A dissertation on

INCIDENCE OF HYPOTENSION IN LSCS - A COMPARISON OF INTRATHECAL FENTANYL-BUPIVACAINE COMBINATION WITH BUPIVACAINE ALONE

THANJAVUR MEDICAL COLLEGE

M.D.DEGREE EXAMINATION
BRANCH X
(ANAESTHESIOLOGY)

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY
CHENNAI

MARCH 2007

CERTIFICATE

This is to certify that this dissertation entitled "Incidence of hypotension in LSCS-A comparison of intrathecal fentanyl – bupivacaine combination with bupivacaine alone" is the bonafide record of work done by Dr.A.Prakash in the Department of Anesthesiology, Thanjavur medical college, Thanjavur, during his post graduate course from 2004-2007.This is submitted as partial fulfillment for the requirement of M.D. degree Examination- Branch X(Anesthesiology) to be held in march 2007

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ACKNOWLEDGEMENT

I am extremely thankful to Dr.S.Balakrishnan M.D., The Dean, Thanjavur medical college, for his kind permission to carry out this study.

I sincerely extend my thanks to Dr.R.Thenmozhi, M.D; D.A, Professor and Head of the Department of Anaesthesiology, for her concern and support in conducting the study.

I am very grateful to Prof. Dr.R.Muthukumaran, M.D; D.A, for his expert guidance and teaching through every step.

I am thankful to Prof. Dr.AL.Meenatshisundaram M.D; D.A, for his constant motivation and valuable suggestions.

I am greatly indebted to my assistant Professor Dr.S.Uthirapathi M.D; D.A for his unaccountable helps to meet the needs of this dissertation.

My sincere thanks to my assistant Professors for their help and support throughout the study.

My special thanks to all my colleagues of the Department of Anaesthesiology for their support.

Finally, I would like to extend my sincere gratitude to all my patients in whom this study was conducted for their kind cooperation.

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INTRODUCTION

Caesarean section in an awake patient is undoubtedly a major test of regional anaesthesia. The surgery is major, profound blockade of many spinal segments required, strong visceral stimulation present, sudden cardiovascular changes are compounded by posture and fetal well-being may be influenced by several physiologic variables and drugs.

Spinal anaesthesia is perhaps the most efficient and elegant approach to this challenge. With a small needle and an almost homeopathic amount of drug, profound anaesthesia and excellent operating conditions can be readily provided for this major intrabdominal surgery.

Spinal hypotension, the most clinically significant aspect of spinal anaesthesia can occur rapidly and may have a significant impact on the neonatal outcome. Recently, there has been an interest in using analgesic additives to subarachnoid local anaesthetics to decrease the local anaesthetic dose so as to reduce the incidence and degree of hypotension but at the same time without compromising intra operative analgesia and also to enable faster recovery and providing efficient post operative analgesia.

Opioids were the first clinically used selective spinal analgesics after the discovery of opioid receptors in the spinal cord. Lipophilic opioids (fentanyl and sufentanil) are increasingly being administered intrathecally as adjuvants to local anaesthetics[1]. They have been shown to enhance the quality of local anaesthetic induced subarachnoid block and to provide postoperative analgesia and also, they reduce the hypotension due to subarachnoid block by reducing the dose of the local anaesthetics and decrease the ephedrine requirements to combat hypotension.

In our study, we compare the efficacy of the combination of intrathecal 25 μg fentanyl and 5mg of hyperbaric bupivacaine 0.5% with that of 7.5mg hyperbaric bupivacaine 0.5% alone regarding the incidence of hypotension and ephedrine requirements in lower segment Caesarean section during surgery and early post operative period.

AIM OF THE STUDY

To evaluate the efficacy of the combination of intrathecal fentanyl 25 μg and 5mg of 0.5% hyperbaric bupivacaine in comparison with 7.5mg of 0.5% hyperbaric bupivacaine used alone for lower segment caesarean section with respect to

- Time of onset of analgesia and motor blockade
- Duration of sensory and motor block
- Quality of intraoperative anaesthesia and period of effective analgesia
- Incidence of hypotension
- Ephedrine requirements to combat hypotension

To evaluate the side effects and complications that may arise with the use of intrathecal fentanyl as an adjuvant

SPINAL ANAESTHESIA

Spinal (subarachnoid/intrathecal) anaesthesia is a form of central neuraxial block in which, a temporary interruption of nerve transmission is achieved following injection of local anaesthetic and/or adjuvant solution into the subarachnoid space. Spinal anaesthesia is one of the most frequently employed methods of regional anesthesia.

Anatomy

The vertebral canal extends from the foramen magnum to the sacral hiatus. It is formed by the dorsal spines, pedicles and laminae of successive vertebrae

(7 cervical, 12 thoracic, 5 lumbar and 5 sacral). The vertebrae are held together by a series of overlapping ligaments namely, the anterior and posterior longitudinal ligaments, ligamentum flavum, interspinous ligament, supraspinous ligament and the intervertebral discs.

The spinal cord, a direct continuation of the medulla oblongata begins at the upper border of the atlas and terminates distally in the conus medullaris. The distal termination, because of the differential growth rates between the bony vertebral canal and central nervous system varies from L3 in the infant, to the lower border of LI in the adult.

Surrounding the spinal cord in the bony vertebral column are three membranes

(from within to the periphery); the pia mater, arachnoid mater and dura mater. The pia mater is a highly vascular membrane that closely invests the spinal cord. The arachnoid mater is a delicate nonvascular membrane closely attached to the outermost dura mater. Between the two innermost membranes is the subarachnoid space. In this space are the cerebrospinal fluid (CSF), spinal nerves, blood vessels that supply the spinal cord and the dentate ligaments. Although the spinal cord ends at the lower border of LI in adults, the subarachnoid space continues to S2. The outermost membrane in the spinal canal is the longitudinally organized fibroelastic membrane, the dura mater. This layer is the direct extension of the cranial dura mater and extends as the spinal dura mater from the foramen magnum to S2, where the filum terminale (an extension of the of the pia mater beginning at the conus medullaris) blends with the periosteum of the coccyx. There is a potential space between the dura mater and arachnoid, the subdural space which contains only small amounts of serous fluid to allow the dura and arachnoid move over each other. Surrounding the dura mater is the epidural space which extends form the foramen magnum to the sacral hiatus. Posterior to the epidural space is the ligamentum flavum which extends from the foramen magnum to the sacral hiatus. Immediately posterior to the ligamentum flavum is the interspinous ligament. Extending from the external occipital protuberence to the coccyx, posterior to these structures is the supraspinous ligament.

Lumbar puncture is routinely done below the L2 vertebra down to the L5-S1 interspace to avoid damaging the spinal cord which ends at the lower border of L1 vertebra in adults.

Cerebrospinal Fluid

The cerebrospinal fluid (CSF) in an ultrafiltrate of blood plasma with

which it is in hydrostatic and osmotic equilibrium. It is a clear, colourless fluid found in the spinal and cranial subarachnoid space and in the ventricles of the brain. The average volume in the adult ranges from 120-150ml of which 35ml is in the ventricles, 25ml is in the cerebral subarachnoid space and 75ml is in the spinal subarachnoid space. It is secreted by the choroid plexus at a rate of 0.3-0.4ml/ minute and is absorbed into the venous sinuses through the arachnoid villi.

Physical Characteristics Of Cerebrospinal Fluid [2]

PH	7.4
Specific gravity	
referred to H2O	
- at body temperature	1.007
- at 40C	1.0003
Density	1.0003g/ml
Baricity	1.000
Pressure	
8-12mmHg/70-80mmH2O	
Cells	3-5/cu.mm
Proteins	20mg/dl
Glucose	45-80 mgdl

The cerebrospinal fluid plays an important role in spinal anaesthesia as media for dispersion of the local anesthetic drug to the spinal nerve roots. An important factor determining the spread of drugs in the subarachnoid space is the specific gravity of the injected solution compared with that of CSF.

Mechanism of Spinal Anaesthesia

Injection of local anaesthetics into the spinal CSF allows access to sites of action both within the spinal cord and the peripheral nerve roots. The nerve roots leaving the spinal canal are not covered by epineurium and are readily exposed to the local anaesthetics within the CSF. Therefore afferent impulses entering the central nervous system via the dorsal nerve roots and efferent impulses leaving via the ventral nerve roots are blocked during spinal anaesthesia. Spinal local anaesthetics block sodium channels and electrical conduction in spinal nerve roots. There are also multiple potential action of local anaesthetics within the spinal cord at different sites. Local anaesthetics can exert sodium channel block within the dorsal and ventral horns, inhibiting generation and propogation of electrical activity[3]. The order in which the nerve fibres are blocked are preganglionic sympathetic B fibres followed by temperature fibres (cold before warmth), fibres carrying pin- prick sensation, touch, deep pressure, somatic motor sensation and lastly fibres conveying vibration sense and proprioceptive impulses. Sympathetic fibres are blocked 2-3 segments higher than sensory level. Sensory fibres are blocked 2 segments higher than motor fibres. Recovery is roughly in the reverse order.

Physiologic effects of spinal anaesthesia

Cardiovascular effects

Sympathetic blockade leads to dilatation of resistance and capacitance vessels

below the level of blockade. The diminished cardiac output consequent to diminished venous return decreases the blood pressure - hence spinal hypotension occurs. Other factors contributing to spinal hypotension are:

- Dilatation of post arteriolar capillaries and small venules due to blockade of vasoconstrictors.
- Blockade of sympathetic supply to heart – T1-T4
- Blockade of sympathetic supply to adrenals with consequent catecholamine depletion
- Compression of great vessels within the abdomen by gravid uterus

Compensatory vasoconstriction in the upper part of the body can help to maintain the blood pressure. The effect of posture promoting venous return will mimise hypotension. During spinal anaesthesia, both Marey's law and Bainbridge reflex operate, but the latter predominates.

Respiratory system

Correctly placed and conducted spinal anaesthesia should not depress respiration. Even with high thoracic levels, tidal volume is unchanged. A small decrease in vital capacity occurs because of loss of contribution from abdominal muscles in forced expiration. Phrenic nerve block may not occur even with total spinal anesthesia .

Metabolic and hormonal effects

Spinal anaesthesia can minimise or prevent the rise in blood sugar, cortisol and catecholamine response to surgery.

Gastrointestinal effects

There is contracted bowel with relaxed sphincters, increased peristalsis and increased intraluminal pressure.

Factors affecting height of blockade

The major factors affecting the height of blockade are

1) Baricity of the drug
2) Dosage (mass) of drug
3) Volume and concentration of the drug
4) Position of the patient
5) Site of injection
6) Volume and pressure of CSF

Fate of Local Anaesthetics in subarachnoid Space

Following injection local anaesthetic solution into subarachnoid space, its concentration falls rapidly. The initial steep fall is due to mixing with CSF and

subsequent absorption into nerve roots and spinal cord. The egress of local anaesthetics following subarachnoid injection is primarily by vascular absorption with no hydrolysis or degradation taking place in the CSF[4]. Depending on the type of drug used, it is metabolized in plasma by pseudocholinesterase or in the liver.

Indications for Subarachnoid block

Spinal anaesthesia can be administered whenever a surgical procedure can be done with a sensory level of anaesthesia that does not produce adverse patient outcome, mostly below T6. Such procedures include lower abdominal surgeries, lower limb surgeries, urological procedures, obstetric procedures, gynaecological surgeries and perineal & rectal surgeries.

Contraindications for Subarachnoid block

An absolute contraindication for subarachnoid block is patient refusal.

Other contraindications are;

- Local sepsis
- Uncorrected coagulopathy
- Uncontrolled blood loss/ shock

- Fixed cardiac output states, severe cardiac disease
- Documented allergy to local anaesthetics
- Raised intracranial pressure
- Neurological disease
- Major spine deformities/ previous surgery on the spine

Complications of Subarachnoid Block

Immediate

1. Hypotension
2. Bradycardia

Physiological effects

3. Toxicity due to intravascular injection
4. Allergic reaction to local anaesthetic
5. Hypoventilation in patients with higher thoracic levels.

Late

1. Post dural puncture headache
2. Retention of urine
3. Backache
4. Meningitis

5. Transient lesions of cauda equina
6. Sixth nerve palsy
7. Anterior spinal artery syndrome
8. Horner's syndrome

INTRATHECAL OPIOIDS

History

Opiate receptors were first identified in the central nervous system in 1973 by Pert CB and Snyder SH[5]. Subsequently, large populations of these receptors were localized in the dorsal horn of the spinal cord[4]. In 1976, Yaksh TL and Rudy TA performed animal studies and demonstrated the ability of intrathecal opioids to produce analgesia[6]. In 1979, Wang and colleagues reported pain relief using intrathecal morphine in cancer patients and in the same year, Behar et al. achieved the same result injecting the drug into the epidural space[7,8].

Spinal Opioid Receptors-Location

Opioid receptors are synthesized in the cell body of the sensory

neuron and are transported in both the central and peripheral directions. In the spinal cord, opioid receptors are found in the dorsal horn in the terminal zones of C fibers primarily in lamina II of the substantia gelatinosa[9]. Spinal opioid receptors are 70% μ 24% δ and 6% κ.

Mechanism of Action

Spinal opioids act at nerve synapses either presynaptically (as neuromodulators) or postsynaptically (as neurotransmitters)[10]. Stimulation of presynaptic receptors is associated with hyperpolarisation of the terminal and reduced substance P release[11]. This relates primarily to inhibition of voltage-gated calcium channels. Postsynaptic membranes contain opioid receptors linked to potassium channels. Stimulation of these receptors enhances outward flow of potassium, thereby stabilizing the membrane, making it less sensitive to neurotransmitters[12]. These actions are carried out by second messengers (G proteins).

With the injection of an opioid into the CSF, a reservoir of drug is created that passively diffuses into the dorsal horn of the spinal cord where it exerts its action by binding to opioid receptors.

Pharmacokinetics

The onset of analgesic effect following intrathecal administration of an opioid is directly proportional to the lipid solubility of the drug, whereas the duration of effect is longer with more hydrophilic compounds. Opioids

placed in the epidural space undergo significant systemic absorption and passage into the subarachnoid space. Vascular absorption after intrathecal administration of opioids is insignificant. Cephalad movement of opioids in the CSF is dependent on lipid solubility. Lipid soluble opioids like fentanyl are limited in the cephalad migration by uptake into the spinal cord, while hydrophilic opioids like morphine remain in the CSF for transfer to more cephalad locations.

Loss of analgesia after intraspinal injection primarily results from clearance of drug from the site of action. Intrathecal opioids are eliminated by diffusion along the neuraxis and vascular absorption. It is not yet established what role metabolism plays in the termination of action of intrathecal opioids.

Tolerance

Decrease in effect over time to a given dose of drugs has been demonstrated with intrathecal opioids. There is good evidence in support of the glutamate receptor of the NMDA type to be involved in the mechanism of tolerance.

Benefits

- Long lasting post operative analgesia after a single injection
- Precise and reliable placement of low concentration of drug near its site of action[13]

The principle disadvantage is its lack of titrability and the need to either repeat the injection or consider other options when the analgesic effect of the initial dose wanes.

Nevertheless, it is common clinical experience that after the analgesic effect of the initial intrathecal dose wanes, the intensity of post operative pain is greatly diminished and can be satisfactorily managed by other modalities.

Side Effects[14,15]

The side effects of neuraxial opioids are due to the presence of drug in the cerebrospinal fluid and/or systemic circulation. Typically most side effects are dose dependent.

The common side effects are 1. respiratory depression, 2. pruritus, 3. nausea and vomiting, 4. urinary retention and 5. sedation.

Respiratory Depression

The real incidence of respiratory depression is not known. Early respiratory depression is thought to be secondary to the effect of systemically absorbed drug and occurs in the first two hours after intrathecal opioid injection. Delayed respiratory depression is likely the consequence of rostral spread of opioid in the CSF, the target site being the respiratory center in the floor of the fourth ventricle. The risk of delayed respiratory depression appears to peak at six to twelve hours after beginning therapy. Factors that increase the risk of delayed respiratory depression are

- High opioid doses

- Concomitant administration of parenteral opioids and other sedatives
- Hydrophilic opioid use
- Advanced age

Pulse oximetry reliably detects opioid induced arterial hypoxemia and supplemental oxygen is an effective treatment. A slow breath rate (<8/min) may accompany respiratory depression. Perhaps, the most reliable clinical sign of respiratory depression is a depression of level of consciousness, possibly caused by hypercarbia. Naloxone is effective in reversing opioid induced respiratory depression.

Pruritus

It is a common and distressing symptom seen in many patients. It may be generalized or localized, with the face being the most common site. Although probably not due to histamine release, antihistamines often provide symptomatic relief. Nalbuphine and Naloxone are also effective. The mechanism by which pruritis occurs is not known with certainty.

Nausea and vomiting

This is due to rostral spread of opioid in the CSF to the vomiting center and chemoreceptor trigger zone in the floor of the fourth ventricle. Relief is possible with antiemetic use.

Urinary Retention

The incidence of urinary retention is quite significant. Naloxone may help prevent or reverse urinary retention, but doses approaching those that antagonize analgesia may be needed.

Sedation

Sedation caused by intrathecal opioids is attributed to the spread of drug in CSF receptors in the thalamus, limbic system or cortex. Pharmacologic treatment is seldom indicated. Respiratory depression must be suspected whenever sedation occurs following intrathecal opioid administration.

Myoclonus has been reported occasionally in patients receiving high does of intrathecal opioids

Neurotoxicity

Animal and human studies have not demonstrated neurotoxicity with any of the commercially available preservative free opioid agents administered by the subarachnoid route[16].

Opioid- Local anaesthetic mixtures

Adding a local anaesthetic to spinal opioids result in synergistic interaction. The rationale for combining intrathecal opioids and local anaesthetic is to use lower doses of each agent, to preserve effective analgesia and to reduce the side effect and problems associated with use of individual drugs[17]. Nociceptive pathways are interrupted at different sites with the two drugs. The opioid in the mixture acts by inhibiting the release of substance P in the dorsal horn of the spinal cord while the local anesthetic blocks transmission of impulses at the level of nerve axonal membrane. These two distinctive action may contribute to the synergy of analgesic effects that have been demonstrated.

PHARMACOLOGY OF BUPIVACAINE

Bupivacaine is an amide local anaesthetic, synthesized by A.F.Ekenstam in 1957 and brought into clinical use in 1963.

It is produced for clinical use as a racemic mixture, containing equal

proportion of the ‘S’ and ‘R’ enantiomers. It is supplied for clinical use as a hydrochloride salt.

Physico- chemical profile

Molecular weight (base)	288
PKa	8.1
Solubility in	
Alcohol	1in 8
Water	1in 25
Octanol/ water partition coefficient	high
Lipid solubility	28
Plasma protein binding	95%

Mechanism of Action

Bupivacaine exerts its effect by inhibition of sodium channels. It blocks conduction in the nerves by decreasing or preventing the large transient increase in permeability of the cell membrane to sodium ions that follows depolarization of the membrane. Bupivacaine also reduces the permeability of the resting nerve membrane to potassium as well as sodium ions[18].

Pharmacodynamics

Bupivacaine by virtue of its pharmacological effect, has a stabilizing

action on all excitable membranes. In the central nervous system, stimulation can occur producing restlessness, tremors and convulsions in overdosage. Bupivacaine also causes a reduction of automaticity in the heart.

The clinical profile of nerve blockade produced by bupivacaine differs from that of lignocaine. It is 4 times more potent than lignocaine, but the onset of action is slower. The duration of action is considerably longer. The sensory block produced by bupivacaine tends to be more marked than the motor block.

Pharmacokinetics

Bupivacaine is rapidly absorbed from the site of injection. The rate of rise in plasma bupivacaine concentration and the peak plasma concentration obtained depend on the route of administration. There is also some inter-individual variation and peak systemic concentration may occur between 5and 30 minutes after administration. The addition of a vasoconstrictor delays absorption and result in lower plasma concentration of bupivacaine.

Pharmacokinetic Profile[19]

Volume of distribution at steady state (VDss)	**72 litres**
Clearance	0.471/min
t ½ α	2.7 min
t ½ β	28 min

t ½ γ	3.5 hrs

Metabolism

Possible pathways for metabolism of bupivacaine include aromatic hydroxylation, N-dealkylation, amide hydrolysis and conjugation. Only the N-dealkylated metabolite N-desmethylbupivacaine has been measured in blood and urine after epidural and spinal administration. The degradation of bupivacaine takes place in the liver. Renal disease is unlikely to alter the kinetics of bupivacaine to any great extent. Less than 10% of the drug is excreted unchanged in urine[20].

The onset of action of bupivacaine occurs 20-30 minutes after a peripheral nerve block and duration lasts for 8-9 hours.

Clinical Applications

- Infiltration anaesthesia
- Peripheral nerve blocks
- Central neuraxial blocks (intrathecal, epidural and caudal)

Contraindications

- Paracervical block (in obstetrics)
- Known hypersensitivity to amide local anaesthetics
- Intravenous regional anaesthesia (IVRA)

Preparations Available

0.25%,0.5% solutions in 10ml and 20ml vials.

5mg/ml (0.5%) bupivacaine and 80 mg dextrose in 4ml ampoules for intrathecal injection

Recommended Safe Dose

Concentration used	Max. permitted dose
0.125%-0.5%	2mg/kg body wt
0.75% (not to be used in obstetric epidurals)	Max. over 4hrs – 150mg Max. during 24hrs – 400mg
0.5% plain / hyperbaric solution (intrathecal use)	20mg

Adverse reactions

Adverse reactions are associated mainly with excess plasma levels of the drug, which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

• CNS Reactions

Excitation characterized by restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors possibly proceeding to convulsions, followed by drowsiness, unconsciousness and cardiac arrest.

• Cardiovascular system effects

Part of the cardiac toxicity that occurs from high plasma concentrations of bupivacaine occurs because of blockade of cardiac sodium channels. Accidental

intravenous injection of bupivacaine causes cardiac dysrhythmias, atrioventricular block, ventricular tachycardia and ventricular fibrillation. Pregnancy increases the sensitivity to cardiotoxic effects of bupivacaine.

- **Allergic reactions**

Manifests as urticaria, pruritus, angioneurotic edema etc. Cross sensitivity among members of amide type local anaesthetics has been reported.

PHARMACOLOGY OF FENTANYL

Fentanyl is a synthetic phenylpiperidine opioid of the 4-anilopiperidine series which is structurally related to pethidine.

Commercially, fentanyl is formulated as a citrate, available as an aqueous solution without preservatives. Each ml contains a base of 50μg of fentanyl.

Physico-chemical Profile[21]

Molecular weight	**528.29**
pKa	8.4
% unionized pH 7.4	8.5
Octanol / water partition coefficient	816
% bound to plasma proteins	84
Potency	80 times more potent than morphine

Pharmacodynamics

• Analgesia

This results from action of fentanyl on opioid μ receptors both suprapinally in the brain and spinal cord. Intravenous fentanyl produces effective analgesia at plasma concentrations between 0.6-3.0 ng/ml.

• Cardiovascular System

Arterial blood pressure, cardiac output and pulmonary vascular resistance remain unchanged after large doses of intravenous fentanyl. Fentanyl like other opioid agonists (except pethidine) causes bradycardia, that responds to intravenous atropine. Peripheral vasodilation is much less than morphine due to absence of histamine release.

• Respiratory System

Fentanyl causes a direct dose related respiratory depression by its depressant effect on the medullary respiratory center, manifested as a decreased sensitivity to

carbondioxide and reduced respiratory rate. It is reversed by intravenous Naloxone administration. Plasma fentanyl concentrations >2ng/ml is associated with clinical respiratory depression. The degree of respiratory depression is affected by various factors, including type of surgical population, age and individual pharmacodynamic response.

• Central nervous system

Fentanyl causes less sedation than equianalgesic doses of morphine. In doses of 100 μg/kg, fentanyl causes dose related reduction in cerebral blood flow and $CMRO_2$. Muscle rigidity probably reflects a manifestation of a catatonic state, a basic pharmacologic property of opioids, related to enhancement of dopamine biosynthesis in the caudate nucleus.

• Gastrointestinal Tract

Fentanyl decreases gastrointestinal tract motility, increases intrabiliary pressure and causes a varying incidence of nausea and vomiting. The vomiting is mediated via stimulation of the chemoreceptor trigger zone in the area postrema.

• Genito-urinary system

Fentanyl like other opioids causes relaxation of detrusor muscle and increase in urethral sphincter tone leading to urinary retention. This is probably not dose related and is more common with central neuraxial administration.

Pharmacokinetics

Fentanyl is a potent opioid, highly lipophilic, producing a rapid onset of action of relatively short duration. After intravenous administration, fentanyl is rapidly distributed to brain, heart and other highly perfused tissues. It also crosses the placental barrier easily. Peak effect occurs in 5 minutes. Within a short time, the drug redistributes to inactive tissue sites like skeletal muscle and fat, associated with decrease in plasma concentration of drug, thus terminating its effect, About 75% of initial dose undergoes first pass pulmonary uptake.

When low doses (1-2μg/kg) are administered, redistribution terminates the effect and the drug appears short acting. With administration of large intravenous doses or continuous infusion, progressive saturation of inactive tissue sites occur, with redistribution becoming insufficient to terminate drug action which becomes dependent on slow elimination process and the drug appears to be long acting.

Pharamcokinetic Profile[22]

Volume of distribution at steady state (VDss) 335 litres

Clearance	1530 ml/min
Effect-site equilibration time	6.8min
Hepatic extraction ratio	0.8-0.1
Context – sensitive t½ (4hrs infusion)	260 min
Elimination t½	3.1 to 6.6 hours

Metabolism

Fentanyl is biotransformed in the liver to inactive metabolites, primarily norfentanyl and several hydroxylation products. Only 4-7% of drug is excreted unchanged in urine. Elimination t½ of fentanyl is longer than that of morphine because of high lipid solubility of fentanyl. Elimination t½ is prolonged in elderly patients. A high hepatic extraction ratio means that the clearance of fentanyl is limited by hepatic blood flow.

Routes of Administration and Dosage

- **Intramuscular**

  50-100µg may be administered intramuscularly as premedication 30-60 minutes prior to surgery.

- **Intravenous**

Can be given intraoperatively and for postoperative analgesia. Postoperative analgesia is achieved by intravenous loading dose of 1-2µg/kg followed by a continuous / variable infusion at rate of 1-2µg/kg/hr. It can be used for Patient – Controlled Analgesia (PCA) as a bolus dose of 20-50µg with lockout intervals.

- **Transdermal**

Transdermal fentanyl patch is available in four sizes, providing sustained release of fentanyl at rates of 25, 50, 75 and 100µg/hr for periods of 48-72

hours. Skin acts as a secondary reservoir contributing to prolonged residual fentanyl concentrations.

- **Transmucosal**

Oral transmucosal fentanyl citrate (OTFC) incorporates fentanyl citrate in a candy mixture shaped into a lozenge or stick. The median time to onset of analgesia is 4 minutes and duration of analgesia lasts for about 150 minutes.

• Intranasal

Fentanyl is administered with a metered dose device, with each spray delivering 4.5µg fentanyl. Time to onset of analgesia is about 15 minutes.

• Transpulmonary

Inhalational administration of fentanyl produces rapid, effective drug delivery. A dose of 300µg of fentanyl administered via an oxygen driven nebulizer produces effective postoperative analgesia in 5 min and lasts for about 2 hours.

• Neuraxial administration

Epidural and intrathecal administration of fentanyl are long established routes for intraoperative and postoperative analgesia.

Epidural dose as a single bolus administration varies from 1-3µg/kg. Analgesia begins in 15 minutes, lasting for 2-4 hours. Epidural infusion rates

range from 0.5-2.5μg/kg/h. In addition, fentanyl has been used in patient controlled epidural analgesia (PCEA) in doses of 20-25μg with a lockout interval of 6-10min and background infusion in the rate 0.5-1μg/kg/h.

The minimum intrathecal bolus requirement for postoperative analgesia is 20μg while a dose of 10μg is effective in obstetric patients. Onset of analgesia is usually within 5-15min and duration is variable, ranging from 1 to 5 hours. Other modes of administration include continuous / bolus administration via an intrathecal catheter.

Clinical Applications

• Premedication

Fentanyl in doses of 50-100μg may be administered intramuscularly 30-60 minutes prior to surgery. Oral transmucosal fentanyl citrate in doses between 15-20μg/kg, administration 45 minutes before surgery produces reliable preoperative sedation and facilitates induction of anaesthesia in children.

• Adjunct to general anaesthesia.

Fentanyl in doses of 1-2μg/kg given intravenously provides analgesia. It can be used as an adjuvant to blunt circulatory responses that occur during direct laryngoscopy for endotracheal intubation and sudden changes in the level of surgical stimulation. Large doses of fentanyl, 50-150μg/kg intravenously has been used as sole anesthetic agent

especially in cardiothoracic procedures, principally because of its stable hemodynamic effects.

- **Neruolept analgesia**

Innovar is a premixed combination, containing 2.5mg Droperidol and 0.05mg Fentanyl in each ml (50:1) used for neurolept analgesia and anesthesia.

- **Adjunct in Central neuraxial Block**

Fentanyl added to local anesthetic either intrathecally or epidurally, improves the quality of intraoperative analgesia and also provides good post operative analgesia.

- **Postoperative analgesia**

Fentanyl administration by intravenous, epidural, intrathecal and transdermal routes provide effective postoperative analgesia. Newer routes like intranasal and inhalational administration are being evaluated as minimally invasive means of post operative analgesia.

Side Effects

Commonly occurring side effects include dose dependent respiratory depression, nausea and vomiting, pruritus, urinary retention and bradycardia. These effects are reversed by administration of Naloxone intravenously.

Intrathecal fentanyl

Intrathecal fentanyl administration is an established route for intraoperative and postoperative analgesia.

Pharmacokinetics[22]

Fentanyl has the same baricity as cerebrospinal fluid at room temperature and addition to hyperbaric lignocaine or bupivacaine makes the solution hyperbaric. On injection into subarachnoid space, fentanyl mixes with CSF and attaches itself to spinal opioid receptors. Protein binding of drug in the CSF is negligible and the concentration of opioid in the CSF is thus free drug concentration. CSF dynamics do not provide any means of drug removal. Diffusion into the spinal cord and absorption into the blood flowing through spinal cord must remove all the fentanyl. The rate determining step of drug removal is likely to be the rate constant for fentanyl transfer from CSF to spinal cord and this rate constant is directly related to lipophilicity. Fentanyl can also migrate from the CSF into epidural vascular compartment via the dura. However, details of systemic pharmacokinetics of fentanyl are not known. Once in the CSF, fentanyl like other opioids, spreads rostrally. Because of the high affinity of fentanyl with binding sites in the lipid-rich spinal cord, only 10% of administered dose migrates to cervical region.

Application

Intrathecal fentanyl is usually combined with local anaesthetics for perioperative anaesthesia and analgesia, particularly in obstetrics.

Fentanyl administration intrathecally provides more intense and complete analgesia at rest, at a lower dose requirement when compared to the epidural or intravenous routes.

Modes of Administration and Dosage

Fentanyl is administered intrathecally as single bolus injection or as repeated observer-administered, PCA boluses and continuous infusion via an intrathecal catheter. Effective postoperative analgesia can be achieved with bolus doses of 20μg. Infusions of 0.8μg/kg/h produces satisfactory analgesia in patients undergoing thoracotomy.

Side Effects of Intrathecal fentanyl

Side effects are relatively minor with intrathecal fentanyl. The incidence of clinically significant respiratory depression is relatively low, as intrathecal administration of fentanyl results in lower systemic absorption than epidural route and the intrathecal dose requirement is lower than the epidural dose requirement. A 30% incidence of urinary retention, varying incidence of pruritus and occasional episodes of nausea have been observed.

PHYSIOLOGICAL AND ANATOMICAL CHANGES IN PREGNANCY

The hormone progesterone could be considered as the most important physiologic substance in pregnancy. The most important physiologic role of progesterone is its ability to relax smooth muscle. All other physiological changes stem from this pivotal function.

Cardiovascular system

Blood Constituents

The blood volume increases by 35% in pregnancy and is seen from first trimester and consists of increased red cell mass by 20% and to a greater extent, plasma by about 45% with consequent reduction in hemoglobin concentration despite a raised total hemoglobin content.

Cardiac output

Cardiac output increases by 40-50%, heart rate increases by 15% and stroke volume is increased by 30%. The increase in cardiac output starts in the first trimester

Peripheral circulation

There is decreased peripheral resistance and no change in venous pressure. Blocking autonomic system may result in dramatic decrease in arterial blood pressure suggesting a chronically active sympathetic tone.

Respiratory system

There is edema of upper respiratory tract due to mucosal capillary engorgement. Minute ventilation is increased by 50%. Tidal volume increases by 40% Respiratory rate increases by 15%. Total lung compliance reduces by 30% The functional residual capacity is reduced by about 15-20% at term. Residual volume is reduced by 20%.

Other systems

Oxygen consumption increases. Renal blood flow and glomerular filtration rate increase. A reduction in lower esophageal sphincter tone occurs. Placental gastin increase gastric acidity.

Epidural and subarachnoid spaces

Engorgement of epidural veins is seen due to increased intra abdominal pressure caused by gravid uterus. Gravid uterus ultimately reduces both epidural and sub arachnoid spaces. The nerve fibers have

increased sensitivity to local anaesthetics during pregrancy (due to increased progesterone).

Supine hypotension syndrome

The incidence of reduction of maternal BP associated with supine position is 10%. The reduction is associated with diaphoresis, nausea and vomiting, changes in cerebration is called supine hypotension syndrome.

On assuming supine position, gravid uterus totally compresses inferior vena cava resulting in pooling of venous blood and increased venous pressure in the lower extremities eventually decreasing the venous return to the heart. Hence cardiac output decreases and ultimately systemic blood pressure falls. The increase in uterine venous pressure may affect the well being of the fetus through a resultant decrease in uterine blood flow.

Compression of the aorta causes arterial hypotension in the lower extremities and uterine arteries which can further compromise utero placental blood flow and result in fetal hypoxia. Since uterine blood flow is not auto regulated, blood flow to the uterus is directly proportional to the perfusion pressure, that is, the difference between uterine artery and venous

pressure. Hence even with normal upper extremity blood pressure, utero placental perfusion may decrease in supine position.

Sympathetic blockade under spinal anaesthesia further decreases the venous return and the parturient's ability to compensate by vasoconstriction. Thus hypotension is much more common and severe under spinal anaesthesia.

The incidence of supine hypotension can be minimised by nursing the patient in lateral position. Displacement of uterus can be achieved by giving a left lateral tilt of 15^0 to the operating table or elevation of right buttock 10-15 cm with a wedge.

MATERIALS AND METHODS

This study was conducted between March 2006 and July 2006 at Government Raja Mirasudar Hospital, Thanjavur Medical college, Thanjavur after getting approval from the ethics committee. A total of 50 patients who underwent elective caesarean section were taken up for the study. The age of the patients ranged from 20-37 years weighing 40-65 kg and height ranging from 140-167gms. All patients were thoroughly examined pre-operatively. Only patients belonging to ASA grade I and grade II were selected for the study. An initial preoperative counselling and reassurance to gain confidence of the patient was done. Informed consent was obtained and procedure was explained.

Inj.Ranitidine 50mg was given intravenously as premedication 45minutes before surgery and patients were randomized into 2 groups of 25 each

Group A – patients received 1.5ml of 0.5% hyperbaric bupivacaine (7.5mg)

Group B – patients received 1ml of 0.5% Bupivacaine (5mg) with 0.5 ml

fentanyl (25 μg)

The final volume of the injected solution is 1.5ml on both groups.

In the assessment room, vital parameters like pulse rate, blood pressure, respiratory rate and baseline investigations like hemoglobin, urine analysis for albumin and sugar, blood sugar, urea and creatinine and ECG were checked. Though examination of all the systems and airway assessment was done.

Visual Analog scale (VAS) was explained to the patient. The patients were shown a 10 cm long scale marked 0-10 on a blank paper and told that '0' represented 'no pain' and 10 represented worst possible pain. Patients were advised nil per oral 6 hours before the procedure.

Procedure

In the operating room, appropriate equipment for airway management and emergency drugs were kept ready. Patients were shifted to the operating room. The horizontal position of the operating table was checked and the patient was placed on it. A Crawford wedge was kept under the right buttock to give a lateral tilt to the uterus. The noninvasive blood pressure monitor, pulse oximeter and electro cardiogram leads were connected to the patient. Preoperative baseline systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation was recorded. Patients were cannulated with 18G intravenous cannula and preloaded with 1000ml of Ringers lactate. The patient was placed in left lateral position. The skin over the back was prepared with antiseptic solution and draped with sterile towel. The L3- L4 interspaces was identified and 25G

Quincke Babcock spinal needle was introduced in this space through midline approach. After confirming free flow of CSF, the prepared solution was injected. The patients were made to lie supine immediately after injection and left lateral tilt was provided by wedge under right buttock. The following parameters were observed:

Sensory Block

Sensory block was assessed by loss of sensation to pinprick using 21G sterile needle bilaterally along the mid-clavicular line. This assessment was started immediately after turning the patient supine and continued every 15 seconds till loss of sensation to pinprick at T_{10} level was noticed. Onset of sensory block was taken as the time from intrathecal injection to loss of pinprick sensation at T_{10} dermatome. This pin prick testing was continued till the peak block height was reached and the time was noted. Sensory block was checked every 15 minutes till sensory regression to L_1 from the maximal level of sensory block . This interval is taken as the time to regression to L_1.

Motor block

Motor block was assessed bilaterally using modified Bromage scale.

Modified Bromage scale

0 - No block. Able to raise extended leg against gravity

1 - unable to raise extended leg, just able to flex knees

2 - unable to flex knees, but able to flex ankle

3 - Total block. Inability to flex ankle / move leg.

Assessment of motor block was started immediately after turning the patients supine. It was tested every 15 seconds till Bromage score of 1 was reached. Onset of motor block was taken as the time to achieve Bromage score 1 from the time of injection. The degree of motor block after 30 minutes of injection was noted and this was taken as the maximum degree of motor block. Thereafter, motor block was assessed every 15 minutes till it reached Bromage score or 0. Duration of motor block was taken as time from subarachnoid injection to return of Bromage score to 0.

Vital signs and side effects

The systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation were recorded every minute for the first 10 minutes and thereafter every 5 minutes until the immediate post operative period.

Hypotension was defined as fall in systolic blood pressure >30% from baseline or systolic blood pressure <90 mm Hg. This was planned to be managed with intravenous ephedrine in increments of 6mg. Bradycardia was defined as heart rate <60/ min and was planned to he managed with intravenous atropine 0.6 mg. Respiratory depression was said to be present if respiratory rate <8/ min and /or Spo_2 <85%. This was planned to be managed

with mask ventilation or intubation and IPPV.

The occurrence of sedation was assessed using a bedside scale .

Sedation scale

0 – none	Patient alert
1 - mild	occasionally drowsy, easily aroused
2- moderate	Frequently drowsy, easily aroused
3- Somnolent	difficult to arouse

Vomiting was planned to be managed with inj. ondansetron 8mg intravenously. Pruritus was planned to be managed with reassurance or inj. pheneramine maleate 22.5mg intravenously. Urinary retention was monitored post operatively and catheterization was planned in patients with retention>6 hours.

Quality of surgical anaesthesia

Surgical anaesthesia was graded 'Excellent' if there was no complaint of pain from the patient at any time during surgery, 'Good' if there was minimal pain or discomfort which was relieved by small dose of intravenous fentanyl 10µg and 'poor' if general anaesthesia had to be administered.

Assessment of pain in Post Anaesthesia care unit

Patients were shifted to post anaesthesia care unit after completion of surgery. Vital signs were recorded every 15 minutes in the first hour after surgery, 30 minutes for the next 2 hours and thereafter every hour for the

next 3 hours. Sensory and motor block assessment was done every 15 minutes till recovery of pinprick sensation to L_1 level and Bromage score 0 respectively. Patients were shifted to post operative ward after complete resolution of motor blockade and stabilization of blood pressure.

Assessment of pain and duration of analgesia

At the end of surgery, the degree of pain was assessed using Visual Analog scale (VAS). In the post anaesthesia care unit, pain assessment using VAS was done every 15 minutes till VAS score ≥ 4was reached. The VAS was also noted whenever the patient complained of pain. Duration of effective analgesia was defined as time interval between subarachnoid block and the time to reach VAS ≥ 4. Inj. Diclofenac sodium 50mg was given intramuscularly as the rescue analgesic when VAS reached ≥ 4.

Patients were monitored for 24 hours to detect side effect like respiratory depression, urinary retention, pruritus and nausea and vomiting.

Assessment of the fetus

The APGAR scores at 1 minute and 5 minute intervals after delivery of the baby was noted. Significant depression was planned to he managed with proper resuscitative measures and by inj. naloxone 1-4µg/ kg .

OBSERVATION AND RESULTS

Of the 50 patients taken up for this study, 25 patients were randomly allocated to two groups.

Group A – Patients received 7.5mg of 0.5% hyperbaric bupivacaine (1.5 ml)

Group B – Patients received 5mg of 0.5% hyperbaric bupivacaine (1ml) with 25μg fentanyl (0.5ml).

Total volume was 1.5ml in both groups.

Age Distribution

The range of ages in group A was 20-37 years while in group B, it was 20-35 years. The average age in both groups were similar.

Age in years	Group A	Group B
Minimum	20	20
Maximum	37	35
Mean	26.04	25.68

The distribution of ages were also similar in both groups as shown by the following table and multiple bar diagram.

Age in years	Group A	Group B
20 – 24	11	12

25 – 29	7	8
30 – 34	5	4
35 – 37	2	1

Weight distribution

The mean weight of the patients were comparable in both groups as shown by the table and bar diagram.

Weight	Group A	Group B
Range	40-65	40-65
Mean	52.68	52.2

Height distribution

The mean height of the patients were comparable in both groups as shown by the table and bar diagram.

Height in cm	Group A	Group B
Range	140-165	140-165
Mean	153.12	153.72

Sensory Block

Onset at T_{10}

The mean time of onset of sensory block at T_{10} was **130.8 ± 22.3 seconds** in Group A with a range of 105-180 seconds and **138.6 ± 22.61 seconds** in Group B with a range of 105 – 180 seconds. They were similar and statistically not significant which was confirmed by unpaired Student's t test($p > 0.1$) as shown in the bar diagram.

Maximum level of sensory block

The range of maximal level of sensory block was **T_4 – T_7** in Group A and in Group B, it was between **T_4 – T_8**.

LEVEL	Group A	Group B
T_4	6	3
T_5	13	3
T_6	5	15
T_7	1	3
T_8	0	1

Time to peak sensory block

In group A, the time taken to reach the maximum level was **259.2 ± 26.88 seconds** with a range of 210 – 300 seconds, whereas in Group B, it was **318 ± 33.26 seconds.** This was statistically significant ($P < 0.05$)

Time to regression to L_1

The mean time to regression of sensory blockade to L_1 was **122.4 ± 10.31 minutes** in Group A with a range of 105 – 135 minutes In Group B, it was **159.6 ± 14.28 minutes** with a range of 135 – 195 minutes. This was statistically significant ($P < 0.01$).

Motor Block

Onset of Grade I motor block

The time taken to achieve Grade 1 motor block was **159 ± 20.31**

seconds in group A with a range of 120 – 195 seconds. In group B, it was **160.8 ± 22.3 seconds** with a range of 135 – 210 seconds. This was found to be statistically insignificant

(P > 0.1).

Maximum degree of motor block

The maximum degree motor block ranged between grade 3 and grade 2 in both the groups. The distribution of patients in each grade is shown in the table.

DEGREE OF MOTOR BLOCK	Group A	Group B
GR O	0	0
GR 1	0	0
GR 2	3	7
GR 3	22	18

Duration of motor block

The mean duration of motor block was **102±10.06 minutes** in group A with a range of 75-120 minutes. In group B ,it was **70.8±11.06 minutes** with a range of 60-90 minutes. This was found to be statistically highly significant (P < 0.01)

Duration of effective analgesia

The mean duration of effective analgesia was **148.56 ± 13.13 minutes** with a range of 115 – 174 minutes in group A, but in group B, it was **200.32minutes** with a range of 173 – 234 minutes. This was statistically highly significant. ($P < 0.01$).

Quality of surgical anaesthesia

In this study, the quality of surgical anesthesia was graded as 'excellent' in all but 3 patients in group A who complained of discomfort intraoperatively and required 10μg fentanyl intravenously.

Incidence of hypotension

In group A, 21 patients had hypotension whereas in group B, only 9 patients had hypotension. The incidence is **84%** with group A against **36%** in group B. This was tested to be statistically significant ($P < 0.001$).

Mean ephedrine requirements

The mean ephedrine required to counter hypotension was **12mg** in group A whereas it was **3.12mg** in group B.

Side effects

The incidence of pruritus was **32%** in Group B (8 patients) whereas it was nil with group A. Pruritus in Group B was mild and settled with reassurance.

3 patients complained of nausea in Group A and none in Group B. This was attributed to the discomfort for which they received intreoperative supplemental analgesia. Bradycardia and respiratory depression did not occur in any of the patients involved in the study.

Urinary retention was seen in 3 patients in Group B, they were managed conservatively and one patient required catheterization.

Sedation of Grade 1 was seen with 7 patients in Group B.

Assessment of the fetus

All the babies showed 1 minute APGAR of 8 and above and 5 minute APGAR of 9 and above in both the groups. The difference was statistically insignificant.

REVIEW OF LITERATURE

Effects of Intrathecal Local Anaesthetic-Opioid Combination

Akerman B, Arwestrom E, and Post C[23] undertook a study in mice, to compare the antinociceptive effects of intrathecal injection of mixtures of morphine with bupivacaine or lignocaine, with the effect of these agents when administered alone. They observed an increase in the intensity and duration of antinociception when morphine was administered with local anaesthetics. They confirmed that morphine did not affect the motor block produced by local anaesthetics and confirmed the synergistic analgesic effect of the combination.

Maves TJ and Gebhart GF[24] conducted a study in rats to quantify the interaction between intrathecal morphine and lignocaine using models of visceral and somatic nociception. They demonstrated antinociceptive synergy between intrathecal morphine and lignocaine during visceral and somatic nociception at dosages that did not impair motor function.

Fraser HM, Chapman V and Dickenson AH [25] tested the effect of intrathecal lignocaine either alone or in combination with low dose morphine on the C, A δ and Aβ evoked responses of nociceptive neurons in the dorsal

horn of rats. They observed marked potentiation of the inhibition of C-fibre responses when lignocaine and morphine were used in combination, compared to either agent used alone.

Wang C, Chakrabarti MK and Whitman JG[26] examined the effects of bupivacaine administered intrathecally on sympathetic efferent and Aδ, C fiber mediated afferent pathways in dogs and its interactions with intrathecal fentanyl. The concluded that intrathecal bupivacaine had no selectivity for the afferent and efferent pathways and that intrathecal fentanyl acted synergistically to enhance the effect of bupivacaine on the afferent pathway without a measurable effect on sympathetic outflow.

Intrathecal Fentanyl as Adjunct to Subarachnoid Local Anaesthetics

Hamber EA and Viscomi CN[1] analyzed the efficacy of intrathecal lipophilic opioids as adjuncts to spinal anaesthesia by reviewing medline literature from 1980 to the present. They reported benefits that included an enhancement of the quality of spinal anaesthesia without prologation of motor block, the need for smaller doses of local anaesthetic and less troublesome side effects than intrathecal morphine. They suggested significant roles for these agents as adjuncts for spinal anaesthesia in obstetric and outpatient procedures.

A study to evaluate the effect of intrathecal fentanyl on hyperbaric bupivacaine induced subarachnoid block was done by Singh H, Yang J, Thornton K and Giesecke AH on forty three male patients undergoing lower extremity or genitourinary surgery[27]. They concluded that addition of 25μg fentanyl to 13.5mg of hyperbaric bupivacaine prolonged the duration of bupivacaine induced sensory block by 28% and reduced the analgesic requirement in the early postoperative period by 40%, without enhancing the onset of sensory and motor blocks or prolonging the duration of bupivacaine induced motor block.

Kuusniemi KS, Pihlajamaki KK, Pitkanen MT, Helenius HY and Kirvela OA[28] evaluated the effect of 25μg fentanyl added intrathecally to 10 mg, 7.5 mg and 5 mg of 0.5% bupivacaine in eighty patients undergoing urological procedures. They concluded that the addition of 25μg fentanyl to 5 mg bupivacaine resulted in a short lasting motor block but the same level of sensory analgesia when compared to larger doses of bupivacaine with or without fentanyl.

The effect of addition of fentanyl to bupivacaine administered

intrathecally for cesarean delivery was evaluated in 56 term parturients by Hunt CO et al[29]. They concluded that 67% of patients in the bupivacaine only group complained of intraoperative pain and required opioids. None of the patients who received greater than or equal to 6.25µg fentanyl required intraoperative opioids and the duration of effective analgesia was prolonged by 120 minutes in the fentanyl group.

Belzarena SD[30] studied the clinical effects of subarachnoid fentanyl in 120 women undergoing cesarean section under spinal anesthesia with 0.5% hyperbaric bupivacaine and concluded that a combination of bupivacaine with low dose (0.25µg/kg) fentanyl provided excellent surgical anaesthesia with short acting postoperative analgesia.

Chu CC et al[31]. studied the effect of 0.5% hyperbaric bupivacaine combined with fentanyl in cesarean section. They concluded that 12.5µg fentanyl increased the quality of surgical analgesia and prolonged postoperative analgesia.

Shende G, Cooper M and Bowden MI[32] concluded that adding 15 µg fentanyl to hyperbaric bupivacaine in spinal anesthesia markedly improves intraoperative anaesthesia for caesarean section.

Local Anaesthetic Sparing Effect of Intrathecal Fentanyl

In a study conducted by Ben-David B, Miller G, Gavriel R and Gurevitch A[33], 32 women scheduled for cesarean delivery were randomized to receive spinal injection of either 10mg 0.5% isobaric bupivacaine or 5mg 0.5% isobaric bupivacaine with 25µg fentanyl. They concluded that bupivacaine 5mg with fentanyl 25µg provided good surgical anaesthesia with less incidence of hypotension, vasopressor requirement and nausea than 10mg bupivacaine.

Ben-David B, Frankel, R, Arzumonov T, Marchevsky Y and Volpin G[34] conducted a study on 20 patients aged > 70 years, undergoing surgical repair of hip fracture. Patients were randomized to receive either 4mg bupivacaine with 20µg fentanyl or 10 mg bupivacaine alone intrathecally. They concluded that a 'minidose' of 4mg bupivacaine in combination with 20µg fentanyl provided good surgical anaesthesia, while causing less hypotension and nearly eliminating the need for vasopressors compared to the 10mg bupivacaine group.

Kang FC, Tsai YC, Chang PJ and Chen TY[35] studied the effects of 5 mg hyperbaric bupivacaine with 25µg fentanyl against 8 mg hyperbaric

bupivacaine in spinal anaesthesia for caesarean section and concluded that small dose bupivacaine – fentanyl combination provided more hemodynamic stability when compared to bupivacaine alone.

Grant GJ, Susser, Cascio M, Moses M and Zakowski MI[36]conducted a study on non labouring partiurients and concluded that 25µg fentanyl does not produce clinically important maternal hemodynamic changes.

Karmarez A, Kaya S, Turhanoglu S and Ozhyilmaz MA[37] studied the effects of adding 25µg fentanyl to 4 mg plain bupivacaine with 0.5% plain bupivacaine alone in spinal anaesthesia for TURP and concluded that hypotension was significantly more common in plain bupivacaine group.

Jain K, Grover VK, Mahajan R and Batra YK[38] evaluated the hemodynamic stability offered by varying doses of fentanyl with low dose bupivacaine for spinal anaesthesia in caesarean delivery and concluded that intrathecal fentanyl with low dose bupivacaine provides good surgical anaesthesia without compromising hemodynamics and neonatal outcome.

Side Effect Profile of Intrathecal Fentanyl

Chaney MA[39] in a retrospective review of literature on the side effects of intrathecal and epidural opioids reported pruritus, nausea and vomiting,

urinary retention and respiratory depression as the four classic side effects, most of which were found to be dose related.

Varrassi G et al[40]. conducted a study to evaluate the ventilatory effects of subarachnoid fentanyl 50, 25 or 12.5µg. They concluded that 50µg subarchnoid fentanyl caused an early respiratory depression and recommended avoiding the dose for postoperative analgesia in the elderly. The other groups did not show occurrence of respiratory depression. Mild pruritus, sedation, nausea and vomiting were the other observed side effects in groups receiving 50 and 25µg fentanyl.

Siddik-Sayyid et al[41]. in a study on 48 parturients undergoing cesarean section concluded that supplementation of spinal bupivacaine anaesthesia for cesarean delivery with intrathecal fentanyl 12.5µg provided a better quality of anaesthesia and was associated with a decreased incidence of side effects when compared to supplementation with the same dose of fentanyl intravenously.

Dahlgren G et al[42]. compared the effects of intrathecal fentanyl, sufentanil or placebo when administered with 12.5mg of 0.5% hyperbaric bupivacaine for cesarean section. They observed that small doses of opioid

added to bupivacaine reduced the need for intraoperative antiemetic medication and increased duration of analgesia in the early postoperative period. Pruritus was a frequent and dose related side effect.

Herman NL et al[43]. performed a study to establish dose-response relationship of intrathecal fentanyl for both analgesia and ventilatory depression. They observed that $ETCO_2$ displayed a dose-related increase at fentanyl doses > 15ug. They observed that even in the absence of overt signs and symptoms of somnolence, intrathecal fentanyl induced a change in ventilation within the effective analgesic dose range. Pruritis also showed a dose-response relationship.

Manullung TR, Viscomi CM and Pace NL[44] compared intrathecal 20μg fentanyl with intravenous ondanseteron 4 mg for prevention of nausea and vomiting during cesarean deliveries under spinal anaesthesia. They concluded that intrathecal fentanyl as part of the spinal anaesthetic for cesarean delivery was superior to intravenous ondanseteron for prevention of intraoperative nausea.

Neonatal outcome

Corke BC, Datta S, Ostheimer GW, Weiss JB and Alper MH[45] studied the effects of short period of maternal hypotension upon the neonate during

initiation of spinal anaesthesia for cesarean section and concluded that short period of hypotension (< 2 minutes) was not harmful to the neonate.

Kangas- Saarela T et al[46] in a study on recovery of 16 infants born by spinal anaesthesia in which either ephedrine or fluid load was used to prevent maternal hypotension concluded that smaller doses of ephedrine given to mother to prevent maternal hypotension have only short lived effects on neonate's central nervous system.

Craig M, Palmer, James Mackintosh and Ronald C Cork et al[47] studied the effects of intrathecal fentanyl on fetal heart rate changes and concluded that incidence of fetal heart rate changes was 6 to 12% and there was no changes in neonatal outcome.

DISCUSSION

The primary aim of this study was to compare the efficacy of the combination of 25µg fentanyl and 5 mg of hyperbaric bupivacaine 0.5% with that of 7.5mg hyperbric bupivacaine alone for spinal anesthesia in LSCS regarding incidence of hypotension and mean ephedrine requirements apart from other usual parameters.

Onset of sensory block

The mean time to onset at T10 was **130.8 seconds** in Group A and **138.6 seconds** in Group B, Here, no statistically significant difference was

noted.

This correlates with the study done by Singh H, Yang J, Thornton K and Giesecke AH[27] who concluded that addition of intrathecal fentanyl 25µg to hyperbaric bupivacaine did not hasten the onset of sensory block.

Roussel JR and Heindel LS[48] also concluded that addition of fentanyl 25µg to 0.5% hyperbaric bupivacaine did not enhance the onset of sensory block.

Maximum level of sensory block

The median of the upper limit of sensory block was **T_5** in Group A and **T_6** in Group B, The addition of fentanyl to smaller dose of subarachnoid hyperbaric bupivacaine provided adequate level of sensory block.

This correlated with the study of Kuusniemi et al[28] who demonstrated a sensory block height of greater than T_7. They did not observe an increase in height of sensory block by the addition of 25µg fentanyl to intrathecal hyperbaric bupivacaine.

Time to peak sensory block

The time to peak sensory block was **259.2 seconds** in Group A while it was **318 seconds** in group B, a statistically significant observation. This may be probably attributed to the lower dose of bupivacaine in Group B.

Time to regression to L_1

The mean time to regression to L_1 was **122.4 minutes** in group A whereas in Group B, it was **159.6 minutes**. The addition of fentanyl 25µg to bupivacaine prolonged the time to regression to L_1. This could be attributed to selective blockade of Aδ and C afferents which mediate the sensation of pin prick.

This correlated with findings of Liu S et al[49] who concluded that regression of pinprick, touch and cold was prolonged by addition of fentanyl to subarachnoid local anaesthetic.

Belzarena SD[30] concluded that addition of fentanyl increased the time required for regression to T_{12} in patients receiving fentanyl – local anaesthetic combination intrathecally for caesarean section.

Kuusniemi KS et al[28] also showed a prolongation of sensory block with addition of fentanyl to bupivacaine intrathecally.

Ben David B, Solomon E, Levin H, Admoni H and Goldik Z[50] showed that the addition of 10µg fentanyl to small dose bupivacaine intensified and increased the duration of block.

Onset of Motor block

The time to achieve Grade I motor block on Bromage scale was **159**

seconds in group A and **160.8 seconds** in group B which was statistically insignificant.

This observation correlated with the study done by Singh H, Yang JS, Thornton K and Giesecke AH[27] who demonstrated that intrathecal fentanyl does not enhance the onset of bupivacaine induced motor block.

Maximum Grade of motor block

The median grade of motor block at 30 minute testing time measured using modified Bromage scale was Grade III in majority of patients among both groups. Patients with grade II block were also comfortable intra operatively.

Duration of Motor block

In our study, the mean duration of motor block was **102 minutes** in group A and **70.8 minutes** in group B which was significant. Hence we conclude that addition of 25μg fentanyl to 0.5% hyperbaric bupivacaine intrathecally did not prolong the duration of motor block.

This correlated with the study of Singh H et al[27] who showed that addition of fentanyl 25μg to intrathecal bupivacaine did not prolong the duration of motor block.

The duration of motor block produced by bupivacaine intrethecally was shown to be dose dependent. Our findings correlated with Liu et al[49],

who reported that each additional mg of bupivacaine was associated with an increase in the duration of motor block.

Duration of effective analgesia

The mean duration of effective analgesia was **148.56 minutes** in Group A and **200.32 minutes** in group B which was highly significant statistically.

This correlated with the study of Singh et al[27]who demonstrated that only fewer patients receiving fentanyl 25µg with 0.5% bupivacaine demanded pain relief in the early postoperative period when compared to patients receiving bupivacaine alone intrathecally.

Fernandez Galinski et al[51]showed that 25µg fentanyl added to 12.5mg intrathecal bupivacaine significantly decreased postoperative pain intensity.

Quality of surgical anaesthesia

In our study, 3 patients in group A complained of discomfort intraoperatively and required supplementation with intravenous fentanyl 10µg. The quality of surgical anaesthesia was excellent in all other patients.

Intrathecal opiords produce analgesia by inhibition of synaptic transmission in nociceptive afferent pathways. The improvement in quality of surgical anaesthesia by the addition of fentanyl to intrathecal bupivacaine

was evident in our study.

This correlated with the study of Belzarena SD[30] which showed that the combination of bupivacaine and low dose fentanyl provide excellent surgical anaesthesia (100%) when compared to bupivacaine used alone (87%) in spinal anaesthesia for caesarean section.

Our findings correlated with the study of Siddik – Sayyid et al[41] who reported that spinal anesthesia with 0.5% bupivacaine and 12.5 μg fentanyl provided better quality of anaesthesia when compared to supplementation with same dose of fentanyl intravenously for cesarean section.

Synergistic blockade of Aδ and C afferents by fentanyl allowed sub-therapetic dose of bupivacaine to maintain surgical anaesthesia during regression of spinal anaesthesia in our study.

Our results are consistent with experimental studies done by Tejwani GA et al[52] and Akerman B et al who have shown that the combination of opioids and local anaesthetics are synergistic for somatic analgesia and that intrathecal opioids markedly enhanced analgesia from sub therapeutic dose of intrathecal local anaesthetics.

Incidence of hypotension

In our study, the incidence of hypotension was 84% in group A and

36% in group B. This was statistically significant and could be attributed to the lower dose of bupivacaine used in the group. Our study confirmed the fact that the decrease in sympathetic efferent activity after spinal anesthesia with bupivacaine was dose related and that intrathecal fentanyl caused neither by itself nor in combination with bupivacaine ,any further depression of efferent sympathetic activity

This correlated with the study of Ben David et al[34] who showed that a minidose of 4mg bupivacaine and 20µg fentanyl given intrathecally dramatically lowered the incidence of hypotension and nearly eliminated the need for vasopressors.

Another study by Ben David B et al[33] confirms that 25µg fentanyl in combination with 5 mg isobaric bupivacaine caused less incidence of hypotension (31%) when compared to 10mg isobaric bupivacaine (94%)in spinal anesthesia for caesearean section.

In the study done by Grant GJ et al[36], it was confirmed that intrathecal administration of 25µg fentanyl did not produce clnically important maternal hemodynamic changes in non-laboring term parturients.

Kang FC et al[35], in their study on spinal anaesthesia for caesarean delivery revealed that the combination of small dose bupivacaine 5mg and

fentanyl 25µg provided more stable hemodynamic status when compared to 8mg hyberbaric bupivacaine used alone.

Mean ephedrine requirements

The mean ephedrine requirements were 12mg with group A and 3.12 mg in group B. This is highly significant.

Ben David B et al[33] confirms that the mean ephedrine requirements were 23.8mg with the combination of 5mg isobaric bupivacaine and 25µg fentanyl but it was 2.8mg with 10mg bupivacaine when used intrathecally for caesarean section.

Kangas Saarala et al[46]has concluded that small doses of ephedrine given to correct maternal hypotension under spinal anaesthesia have only shortlived effect on the fetal central nervous system.

Side effects

Pruritus occurred in 8 patients in group B, its incidence being 32% .It was mild and occurred most commonly in the face .

Our study correlated with the view of Hamber EA and Viscomi CM that pruritus being a common complication with intrathecal fentanyl.

Kuusniemi KS et al[28] reported pruritus as the most common adverse effect occurring in 22.5 % of the patients receiving intrathecal fentanyl with

bupivacaine which correlated with our study.

In our study, 3 patients in group A complained of nausea intraoperatively. This could be attributed to the discomfort these patients felt intraoperatively for which supplementation of analgesia was given.

The occurrence of excellent surgical anaesthesia in patients receiving fentanyl could be the cause for absence of nausea in group B. This correlates with the study conducted by Manullang TR et al[44] which concludes that intrathecal fentanyl as a part of spinal anesthetic for caesarean delivery was superior to intravenous ondansetron for preventing intraoperative nausea.

Sedation of grade I was seen in 7 patients in group B. Patients were easily arousable and this could be attributed to the addition of fentanyl.

Uninary retention upto 6 hours was noticed in 3 patients in group B. It is thought to be caused by an increase in the urethral sphincter tone and a decrease in detrusor tone. 2 patients were managed conservatively and they passed urine. One patient required catheterisation.

A single dose of intrathecal fentanyl does not migrate to the medullary respiratory center in sufficient concentration to cause respiratory depression. Consistent with this observation, respiratory depression did not occur in our

study

Bradycardia did not occur in either of the groups in our study.

Assessment of the fetus

The APGAR scores at 1 minute and 5 minutes were comparable in both the groups and was statistically insignificant. This proves that intrathecal fentanyl 25µg as an adjuvant to hyperbaric bupivacaine does not adversely affect the neonatal outcome.

SUMMARY

This study was designed to compare the efficacy of the combination of 25µg fentanyl and 5mg hyperbaric bupivacaine 0.5% with that of 7.5mg hyperbaric bupivacaine 0.5% alone intrathecally for lower segment caesarean section. The observations are:

1. The incidence of hypotension was significantly reduced by fentanyl-low dose bupivacaine combination.
2. The low dose bupivacaine–fentanyl combination significantly reduced the ephedrine requirements to treat hypotension.
3. Intrathecal fentanyl improved the quality of surgical anaesthesia.
4. The addition of fentanyl significantly prolonged the time to sensory regression to L1
5. The addition of fentanyl allowed low dose bupivacaine to prolong the duration of effective post operative analgesia with rapid motor recovery.
6. The addition of fentanyl intrathecally had no effect on the onset of bupivacaine induced sensory and motor block .
7. The incidence of side effects was limited to mild pruritus and grade I sedation in the fentanyl added group.

8. Intrathecal fentanyl does not adversely affect the neonatal outcome

CONCLUSION

This study confirms that the combination of intrathecal fentanyl 25µg with 5mg hyperbaric bupivacaine 0.5% reduces the incidence of hypotension and ephedrine requirements, produces excellent surgical anesthesia, prolongs the duration of effective analgesia with rapid motor recovery and minimal side effects when compared to 7.5mg hyperbaric bupivacaine 0.5% in lower segment caesarean section without significant effects on the neonatal outcome.

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ROFORMA

A COMPARISON OF INTRATHECAL FENTANYL –BUPIVACAINE COMBINATION WITH BUPIVACAINE ALONE IN LSCS

NAME: AGE: IP No:

HEIGHT: WEIGHT:

DIAGNOSIS:

PREANAESTHETIC EVALUATION

HISTORY:

PULSE:

BP:

RR:

CVS:

RS:

OTHER:

AIRWAY:

ASA GRADE:

ANAESTHESIOLOGIST:

SURGEON:

INVESTIGATIONS

Hb :

URINE ALBUMIN :

SUGAR :

BLOOD SUGAR :

UREA :

CREATININE :

E.C.G :

PRELOADING :

INTRATHECAL INJECTION

POSITION :

INTERSPACE :

NEEDLE :

ONSET OF SENSORY BLOCK AT T IO :

PEAK LEVEL :

TIME TO PEAK LEVEL :

TIME TO REGRESSION TO L_1 :

ONSET OF MOTOR BLOCK GR I :

MAXIMUM GRADE OF MOTOR BLOCK :

DURATION OF MOTOR BLOCK :

QUALITY OF SURGICAL ANAESTHESIA :

PERIOD OF EFFECTIVE ANALGESIA :

INTRAOPERATIVE MONITORING

Time (min)	1	2	3	4	5	6	7	8	9	10	15	20	25	30	35	40	45	50	55	60
PULSE																				
BP																				
EPHEDRINE																				
RR																				
SPO_2																				

DRUGS : IVFLUIDS:

EPHEDRINE :

ATROPINE :

OTHERS :

APGAR SCORE

1. MINUTE :

5 .MINUTE :

POST OPERATIVE MONITORING

TIME (MIN)	0	15	30	45	60	90	120	180	240	300	360
PULSE											
BP											
RR											
SPO^2											
VAS											

SIDE EFFECTS : ***TREATMENT***

RESPIRATORY DEPRESSION :
NAUSEA & VOMITING :
PRURITUS :
URINARY RETENTION :
OTHERS :

SUPERVISING ANAESTHESIOLOGIST PROF & HOD

DEPT OF ANAESTHESIOLOGY