and rectified spirit
- Sponge holding forceps
- Sterile towel and gauge pieces
- 26G Quincke spinal needle
- Inj. Lignocaine 2%
- Inj. Bupivacaine 0.5%
- Emergency drugs

- Inj. Clonidine
- Inj. Buprenorphine

**PREANESTHESTIC CHECKUP**

A careful preanesthetic checkup of all patients will be done which includes proper systemic examination , medical history, operative history and routine blood investigations. Proper airway assessment will be done. Routine investigations like complete blood counts , coagulation profile, serum urea, serum creatinine, blood sugar level, blood grouping and cross matching, ECG and chest X-ray PA view depending on the age and associated comorbidities and viral profile will be carried out. All the patient will be kept nil orally for 6 hours before procedure. Intradermal xylocaine sensitivity test of all the patients will be done before shifting to operation theatre.

**PROCEDURE AND DATA COLLECTION**

In the operation theatre standard monitors including non invasive blood pressure(NIBP), electrocardiography and pulse oxymeter will be attached to the patient and baseline blood pressure and heart rate will be recorded. Intravenous line will be taken with 18G IV cannula .Then preloading will be done with ringer's lactate 10-15 ml/kg over 10 min.

Under all aseptic precautions spinal anesthesia will be induced with 26G Quincke needle in L3-L4 region in sitting position after confirming free flow of clear cerebrospinal fluid. Then heart rate, blood pressure and oxygen saturation will be monitered every 5 minutes till the end of 20 minutes and then every 10 minutes till 60 mins and then every 30 minutes till 180mins.

Clinically relevant bradycardia defined as heart rate less than 50 per minute will be treated with 0.3-0.6 mg iv atropine and clinically relevant hypotension defined as blood pressure below 20% of baseline will be treated with 3-6 mg mephenteramine. Blood loss, urine output, IV fluid input will be noted.

The highest level of sensory block will be sensed by pinprick method in caudal to cephalic direction every two minute, after the procedure of subarachnoid block will be complete and the time taken to achieve absence of pinprick response at T 10 level in midclavicular line will be taken as onset of sensory block. Motor block will be assessed modified Bromage scale. Time taken to reach Bromage 3 will be noted and will be considered as the onset of motor block. Intraoperative sedation will be tested on Ramsay sedation scale. Satisfactory block will be defined as a sensory level of T 10 and modified Bromage score of three. Duration of sensory block will be defined from completion of drug injection to the re-appearance of response to pinprick at L-1 level. Duration of motor block will be recorded as time from injection of drug into the subarachnoid space to achieve Bromage-0. Both the durations will be noted. Postoperative pain will be assessed by visual analogue scale (VAS) using a plain scale measuring 10cms with 1 mm markings, in which 10 corresponded with most extreme pain and point 0 with no pain at all. Duration of analgesia will be taken from the time of intrathecal drug administration to the time when patient, first complained of pain.

**DATA TO BE ASSESSED -**

- Time of onset of sensory block (loss of sensation to pinprick)
- Level of sensory block
- Duration of sensory block(interval from intrathecal administration anaesthetic to 2 segment regression)

- Time of onset of motor block(assessment by a modified Bromage scale)
- Level of motor block
- Duration of motor block (interval from onset of motor block to time of achievement of modified Bromage scale 0)
- The number of hypotensive episodes(BP<20% of baseline values) and the number of times vasopressors (mephentermine) had to be used
- Duration of analgesia(time from intrathecal injection till the first demand for rescue analgesic when VAS>=4)
- Adverse effects

**RAMSAY SEDATION SCORE**

Ramsay sedation score will be used to assess the level of sedation:

| Score | Interpretation |
|---|---|
| 0 | Awake, conscious, no sedation to slightly restless |
| 1 | Calm and compose |
| 2 | Awake on verbal command |
| 3 | Awake on gentle tactile stimulation |
| 4 | Awake on vigorous tactile stimulation |
| 5 | Unarousable |

**MODIFIED BROMAGE SCORING**

Modified Bromage Scoring will be used for assessment of motor blockade:

| Score | Interpretation |
|---|---|
| 0 | No block |
| 1 | Inability to raise extended leg |
| 2 | Inability to flex knee |
| 3 | Inability to flex ankle and foot |

**STATISTICAL ANALYSIS**

The data will be initially entered into the Microsoft excel from the customized proforma. Then it will be transferred to the IBM SPSS Version 20.0.0 for statistical analysis. The mean of the variables between the two groups will be compared using Unpaired 't' test and within the groups means will be compared using Paired 't' test. Proportional comparisons will be done using Chi-square test or Z test for two sample proportion. A P value of $< 0.05$ will be taken as statistically significant.

**FINANCIAL INPUTS AND FUNDING**

The study does not involve any additional financial burden for the patient or for the institute as the patient will be managed according to the protocol of the institution and patient has to make the payment for the treatment of disease as per the laid down rates of the institution. And also this study is not being sponsored by any pharmaceutical company or any institution. All the expenses towards the conduct of the study viz. questionnaire preparation, etc. shall all be borne by the researcher himself.

## ETHICAL CONSIDERATIONS

The protocol will be submrititted before the ethical committee for approval. After due approval from the Ethics Committee, the study will be initiated in the institution. Also before including any patient for the participation in the study, a voluntary written consent for participation will be obtained from either the patient and/or his/her legally acceptable representatives. This consent will be taken in addition to the other consents that are obtained as per the laid down rules of the institution.

## DISCUSSION

Clonidine is selective partial α2 receptor agonist which acts by reducing norepinephrine release from sympathetic preganglionic neuron. Thus overall effects are analgesia, hypotension, bradycardia and sedation. Clonidine is also associated with few side effects like bradycardia, hypotension and dry mouth. So, 45µg dose of Clonidine was chosen in our study, as higher doses (150ug) are also associated with significant risk of hypotension as reported by Chiari et, al.[63]

Clonidine and other alpha-2-agonists have analgesic actions on the three sites of sensitive afferents: peripheral, spinal and brain. Clonidine may increase the effect of local anesthetics in peripheral nerve blocks, by action on C and Aδ fibers, decreasing the conduction on those fibers, because of increase of trans-membrane potassium conductance, and through vasoconstrictor effect (alpha1-adrenergic effect), which reduces local anesthetics wash-out from perineural tissues[23-25]. It acts on alpha-2 receptors and inhibits the adenylcyclase enzyme, reducing intracellular AMPc, leading to a hyperpolarization membrane state[26]. Inhibition of calcium voltage-dependent channels is another secondary action mechanism of clonidine[22] .

Buprenorphine is a new synthetic analgesic agent derived from thebaine. Buprenorphine is a partial agonist of the mu receptor[40] and potent kappa receptor antagonist[41]. Mu receptor stimulation produces supraspinal analgesia, euphoria, respiratory depression, bradycardia, and dependence. Kappa stimulation produces spinal analgesia, sedation, miosis, and dysphoria; these latter effects are antagonized with buprenorphine.

In our study we took total 60 patients who were randomly divided by using computer generated random number list into two groups. Group C received 3ml of 0.5% hyperbaric Bupivacaine + 45 µg of clonidine in 0.2 ml normal saline, total volume was 3.5 ml. While Group B received 3ml of 0.5% hyperbaric Bupivacaine + 90 µgm of buprenorphine in 0.2 ml normal saline, total volume was 3.5 ml.

## DEMOGRAPHIC PROFILE

The age of the patients in the present study ranged from 18 to 60 years. The mean age in Group B was 37.67 ± 12.64 years and in Group C it was 34.33 ± 11.31 years. The difference was found to be statistically not significant (p=0.286), showing a comparable mean age between the two groups.

Though patients are selected randomly, there was a male preponderance in the study as males are more prone to accidents than female because of there nature of job. In **Group B,** there were 6 (20.0%) females and 24 (80.0%) males and in **Group C,** there were 7 (23.3%) females and 23 (76.7%) males.

Majority of the patients in both the groups were in ASA Grade I. In **Group B**, there were 17 (56.7%) patients in ASA Grade I and 13 (43.3%) patients were in ASA Grade II and in **Group C**, there were 20 (66.7%) patients in ASA Grade I and 10 (33.3%) patients were in ASA Grade II.

**Duration of surgery:** The mean duration of surgery in Group B was 101.70 ± 21.26 minutes and in Group C it was 110.33 ± 22.47 minutes. The difference was found to be statistically not significant (p=0.132), showing a comparable mean duration of surgery in Group B and Group C.

**Onset and duration of sensory block:** The mean onset of sensory block in Group B was 247.33 ± 35.04 seconds, while in Group C it was 246.30 ± 18.12 seconds. The difference was found to be statistically not significant (p=0.886), showing a comparable mean onset of sensory block. This result was supported by studies done by **Strebel et al,**[63] where they concluded that small doses of intrathecal clonidine does not alter the onset of sensory block. This result was also in accordance with Krishnakumar et al [49],where there was no significant difference in onset of sensory block of three groups. The mean duration of sensory block in Group B was 249.87 ± 19.61 minutes, while in Group C it was 240.67 ± 28.49 minutes. The difference was found to be statistically not significant (p=0.150), showing a comparable mean duration of sensory block

**Regression of sensory:** The mean sensory regression in Group B was 58.10 ± 3.04 minutes, while in Group C it was 56.07 ± 3.98 minutes. The difference was found to be statistically significant (p=0.030), showing a faster sensory regression in Group C in comparison to Group B with regression occurring more slowly in buprenorphine group than in the clonidine group Sethi *et al*.[64] in a similar study in gynecological patients found that the mean time from injection to regression of the level of sensory analgesia by two segments was longer in the clonidine group than in control group ($P < 0.001$). Similar findings were also obtained by M V Arora et al [8] who found that The difference in the meantime of sensory regression to L1 in our study was found to be statistically highly significant ($P < 0.001$), with regression occurring more slowly in buprenorphine group (209 min) than in the clonidine group (183 min).

**Onset and duration of motor block:** The mean onset of motor block in Group B was 343.73 ± 66.61 seconds, while in the Group C it was 329.67 ± 21.43 seconds. The difference was found to be statistically not significant (p=0.275), showing a comparable mean onset of motor block. The mean duration of motor block in Group B was 224.87 ± 25.88 minutes, while in the Group C it was 214.37 ± 28.75 minutes. The difference was found to be statistically not significant (p=0.142), showing a comparable mean duration of motor block. Clonidine significantly prolongs the duration of motor block up to 214.37 ± 28.75 minutes as supported by the studies of Elia et al[65] and Jain et al.[66] The duration of motor block in group B(224.87 ± 25.88 minutes)was comparable to 205.17±63.0 minutes achieved with 60µg of buprenorphine, in a study done by Gupta M. et al.[47]

**Time required for first rescue analgesia:** The mean time required for first rescue analgesia in Group B was 5.87 ± 1.14 minutes and in Group C was 4.47 ± 0.86 minutes. The difference was found to be statistically significant (p=0.000), showing a longer time required for first rescue analgesia in Group B. This observation is in accordance with study done by Arora et al[50] where they found that There was a statistically significant difference ($P < 0.001$) between the mean time of first rescue analgesic request among the buprenorphine Group B (383 ± 38.9), clonidine Group C (278.2 ± 56.4), and control Group A (175.6 ± 26.1). Similar results were also demonstrated by Strebel *et al*. [63]while studying the effect of varying doses of intrathecal clonidine (37.5 µg, 75 µg, 150 µg) along with bupivacaine (in 8% glucose).

**Hemodynamic parameters:**

**Pulse rate:** In **Group B,** the mean preoperative heart rate was 80.03 ± 5.59 beats per minutes, which started falling till 50 minutes intraoperatively, then again started rising from 60 minutes intraoperatively till 150 minutes intraoperatively. In **Group C,** the mean preoperative heart rate was 82.27 ± 7.18 beats

per minutes, which suddenly rose at 0 minutes and then started falling from 5 minutes till 20 minutes, then a slight rise at 30 minutes, then again a fall from 40 minutes till 60 minutes, then again started rising from 90 minutes till the end of 150 minutes. The mean preoperative heart rate was comparable between the two groups ($p>0.05$), while at 0 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutes and 90 minutes the mean heart rate was higher in Group C in comparison to Group B ($p<0.05$), and it was again comparable at 120 minutes and 150 minutes between the two groups ($p>0.05$).

This observation is in accordance with study conducted by Shaikh IS et al[66] who concluded that after administration of 1 mcg/kg of buprenorphine intrathecaly no significant difference is seen in control and study population.

Dutta et al[54 ]in there study did not find any statistically significant difference in change in mean heart rate among the groups at any time interval. Juliao, *et al* [67]found no statistically significant difference in intraoperative heart rate, although they used lower dose of clonidine i.e. 15 µg of clonidine plus 5 µg of sufentanil with 15 mg of bupivacaine. Neither addition nor the increase in dose of the intrathecal clonidine changed the heart rate significantly.

**Blood pressure:** In **Group B,** the mean preoperative systolic blood pressure was 125.83 ± 4.54 mmHg, and In **Group C,** the mean preoperative systolic blood pressure was 123.4 ± 7.34 mm Hg. The mean systolic blood pressure at preoperative, at 0 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutes and 90 minutes was comparable between the two groups ($p>0.05$), while it was significantly lower in Group C in comparison to Group B at 120 minutes and at 150 minutes ($p<0.05$).

In **Group B,** the mean preoperative diastolic blood pressure was 80.13 ± 6.32 mmHg, In **Group C,** the mean preoperative diastolic blood pressure was 77.4 ± 4.14 mm Hg, The mean diastolic blood pressure preoperatively was comparable between the two groups ($p>0.05$). While at 0 minutes, 5 minutes and 10 minutes was higher in Group B in comparison to Group C ($p<0.05$), while at 15 minutes, 20 minutes, 30 minutes and 40 minutes it was comparable between the two groups ($p>0.05$), at 50 minutes and at 60 minutes it was higher in Group C in comparison to the Group B ($P<0.05$), while again at 90 minutes, at 120 minutes and at 150 minutes intraoperatively it was comparable ($p>0.05$).

This is in accordance with the study conducted by Krisnakumar et al [49 ] in which fall in systolic blood pressure was more in group containing clonidine as compared to group containing buprenorphine and fentanyl.

Similarly Arora et al[50 ] in his study found that MAP was lower in the clonidine Group C than that of Groups A containing normal saline and B containing buprenorphine with hyperbaric bupivacaine.

Pal et al [48 ] in there study found that there was decrease in blood pressure in clonidine containing group as compared to group containing buprenorphine and fentanyl.

**Respiratory rate and oxygen saturation:** In **Group B,** the mean preoperative respiratory rate was 14.77 ± 1.22 per minute. In **Group C,** the mean preoperative respiratory rate was 14.53 ± 1.63 per minute. The mean respiratory rate at preoperative, 0 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutes, 90 minutes, 120 minutes and at 150 minutes intraoperatively was comparable between the groups ($p>0.05$).

In **Group B,** the mean preoperative oxygen saturation was 99.83 ± 0.38%, which remained somewhat constant throughout the study period. In **Group C,** the mean preoperative oxygen saturation was 99.57 ±

0.82%, which remained somewhat constant throughout the study period. The mean oxygen saturation between the two groups was comparable throughout all the time intervals (p>0.05).
No significant respiratory depression was seen throughout the study. Similar findings were also obtained by Pal et al [48 ] and Arora et al [50]

## SUMMARY

The present study entitled **"A COMPARATIVE STUDY OF INTRATHECAL CLONIDINE AND INTRATHECAL BUPRENORPHINE AS AN ADJUVANT TO 0.5% HYPERBARIC BUPIVACAINE IN SPINAL ANESTHESIA FOR INFRAUMBILICAL SURGERY."** was carried out in the Department of Anesthesiology, Bombay Hospital, Indore [M.P.] after approval of ethical committee with an aim to compare the efficacy and safety of intrathecal buprenorphine vs intrathecal clonidine as an adjuvant to 0.5%bupivacaine in infraumbilical surgeries.
All the patients of ASA Grade I and II were thoroughly examined preoperatively and their age, sex , pulse rate, oxygen saturation and blood pressures were recorded.
Total 60 patients were divided by simple randomization technique using computer generated random number list into two groups of 30 each. Patients in group C received 3ml of 0.5% hyperbaric Bupivacaine + 45 µg of clonidine in 0.2 ml normal saline, total volume is 3.5 ml. Patients in group B received 3ml of 0.5% hyperbaric Bupivacaine + 90 µgm of buprenorphine in 0.2 ml normal saline, total volume is 3.5 ml. A well informed consent was taken.
Clinical parameters as per module of the study were recorded and tabulated for statistical analysis and interpretations were discussed in detail to draw conclusion.
In the preset study, The mean sensory regression in Group B was 58.10 ± 3.04 minutes, while in Group C it was 56.07 ± 3.98 minutes. The difference was found to be statistically significant (p=0.030), showing a faster sensory regression in Group C in comparison to Group B with regression occurring more slowly in buprenorphine group than in the clonidine group. The mean time required for first rescue analgesia in Group B was 5.87 ± 1.14 hours and in Group C was 4.47 ± 0.86 hours. The difference was found to be statistically significant (p=0.000), showing a longer time required for first rescue analgesia in Group B. Thus a significant prolongation of duration of analgesia was seen in group B as compared to group C.
Patients in both groups were closely monitored for any complication during or after operative procedure. Few side effects were noted in both the groups which were managed immediately.

## Conclusion

Intrathecal buprenorphine 90 µg gives adequate analgesia as the mean time required for first rescue analgesia in Group B was 5.87 ± 1.14 min, which is significantly longer than that of intrathecal clonidine 45 µg, i.e., 4.47 ± 0.86 minutes.. Quality of analgesia was acceptable to patients. Administration of buprenorphine and clonidine intrathecally does potentiate the duration of analgesia, sensory and motor block. The study suggests that combination of two or more drugs from different group (e.g., opioid and α2 agonist) can give better analgesia and less chance of side effects.

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