EVALUATION OF THE EFFICACY OF 150 MICROGRAMS OF INTRATHECAL MORPHINE WITH BUPIVACAINE COMPARED TO 250 MICROGRAMS FOR POST OPERATIVE ANALGESIA FOLLOWING ABDOMINAL HYSTERECTOMY - A DOUBLE BLINDED RANDOMIZED CONTROL STUDY.

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT OF THE TAMILNADU **DR.M.G.R MEDICAL UNIVERSITY TAMILNADU, CHENNAI** FOR THE DEGREE OF **M.D. (ANESTHESIOLOGY – BRANCH-X)** TO BE HELD IN MARCH 2009.

CERTIFICATE

This is to certify that the dissertation entitled "**EVALUATION OF THE EFFICACY OF 150 MICROGRAMS OF INTRA THECAL MORPHINE WITH BUPIVACAINE COMPARED TO 250 MICROGRAMS FOR POST OPERATIVE ANALGESIA FOLLOWING ABDOMINAL HYSTERECTOMY - A DOUBLE BLINDED RANDOMIZED CONTROL STUDY"** is the bonafide work by **Dr. Arul Prahash A**, in the partial fulfillment of the requirement for the M.D. Degree (Anesthesiology –Branch-X) of the Tamil Nadu Dr. M.G.R Medical University, Chennai, to be held in March 2009.

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ETHICAL COMMITTEE CERTIFICATE

CHRISTIAN MEDICAL COLLEGE
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Dr. B. Antonisamy, MSc,PhD
Secretary, IRB

July 3, 2008

Dr. Arul Prahash
PG Registar
Anaesthesia Department
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Sub: FLUID research grant project NEW PROPOSAL:
Evaluation of the efficacy of 150 micrograms of intrathecal morphine with bupivacine compared to 250 micrograms for post operative analgesia following abdominal hysterectomy - a double blinded randomized control study.
Dr. Arul Prahash, PG Registrar, Anaesthesia, Dr. Mary Korula, Dr. Raj, Anaesthesia.

Ref: 1) R.C. Min. No.6494 dt. February 27, 2008.
2) IRB(EC)-27-02-2008

Dear Dr. Prahash,

The Institutional Review Board (Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Evaluation of the efficacy of 150 micrograms of intrathecal morphine with bupivacine compared to 250 micrograms for post operative analgesia following abdominal hysterectomy - a double blinded randomized control study" on February 27, 2008.

The following documents were reviewed:

1. Application for Research/Ethics Committee approval.
2. ICF (English, Tamil, Bengali, Hindi)
3. Patient Information Sheet (English, Tamil, Bengali, Hindi)
4. A CD containing documents 1-3.

The following Ethics Committee members were present at the meeting held on 27 February 2008 at 10:00 am in the CRST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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Deputy Chairman, IRB &
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The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

Yours sincerely,

Dr B. Antonisamy
Secretary,
Institutional Review Board
(Ethics Committee)

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TABLE OF CONTENTS

AIM

The present randomized double blind study was designed to evaluate the effects of addition of morphine to hyperbaric bupivacaine given intrathecally to patients undergoing elective abdominal hysterectomy.

1. To compare the efficacy of two different doses i.e, 150mcg and 250 mcg of intrathecal morphine with bupivacaine in terms of duration of analgesia, time to first dose of rescue analgesia, total dose of rescue analgesic medication required for the first 24 hours.

2. To compare the incidence and severity of side effects after administration of 150 mcg and 250 mcg intrathecal morphine.

INTRODUCTION

Spinal anesthesia continues to be one of the commonest regional anesthetic techniques because of its rapid onset, safety and simplicity. Ignored until the late twentieth century as a substrate for analgesia, the spinal cord has now emerged as one -if not the key target for pain control in clinical anesthesiology. More and more anesthesiologists now give drugs spinally to provide intraoperative anesthesia and post operative analgesia in various surgical procedures.

The use of neuraxial opioids has increased dramatically in recent years, augmenting the analgesia produced by local anesthetics by binding directly to opiate receptors. Animal and human studies have indicated that opioids and local anesthetics administered spinally have a synergistic analgesic effect. The synergistic action of local anesthetics and morphine is well known, morphine probably more superior for post operative analgesia, when compared to other opioids.

Preservative-free morphine is now available in India making intrathecal administration possible. The present randomized double blind study was designed to evaluate the effect of adding preservative free morphine to hyperbaric bupivacaine given intrathecally for abdominal hysterectomy. In India, most of the abdominal hysterectomies are done under regional anesthesia. By adding morphine along with local anesthetic, the duration of analgesia can be increased with minimum side effects and this is also cost- effective.

REVIEW OF LITERATURE

International Association for the Study of Pain (IASP)[1] defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

Acute pain in the perioperative setting has been defined as “pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g.- associated drains, chest or nasogastric tubes, complications) or a combination of disease related and procedure-related sources”. (ASA task force on pain management)[2]

Acute postoperative pain is a complex reaction to tissue injury, visceral distention or disease. It is a manifestation of anatomical and physiological responses that result in unpleasant sensory and emotional experiences.

Pathophysiological consequences of pain[3]

1. Cardiovascular system - tachycardia, hypertension, increased systemic vascular resistance and increased cardiac work.

2. Pulmonary system - hypoxia, hypercarbia, atelectasis, decreased cough, vital capacity, functional residual capacity, and ventilation perfusion mismatch.
3. Gastrointestinal tract - nausea, vomiting and ileus.
4. Renal - oliguria and urinary retention.
5. Extremities - skeletal muscle pain and limited mobility.
6. Endocrine - vagal inhibition, increased adrenergic activity, metabolism and oxygen consumption.
7. CNS - anxiety, fear, sedation and fatigue.
8. Immunological - impairment

This list is a compelling reason why postoperative pain must be treated effectively.

Rationale of Postoperative Pain Relief

Aim of postoperative pain treatment is to provide subjective comfort in addition to inhibiting trauma induced nocioceptive impulses. This is in order to blunt autonomic and somatic reflex responses to pain and subsequently to enhance restoration of function by allowing the patient to breathe, cough and move more easily.

Pain control may have a further benefit of improving clinical outcome by reducing the incidence of postoperative complications such as myocardial infarction or ischaemia, impaired wound healing, risk of atelectasis, thrombo-embolic events, peripheral vasoconstriction and metabolic acidosis.

Effect of post operative analgesia on surgical outcome

Optimal (dynamic) pain relief is a prerequisite for early postoperative recovery. A reduction in the surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby to an improved outcome[4].

Pharmacological management

During recent years, there has been a tremendous increase in our understanding of the physiology of acute pain, development of new analgesics and techniques of administration[5].

Various routes available for postoperative pain control include intramuscular, subcutaneous, intravenous, oral, rectal, transdermal, epidural, intrathecal, caudal etc.

The commonly used drugs are opioids and NSAIDs. The delivery could be in the form of intermittent boluses or continuous infusion or patient-controlled administration(PCA).

A) Systemic Opioids

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is a centrally acting exogenous opioid agonist that mimics the activity of the endogenous opioid peptides. It exerts its analgesic effect by acting in 2 places along the pain pathway. First, morphine binds at u receptors in the nocioceptive synapse of the spinal cord; this inhibits the release of substance

P and hyperpolarizing postsynaptic interneurons, thus decreasing the transfer of the pain signals across the synapse. Second, morphine binds to u receptors in the brainstem, activating the descending analgesic pathway that inhibits signal transduction across the nocioceptive synapse in the spinal cord.[6] Morphine is primarily metabolized in the liver by glucuronidation to morphine-3-glucuronide (M3G; a mostly inactive metabolite) and to morphine-6-glucuronide (M6G; a highly active metabolite). M6G exhibits similar affinity for u receptors and displays an analgesic potency equal or superior to that of morphine. Like morphine, M6G crosses the blood-brain barrier and has been found to prolong the effects of morphine in long-term use.[7] Respiratory depression (rate, tidal volumes, and carbon dioxide sensitivity) results from direct action on u receptors of the pontine and bulbar brainstem respiratory center that inhibits normal (reflex) responses to increasing levels of carbon dioxide.[8] Morphine may cause arterial and venous dilatation due either to direct activity or histamine release. Morphine induces impairment of compensatory sympathetic nervous system responses thereby causing orthostatic hypotension. Morphine's action on u receptors of colonic smooth

muscle cells increases tonic contractions, but reduces the rate of propulsive waves, leading to delayed transit time and constipation. Nausea and vomiting are induced by morphine's activation of the u receptors in the chemoreceptor trigger zone (CTZ) in the area postrema of the medulla; the CTZ is one of many sensory inputs that stimulate the vomiting centre.[9]

LIMITATIONS OF OPIOID ANALGESIA

1)Respiratory depression, sedation and impaired consciousness.

2)Inadequate pain relief on movement postoperatively.

3)Gastrointestinal-frequent nausea and vomiting, postoperative ileus and reduced intestinal secretion.

4) Reductions of REM sleep in early postoperative period.

5) Urinary retention.

6)Histamine release, causing skin flushing and hypotension.

7)Drug abuse

B) NSAID

Pharmacological management of mild to moderate postoperative pain normally is initiated with NSAIDs, unless there is a contraindication to NSAIDs[11].

NSAIDs decrease levels of inflammatory mediators generated at the site of tissue injury. NSAIDs block prostaglandin synthesis, thus preventing this compensatory response and inhibit platelet aggregation. This raises the concern for potential bleeding complications when they are used perioperatively. NSAIDs have several advantages over opioids. They do not have hemodynamic side effects; do not cause respiratory depression, or slow gastric emptying or small-bowel transit time. In addition, preemptive use of NSAIDs can virtually eliminate effects associated with activation of NMDA receptors. NSAIDs may cause significant renal impairment, particularly in patients with renal disease or decreased circulating blood volume.

Limitations of NSAID Analgesia

NSAIDs inhibit prostaglandin synthesis.

1)Patients with peptic ulceration, renal impairment and asthma, if given NSAIDs may have drug induced exacerbations of these diseases.

2)NSAIDs may cause increased surgical bleeding. NSAIDs are not very effective against visceral pain in contrast to the somatic pain where they are very effective.

C) Central Neuraxial blockade

Epidural, subarachnoid and caudal routes have been used to provide postoperative analgesia.

Inadequate Pain Relief

Analgesia for postoperative pain has traditionally been provided with oral or intramuscular opioids. However, despite the widespread belief that intramuscular opioids provide acceptable pain relief, approximately 75 percent of hospitalized patients receiving intramuscular opioids remain in moderate to severe pain[12].

In contrast to the inadequacy of traditional analgesic therapy, newer analgesic techniques can prevent or easily control postoperative pain in most patients. Still there are so many patients who continue to experience moderate to severe pain after surgery, one of the primary causes appears to be the perception that pain is a natural, inevitable accompaniment to illness and disease. Indeed, most patients, physicians and nurses consider moderate to severe postoperative pain to be an acceptable consequence of surgery.[13]

Another important factor contributing to under treatment is that pain is `invisible' in most hospital wards, severity of pain is not assessed, and patients are reluctant to "complain." Unless severity of pain is assessed on a routine basis, pain cannot be effectively treated. Thus, one of the most important changes in the process of improving the efficacy of pain treatment is to introduce pain assessment as the “fifth vital sign” in addition to the traditional four vital signs (temperature, pulse, blood pressure and respiratory rate). Pain assessment should be frequent and can be simply accomplished using a verbal descriptive scale or a visual analog scale.

Recognizing that pain is important enough to be measured and recorded, is the first step in changing attitudes and improving pain management for our patients.

Therapeutic Options for optimal postoperative analgesia

Selecting the most optimal method to control postoperative pain is an individualized prescription based upon the physiological status of the patient, the extent of surgical injury, and the technical expertise of the caregivers and the economical resources of the hospital.

The following methods have been suggested to provide postoperative analgesia for patients having intermediate surgery (e.g., cesarean section, abdominal hysterectomy, radical retro pubic prostatectomy, appendectomy, total joint replacement)

1)Traditional intramuscular opioid analgesia has been demonstrated to provide inadequate analgesia in most patients and has low patient satisfaction.

2)In this group of patients, the major advance in pain therapy has been intravenous patient-controlled analgesia (PCA) with opioids. Intravenous PCA-administered opioids result in improved pain scores, improved patient satisfaction and a more constant analgesia. Although intravenous PCA may not reduce morbidity and mortality, the outcomes of improved analgesia and better patient satisfaction suggest that it is the therapy of choice in hospitalized patients with moderate-to-severe postoperative pain.[14]

3)The addition of parenteral or oral NSAIDs has been demonstrated to decrease requirements for intravenous PCA opioids and to speed recovery of bowel function after intra-abdominal surgery.[15]

4) Infiltration of the surgical wound or the peripheral nerves innervating the wound with bupivacaine 0.125 to 0.25 percent can provide profound postoperative analgesia with minimal adverse side effects. Wound infiltration can also provide benefit when combined with general anesthesia. There have been theoretical concerns that local infiltration might impair wound healing or increase the risk of infection. These complications are not increased in clinical trials of infiltration analgesia. Wound infiltration is an extremely valuable and currently underutilized technique for postoperative analgesia.

5) Finally, single injections of epidural or intrathecal opioids at the time of surgery have shown to provide better pain relief than intravenous PCA opioids. They also appear to improve patient satisfaction and postoperative outcome in various surgical procedures[16].

6) The introduction of intrathecal and epidural opioids marks one of the most important breakthroughs in pain management in the last two decades. Profound segmental antinociception is obtained with doses much smaller than would be required if administered systemically. However, a wide variety of clinically

relevant non-nociceptive side effects may occur, some of which are minor, while others are potentially lethal.

In the past decade, literature citations have shown the effectiveness of spinally administered opioids and their ability to provide powerful regional analgesia without associated motor blockade, sensory autonomic deficits or excessive central nervous system depression.

Historical perspective: With the discovery by Pert and Snyder in 1973 of specific opioid receptors and their subsequent identification in the substantia gelatinosa of the spinal cord, the stage was set for the clinical application of opioids to the subarachnoid or epidural space[17].

The discovery of "selective" mechanism for pain inhibition at spinal cord level has opened up a new era of options for acute and chronic pain management. Evidence of a selective spinal analgesic effect of opioids in humans is provided by two electrophysiological studies of spinal cord function after intravenous morphine, by pharmacokinetic studies and by various indirect studies of changes of neurologic function after intrathecal and epidural opiates.

In 1979 Wang et al reported the first use of spinal intrathecal opioids in humans in the context of a double blind placebo controlled cross over study. 8 patients with intractable pain due to malignancies of the genitourinary tract with invasion of the lumbosacral plexus received morphine 0.5 or 1 mg and physiologic saline at the 2nd or 3rd lumbar interspace to a total of 17 and 12 injections respectively. 2 patients reported pain relief after separate injections of morphine and saline although the duration of pain relief after morphine was 15 hrs, whereas that after saline injection was only 7 hrs. This incidence (25%) of placebo effect and duration of effect is in keeping with many previous studies.

Cousins et al coined the term "selective spinal analgesia" which refers to the presence of analgesia without motor, sensory or autonomic deficits[18]. They reported that 1-2 mg morphine injected in the thoracic region close to appropriate spinal cord segments relieved the pain of breast cancer and lung cancer for 24-48 hours.

Ventrafridda et al employed either cervical (C3-5) or lumbar (L3-4) injections of morphine 1 mg in 1 ml in 30 cancer patients, all of whom had their pain relieved. However, they reported that drowsiness, orthostatic dizziness, itching, sweating and nausea were frequent side effects.

Use of intrathecal opioids for acute and chronic pain relief subsequently were reported in many clinical settings, including post operative pain, cancer pain, chronic pain, obstetrics, post myocardial infarction[19].

Definitive neurophysiological studies performed in the early 1970's demonstrated that morphine selectively suppressed dorsal horn lamina I and V neurons, which mediate noxious information, yet had no effect on lamina IV neurons, which process light touch and proprioceptive input. Encephalin containing neurons and opioid receptors were almost exclusively localized to the substantia gelatinosa provided evidence of an intrinsic spinal modulatory system whose activation could attenuate release of

substance P and other nociceptive transmitters. Spinal opioid analgesia avoided the hypotension, convulsions and risk of cardiovascular collapse associated with the use of local anesthetics[20].

Site of Action of Spinal opioids: The weight of evidence now points to the dorsal horn as one main site of action of spinal opioids based upon

i. iontophoretic and micro injection data that show a strong focus of activity in the substantia gelatinosa.

ii. autoradiographs following application of radio-labeled morphine or fentanyl to the surface of the spinal cord show that the front of radioactivity corresponds to the substantia gelatinosa at a time when the discharge of lamina V neurons to noxious stimuli was reduced significantly.

iii. latencies for inhibition of lamina V neurons following intrathecal administration of morphine are similar to those reported for the latency to block the skin twitch response

following intrathecal morphine in the cat. Also it is likely that there is both presynaptic and postsynaptic inhibition of primary afferent transmission in the spinal cord.

Neurotoxic potential: Solutions of opioids of potential use in spinal injections (morphine, methadone, meperidine, fentanyl, alfentanil, lofentanil, buprenorphine) and local anesthetics in normal saline had pH in the range of 4.52-6.85. When mixed with CSF, all lowered pH of the CSF by 0.3 or less. No histologic evidence of cord pathology was found in animal studies[19].

Characteristics of spinal receptor populations acted upon by spinal opiates:

The premise that opiates act upon a specific spinal receptor site to produce the antinociception observed following intrathecal administration is based exclusively on the pharmacologic profile of the effects produced by spinally administered opiates. In general, these effects are dose dependent, stereospecific, antagonized by naloxone and have a structure activity relationship which closely resembles that observed with systemically administered agents. In a work by Martin et al, three classes of opiate receptors i.e. mu, kappa and sigma were postulated on the

basis of different pharmacological profiles for morphine, ketocyclazocine and SKF 10047 respectively. Lord et al proposed the existence of mu and delta receptors.

Certain opiates have local anesthetic properties. With the high local concentration achieved by a spinally administered agent, drug concentration sufficient to induce non-specific alterations in membrane ionic permeability could be achieved[21] Opioid receptors are coupled to guanosine (G) effector proteins which mediate the changes in calcium and potassium ion flux and membrane polarity necessary to modulate nociceptive input. Activation of kappa receptors directly inhibits Substance P release at primary afferent terminals by blocking calcium influx required for transmitter release. Mu and delta receptors appear to be coupled to voltage dependent potassium channels. Stimulation of mu and delta receptors leads to increased potassium conduction and neuronal hyperpolarization.

This effect is mediated by G protein inhibition of cyclic adenosine monophosphate synthesis and directly counters the pronounced decrease in potassium permeability caused by the nociceptive transmitter substance P.

Antinociception induced by morphine is mediated by stimulation of mu, delta and kappa receptors, whereas fentanyl analgesia is mediated by mu receptors only. This ability to interact with a variety of receptor subtypes may underlie morphine's neuraxial specificity and high analgesic efficacy.

The term "affinity" describes the attraction and successful attachment of opioid ligands to the binding site, whereas "efficacy" characterizes the ability to activate the effector mechanisms. The term "potency"correlates analgesic response versus dose requirement and is influenced by several factors, including receptor binding affinity and intrinsic efficacy. At the spinal level potency is also related to gains in analgesic effectiveness as compared with systemic administration of an equivalent dose. Spinal administration bypasses the blood brain barrier. Hydrophilic opiates such as morphine have increased receptor accessibility and gains in analgesic potency relative to systemic administration.[20]

Genetic variability Klepstad et al in their short review strongly argue that opioid efficacy and side-effects are partly related to

inborn properties caused by genetic variability related to opioid metabolism, opioid receptors and opioid transporters. In addition, clinical effects may be influenced by variations in other biological systems that modify the effects induced by opioid agonists[21]. Alex T. Sia et al showed that the A118G polymorphism of the human mu-opioid receptor has a significant effect on pain perception, analgesic requirement, and nausea for the first 24 h after cesarean delivery for patients who had received intrathecal and PCA intravenous morphine. Genetic variation at position 118 of the mu-opioid receptor is associated with inter individual differences in pain scores, self-administered intravenous morphine, and the incidence of nausea postoperatively. Further research and functional studies would be necessary to elucidate the clinical impact contributed by genetic variations[22].

Spinal systems underlying spinal opiate analgesia:

The substrate upon which intrathecal opioids act to produce a change in the pain threshold can only be implicated if the response of that substrate to local opiates exhibits the same functional, temporal and pharmacological profiles as the analgesia. Thus intrathecal opiates produce a significant elevation

in the nociceptive threshold with little effect at low doses (on the ability to perceive light touch) Similarly, spinal opiates at analgesic doses have little effect on voluntary motor function or on monosynaptic reflex activity such as manifested in tendon reflexes. These observations clearly suggest that intrathecal opiates exert an effect on transmission through systems activated by specific populations of primary afferents.

Factors affecting the time course of spinal opiate activity –

Onset of Analgesia: The antinociceptive effects of agents applied superficially to the spinal cord depend upon the movement of the agent from the surface to receptors associated with its activity. As the ability of the drug to penetrate into brain tissue has been closely correlated with its lipid partition coefficient, the time of onset of analgesia following intrathecal or epidural injection closely corresponds to the lipid partition coefficient of the agent and the pka.

Following intrathecal injection the delay in onset of analgesia clearly indicates the minimum time for the drug to reach locus of action in the spinal cord in concentrations sufficient to produce a behaviourally significant change. A presumed site of

action lies within the spinal gray. The rate of diffusion into tissue within limits varies directly with the lipid partition coefficient of the agent.[23] Lipophilic and weakly ionized opioids rapidly exit the aqueous CSF compartment and penetrate into lipid rich spinal tissue to activate opiate receptors.

In contrast, hydrophilic opioids such as morphine have difficulty traversing neural and vascular membranes and tend to remain in the cerebrospinal fluid. Morphine's delay in reaching spinal sites of activity underlies its observed latency to clinical onset and peak analgesic effect. Additional delay has also been related to morphine's low intrinsic efficacy because a greater number of opioid receptors must be occupied to provide a similar intensity of spinal analgesia as that observed with potent agonist such as sufentanil. Morphine's globular chemical structure is associated with less efficient transport than that observed with the more spindle shaped phenylpiperidine based opioids.[20]

Duration and Analgesic Efficacy: Lipid solubility, polarity and the amount of unionized drug remaining in the CSF play key roles in determining duration of spinal analgesia[5]. Though the extent of

metabolism is likely to be small compared to the concentrations present after a bolus intrathecal injection, the metabolite would render polar molecules such as morphine electrically neutral and therefore might enhance the clearance of the molecule from the brain. With regard to the opiate peptides, rapid metabolism has been noted as one of several variables limiting their activity.[23]

Clearance from epidural and intrathecal sites of deposition plays a major role in determining duration of action. Principal routes of clearance include both rapid vascular absorption and slow rostral diffusion in cerebrospinal fluid with elimination at the arachnoid granulations. Increasing lipid solubility facilitates vascular uptake, therefore this route of clearance has greater importance with lipophilic opioids such alfentanyl and sufentanil. As significant amounts of lipophilic drug are taken up by the epidural venous plexus and spinal blood vessels or become trapped in fatty tissues concentrations at sites of activity rapidly decline. Morphine's hydrophilic properties and polarity allow significant amounts of drug to remain sequestered in the cerebrospinal fluid for relatively long periods.

Receptor dissociation kinetics also influences analgesic duration, as agents associated with greater drug- receptor complex stability provoke prolonged activity. Total dose of opioid administered and volume of injectate represent two additional variables which may influence duration of activity and dermatomal spread of analgesia.

Lack of rostral spread underlies fentanyl's segmental spinal analgesic profile that results from its rapid incorporation into epidural fat and vascular clearance from epidural and intrathecal sites of deposition. Dermatomal spread of lipophilic opioids appears to be directly related to the dural surface area in contact with the drug and may be increased following administration of larger volumes of solution[20]. The duration of action is dose dependant with lipid soluble agents such as fentanyl and meperidine having a shorter time course than more polar agents such as morphine.

Acutely, the duration of the antinociceptive effects observed following intrathecal or epidural opiates following acute

administration is physically governed by metabolism of the drug to an inactive form, or by redistribution. Chronically, the absolute limitation to opiate-induced analgesia is the question of tolerance.

Model of Intrathecal Opiates: For a highly ionized and hydrophilic drug such as morphine, intrathecal injections will produce extremely high CSF concentrations which will move slowly out of the CSF into spinal cord receptor sites and into non specific binding sites and clearance sites (arachnoid granulations). Cephalad flow of CSF will cause redistribution of the injected drug up the spinal subarachnoid space to the brain. Low lipid solubility and slow uptake into spinal cord receptors results in slow egress of action. Slow egress from spinal cord results in a long duration of action.

In the case of a mostly ionized, lipid soluble drug such as fentanyl, there will be only a small amount of unionized lipid soluble drug in CSF after subarachnoid injection. This will penetrate spinal cord receptors and nonspecific binding sites

rapidly, but also will have a rapid egress unless it has particular affinity for lipid or high receptor binding. Thus, for fentanyl (which is less than 10% unionized at pH 7.4), onset of analgesia is rapid, but duration is not as long as for morphine.

Advantages: The particular advantages which accrue from peri and postoperative spinal opiate analgesia are several.

i. The relief of painful input without motor blocks permits the post surgical patient to breathe freely and avoids the compromise of pulmonary function which develops when the pain of chest expansion prevents deep inhalation. Such pain control has been reported to facilitate postoperative respiratory therapy and reduce the incidence of pulmonary complications.

ii. The lack of blockage of sympathetic outflow is of particular significance. This lack of effect on vascular tone also accounts for the lack of any postural hypotension and has been reported to facilitate early patient mobility. Spinal local anesthetic block results in loss of efferent sympathetic activity when producing a reduction

in heart rate and cardiac output. Such blocks serve to relax peripheral vascular beds resulting in a relative hypovolemic state.

iii. The perioperative use of spinal opiates will stabilize hemodynamics by preventing the reflex mediated hypertensive response evoked by particularly intense surgical stimuli.

iv. Pain associated with the metastasis of cancer, low back pain or ischemic pain associated with peripheral vascular disease has been shown to be reduced significantly by the spinal action of opiates.[23]

Side effects of Intrathecal Opioids: The 4 classic side effects are pruritis, nausea and vomiting, urinary retention and respiratory depression. Most side effects are dose dependent. Side effects are less common in patients chronically exposed to either intrathecal, epidural on systemic opioids. Some side effects are mediated via interaction with specific opioid receptors while others are not.

1. Respiratory depression: Delayed respiratory depression after intrathecal morphine for post operative pain was reported towards the end of 1979 independently by Glynn et al and by Liolios and

Anderson.[19]

Definition: From a pathophysiologic point of view, respiration is depressed if the subject fails to respond adequately, on a moment to moment basis to hypercapnia or hypoxia. Central respiratory depression exists when the respiratory neurons of the medulla fail to respond appropriately to these stimuli.

Spinal opioids result in respiratory depression primarily by direct depression of the respiratory nuclei and the chemosensitive areas of the brain stem[17]. Onset of respiratory depression after intrathecal administration seems to be quite variable. Almost all cases with intrathecal morphine may be delayed for hours. The incidence of respiratory depression requiring intervention following conventional doses of intrathecal and epidural opiates is approximately 1% which is the same as that following conventional dosing of intramuscular and intravenous opioids.

Early respiratory depression occurs within 2 hours of injection of opioid. Most reports of clinically important respiratory

depression involve administration of epidural fentanyl or epidural sufentanil and are very rare following the intrathecal use of fentanyl or sufentanil. It likely results from systemic absorption of the drug. However, cephalad migration of opioid in CSF may also initiate early respiratory depression.

Delayed respiratory depression occurs more than 2 hours after injection of opioid. All reports of clinically relevant delayed respiratory depression involve administration of intrathecal or epidural morphine. It results from cephalad migration of opioid in CSF and subsequent interaction with opioid receptors located in the ventral medulla. Delayed respiratory depression characteristically occurs 6-12 hours following intrathecal or epidural administration of morphine and may persist for 24 hours.

Bradypnea appears to be a more reliable clinical sign of early respiratory depression following intrathecal or epidural use of fentanyl or sufentanil. Pulse - oximeter may be valuable but must be interpreted cautiously if supplemental oxygen is being administered. The most reliable clinical sign of respiratory

depression appears to be a depressed level of consciousness, possibly caused by hypercarbia. Most protocols for monitoring assess patients hourly for 4-6 hours if fentanyl or sufentanil has been administered and for 18-24 hours with morphine. Concomitant use of any intravenous sedative increases the risk. Treatment involves administration of supplemental oxygen with mask and, encourage the pt to breathe, if the above measures are not helpful an opioid receptor antagonist, usually naloxone is administered.

2. Urinary retention: The failure to achieve spontaneous micturition, for periods sufficient to require catheterization (10-20 hours) has been observed following spinal opiates in postoperative and chronic pain patients[23]. The incidence varies widely from 0 -80% and the incidence is higher when intrathecal morphine is utilized. It is most likely related to interaction with opioid receptors located in the sacral spinal cord. This interaction promotes inhibition of sacral parasympathetic nervous system outflow which causes detrusor muscle relaxation and an increase in maximum bladder capacity leading to urinary retention.

3. Pruritis: Is defined as subjective, unpleasant & irritating sensation arising from superficial layers of the skin that provokes an urge to scratch.[28]

The most common side effect of intrathecal and epidural opioids is pruritis. The incidence varies widely from 0 to 100%. It may be generalized but is more likely to be localized to the face, neck or upper thorax. The incidence may be higher when the intrathecal route is utilized and is lower following subsequent doses. The sensation appears around or just after the development of analgesia by either epidural or intrathecal opiate injection and normally continues (when it occurs) for the duration of the analgesia. Pruritis is more likely to occur in obstetric patients which may result from an interaction of oestrogen with opioid receptors.

Pruritis induced by intrathecal and epidural opioids is likely due to cephalad migration of the drug in CSF and subsequent interaction with the trigeminal nucleus located superficially in the medulla. Opioid receptors are present in the trigeminal nucleus and trigeminal nerve roots. The most common location of induced

pruritis is in the facial areas innervated by the trigeminal nerve.

Altered central nervous system perception of pain may also play a role. The trigeminal nucleus descends into the cervical region of the spinal cord and becomes continuous with the substantia gelatinosa of the dorsal horn. Opioid interaction in the substantia gelatinosa may thus initiate an "itch reflex" through indirect action on the trigeminal nucleus. Use of a single dose ondansetron 8 mg has been shown to be effective in prevention of intrathecal morphine induced pruritus. In addition to 5HT3 binding, ondansetron also binds at u receptors as an antagonist. Since the u opioid receptors system is also involved in the regulation of intrathecal morphine induced nausea and vomiting, ondansetron may exert its anitemetic action at this level.

4. Nausea and Vomiting: The rate of occurrence of nausea and vomiting in postoperative patients is around 15-35%.[23] the incidence of nausea and vomiting following intrathecal and epidural opiates in approximately 30%. It is likely the result of cephalad migration of drug in CSF and subsequent interaction with opioid receptors located in the vascularized area postrema

lying superficially on the floor of the 4th ventricle. Sensitization of the vestibular system to motion and decreased gastric emptying produced by opiates may also play a role. Tolerance occurs rapidly as the incidence of vomiting is reduced with subsequent administration

Adjuvants to local anesthetics: Experimental effects of intrathecal opiates show that combinations of opiates and local anesthetics are synergistic for somatic analgesia in animal models and that intrathecal opiates can markedly enhance analgesia from sub therapeutic doses of spinal lignocaine.[24]

The addition of epinephrine and narcotics to hyperbaric spinal anesthetic solutions produces significant changes in the baricity of these solutions. These changes in baricity might produce spinal anesthetic levels more characteristic of isobaric spinal solutions.[25]

Belzarena et al, in their study found that morphine, a lipophobic opioid agonist, when administered via the subarachnoid route, provides longer lasting analgesia than fentanyl. Lipophilic

opioids (e.g. fentanyl) have a very fast onset compared with lipophobic opioids (e.g. morphine) and when administered together with a local anesthetic, many of their clinical actions can happen during the intraoperative period.[26]

In further studies, he concluded that the combination of bupivacaine with intrathecal morphine provides excellent post operative analgesia and very few undersirable side effects for women undergoing caesarian section.[26]

Wang et al have shown that bupivacaine alone or in combination with opioids provide adequate pain relief without motor paralysis. Local anesthetics in conjunction with opioids, administered spinally provide good analgesia in patients in labour with less intense motor blockade than that produced by local anesthetics alone. Previous studies in animals indicated that opioids and local anesthetics administered spinally have a synergistic analgesic effect, but opioids do not enhance the motor blockade induced by the local anesthetics. Hypotension caused by sympathetic blockade can be another major unwanted effect of

local anesthetics. Opioids do not cause significant depression of the efferent sympathetic pathway and motor function but administered alone, their analgesic efficacy is often inadequate compared with that provided by local anesthetics.[24]

Opioid u agonists open K+ channels presynaptically to inhibit transmitter release and thus reduce Ca+ influx and have a direct postsynaptic effect, causing hyperpolarization and a reduction in neuronal activity. It has also been suggested that opioids may affect Ca+ flux directly. Local anesthetics act mainly by blockage of voltage gated Na+ channels in the axonal membrane. They may also have effects on synaptic transmission i.e. a presynaptic inhibition of calcium channels, in addition to their effects on nerve conduction. Clearly, a combination of these effects may explain the observed synergism between local anesthetics and opioids, as originally suggested by Fraser et al.[24]

Physicochemical properties and actions of opioids and local anesthetics: There are similarities in molecular weight and pKa between local anesthetics and opioids. The phenylpiperidine derivatives (pethedine, fentanyl, lofentanil) are closest in structure

to local anesthetics. The rate of absorption of Pethedine from the epidural space is similar to that of lignocaine and like lignocaine, has a rapid onset of analgesia after epidural use that coincides with early peak Pethedine concentrations in CSF. Fentanyl and lofentanil are highly lipid soluble. This property should promote rapid onset of action with minimal residual CSF concentrations of drug that could be available to migrate to brain. In contrast, morphine has lower lipid solubility. It has a slow onset of action after epidural use that coincides with delayed peak concentrations of morphine in CSF and its relative hydrophilicity results in slower efflux from the spinal cord and CSF resulting in greater migration to the brain. At pH 7.4 the tertiary amine group in each of the opioids is mostly ionized, making the molecule more water soluble. Additionally in the case of morphine, hydroxyl groups on the molecule confer significant water solubility, so that is why morphine base is much more water soluble than any other opioid base in clinical use.

Studies point to presynaptic and postsynaptic receptors in the substantia gelatinosa of the dorsal horn of the spinal cord as a

major site of action of spinally administered opioids. In contrast, local anesthetics act by axonal membrane blockade, predominantly in the spinal nerve roots.

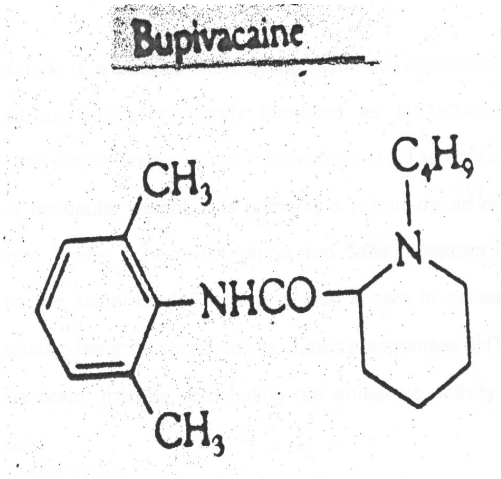
The major advantages of "selective" blockade of pain by spinal opioids lies in the absence of sympathetic blockade and postural hypotension, potentially allowing easy ambulation of patients and avoidance of cardiovascular collapse or convulsions, the major complications of local anesthetic blockade. However, early and later respiratory depressions are major concerns with spinal opioids.

Side effects causing discomfort can result from both classes of drugs, with nausea and vomiting being more common from opioids and urinary retention similar from both classes of drugs, although tolerance to this effect develops with opioids and is antagonized by naloxone. Only spinal opioids appear to cause the strange phenomenon of pruritis.

Bupivacaine: is an aminoacyl amide synthesized by Bo af Ekenstam. First reports of its use were made in 1963. Bupivacaine is

3-4 times as potent as lignocaine and considerably longer lasting. Its speed to onset is marginally slower.

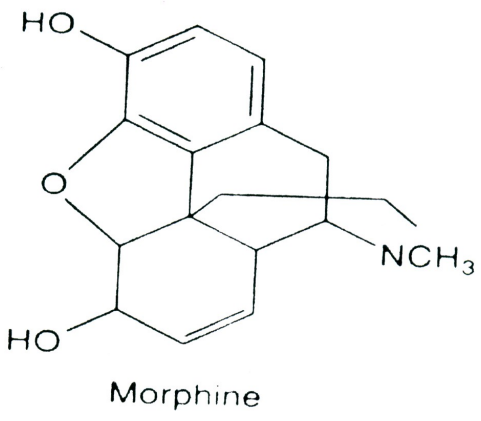
Fig. 1



Bupivacaine is highly protein bound. The first pass pulmonary extraction is dose depedent. Debutylation of bupivacaine results in the production of a xylidide metabolite which undergoes further breakdown.[27]

Morphine

Fig.2



Morphine

Chemistry

Morphine is the prototype opioid antagonist to which all other opioids are compared. It is classified under phenathrene group of opioids. The three rings of phenanthrene nucleus are composed of 14 carbon atoms.

Mechanism of action

Opioids are unique in producing analgesia without loss of touch, proprioception, or consciousness. Analgesia is produced by both interaction of morphine with μ receptors present in spinal cord lamina I, II, and V and also by systemic absorption of morphine from spinal spaces.

Binding properties of morphine to opioid receptors

	μ		δ		κ	
	Affinity	Activity	Affinity	Activity	Affinity	Activity
Morphine	+++	+++	++	+-	+	+

Cephalad movement of opioids in the cerebrospinal fluid

(CSF) principally depends on their lipid solubility. Morphine remains in the CSF for cephalad transfer by bulk flow, reaching the cistrna magna in 1 to 2 hours and the fourth and lateral ventricles by 3 to 6 hours[29]. Coughing or straining, but not body position, can affect movement of CSF. Elimination half time of morphine in CSF is similar to that in plasma[30].

Preservatives

As early as 1954, Moore et al advised that local anesthetic administered epidurally should be free of preservatives. Malinovsky et al suggests that "neurotoxicity can result from the use of adjuvants." Some authors suggest that arachnoiditis occurs as a result of the vasoconstrictive component of the anesthetic, whilst others say that contaminants or preservative agents are responsible.

It must be stressed that any drug preparation injected in to the spine, may contain preservatives such as benzyl alcohol, polyethylene glycol, and chlorobutanol (a derivative of chloroform) and that these carry a risk of neurotoxic effects. Another

preservative that can cause reaction is sodium bisulfate, which may trigger a severe allergic reaction if the patient is susceptible.

Usually the injectable form of morphine sulfate contains 0.5% chlorobutanol and not more than 1% sodium bisulfate in every ml of morphine sulfate injection USP. Malinovsky JM etal showed that 0.05% chlorobutanol injected intrathecally "induced significant severe spinal cord lesions". It is therefore vital to ensure that preservative-free solution is used.

Morphine is recently made available in India as sterile, non-pyrogenic, preservative free aqueous solution in ampolues containing 10mgs of the drug,

MATERIAL AND METHODS

Following approval by the institutional review board and institutional research grant committee, eighty patients presenting for elective abdominal hysterectomy were included in this randomized, double blind study. A pilot study was initially conducted on 20 patients to obtain the sample size required for statistical estimation

Inclusion Criteria

Patients of ASA 1 & ASA 2 physical status

Uterus < 24 weeks size

Patient willing to participate in the study

Age 30-60 years

Exclusion Criteria

Patients of ASA 3 & ASA 4 physical status

Large uterus > 24 weeks size

Age>60 years

Known allergy to the study drug

Morbid obesity

Previous complicated abdominal surgeries

Patient not willing for spinal Anesthesia and study

Other contraindication for spinal Anesthesia such as coagulopathy, systemic or local infection

Preoperative Preparation

All the patients were seen by the anesthetist on the day prior to surgery. The procedure was explained and informed consent obtained. The visual analogue scale (VAS) and post operative nausea and vomiting (PONV) score was explained to the patients. All patients received tablet ondansetron 8 mg orally along with benzodiazepine one hour prior to surgery as premedication.

c. Method of randomization:

The patients were randomised to one of the 2 groups by a computer generated random assignment.

d. Method of allocation concealment

The investigator who was giving the drug was given a sealed envelop mentioning the group and method of preparation of the drug. After the drug was administered it was recorded as bupivacaine with study drug 1 or 2. The envelop and the allocation sheet were destroyed.

e. Blinding and masking:

This is a double blind study as the participant and outcome assesors were blinded to treatment allocation.

PREPARATION OF THE DRUG

All the drug solutions were prepared by an anesthesiologist who was not involved with the administration of spinal anesthesia or with observation of the patients. All drugs used for spinal anesthesia were autoclaved as per the departmental protocol. 3.5 ml of hyperbaric bupivacaine 0.5% [heavy] was given in both groups along with preservative free morphine according to study group.

PROCEDURE

In the operating room monitoring was established with pulse oximetry, ECG, non invasive blood pressure. After establishing intravenous (iv) access, patients were preloaded with 10 ml per kg of crystalloids. Under aseptic precautions, and patient in the lateral position, lumbar subarachnoid block was established and the study drug given the study group along with 3.5 ml of

hyperbaric local anesthetic bupivacaine 0.5% using 25 gauge Whitacre needle, following the intrathecal injection, patients was immediately placed supine Supplemental oxygen (4 litres /min) was administered to all patients using a Hudson's mask. The level of sensory blockade was noted. In case of hypotension following spinal Anesthesia and systolic blood pressure of less than 100mmHg or blood pressure less than 80% from the baseline, iv fluids was administered along with bolus of injection ephedrine 5 mgs boluses intravenously as required

ASSESSMENT OF THE PATIENT: The following variables were assessed and recorded in the operating room.

1 Dermatomal sensory blockade to pin prick was evaluated
2 Extent of motor block was quantified
3 Side effects of intrathecal morphine such as nausea, vomiting, pruritus, arrythimias, shivering, bradycardia, respiratory depression were recorded.
4 Hypotension following spinal Anesthesia was recorded and treated.
5 Nausea and vomiting if present was noted and were treated with intravenous ondansetron 4 mg.

6 In the post operative period, patients were monitored for the quality of pain relief and side effects such as nausea, vomiting, pruritus ,sedation, respiratory depression at 0, 1, 2, 4, 8, 12, 24 hours Pain was assessed using visual analogue scale [VAS] with ‘0’ meaning “no pain” and 10 being the “worst pain imaginable”.

Whenever the VAS score stayed more than 4, additional analgesia in the form of tablet ketorolac 10 mgs every 6 th hourly was given. Post operative nausea and vomiting (PONV) score was more than 1 [i.e. severe nausea, vomiting] or if the patient demanded, intravenous ondansetron 0.1 mg/kg was given. Pruritus was treated with Tab. chlorpheniramine maleate 25 mg on request. Respiratory depression was recorded whenever respiratory rate was less than 10 per minute or oxygen saturation less than 90% and treated with oxygen by face mask at the rate of 6L/ minute, encouraging the patient to be breathe deeply. However if the patient was not responding to the above measures, then naloxone 0.5 to 1 mcg/kg body weight was to be given intravenously and saturation monitoring continued. All these information were recorded in the proforma.

6. All patients were followed up for complications such as headache, like PDPH and any neurological complications until discharge.

STATISTICAL METHEODS:

The data collected from the patients were entered in EXCEL sheet and statistical analysis was done using SPSS 11 software. Comparison of the mean between the two groups was done by Pierson chi-square test.

RESULTS

The results for the 80 patients allocated to the two groups were analysed.

Group A received – 3.5 ml of 0.5% hyperbaric bupivacaine with 250 micro gms of morphine.

Group B received – 3.5 ml of 0.5% hyperbaric bupivacaine with 150 micro gms of morphine.

The data for all the 80 patients are shown in the master chart.

Figure -1 Demographic Data - AGE

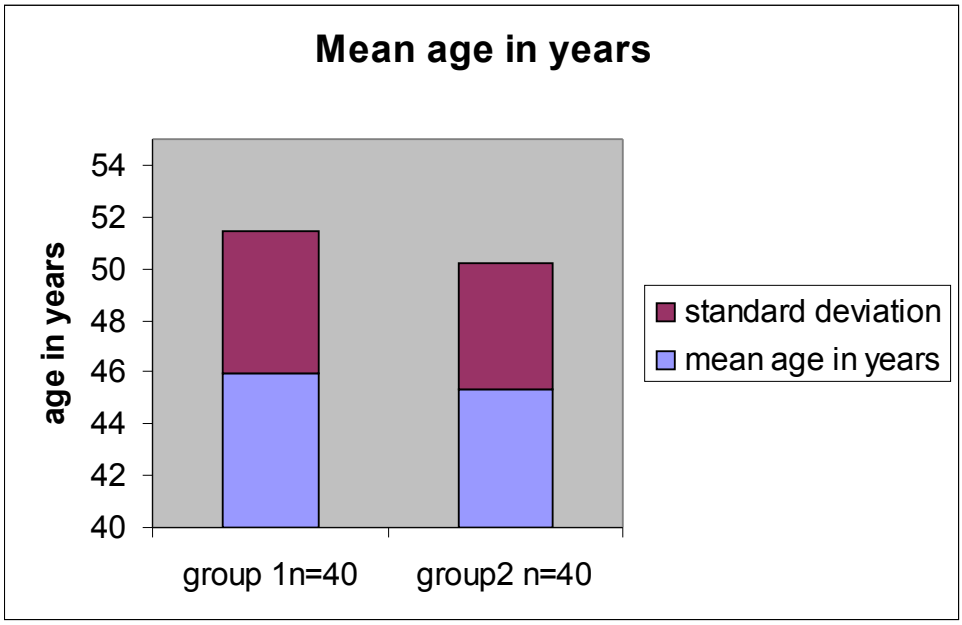


Figure-2: Demographic Data - WEIGHT

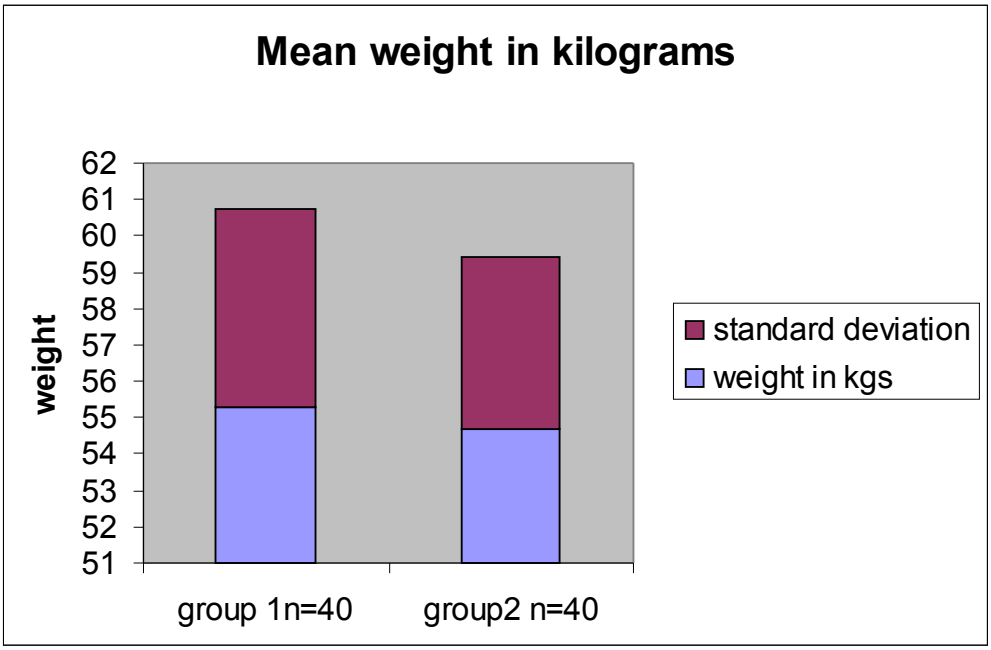


Table 1 Mean age in years

Variable	Group A n=40	Group B n=40
Age in years SD	45.95 ± 5.53	45.3 ± 4.90

The mean age in group A is 45.95 ± SD 5.54 and in group B is 45.3 ± 4.91.

There is no statistically significant difference in age between the two groups.

Table 2 Mean weight in kilograms

Variable	Group A n=40	Group B n=40
Weight in Kgs	55.3 ± 5.41	54.7 ± 4.72

The mean weight in Group A is 55.3 kgs ± 5.41 SD and in group B is 54.7 ± 4.72 SD

There is no statistically significant difference in weight between the two groups.

Figure-3: Demographic Data - HEIGHT

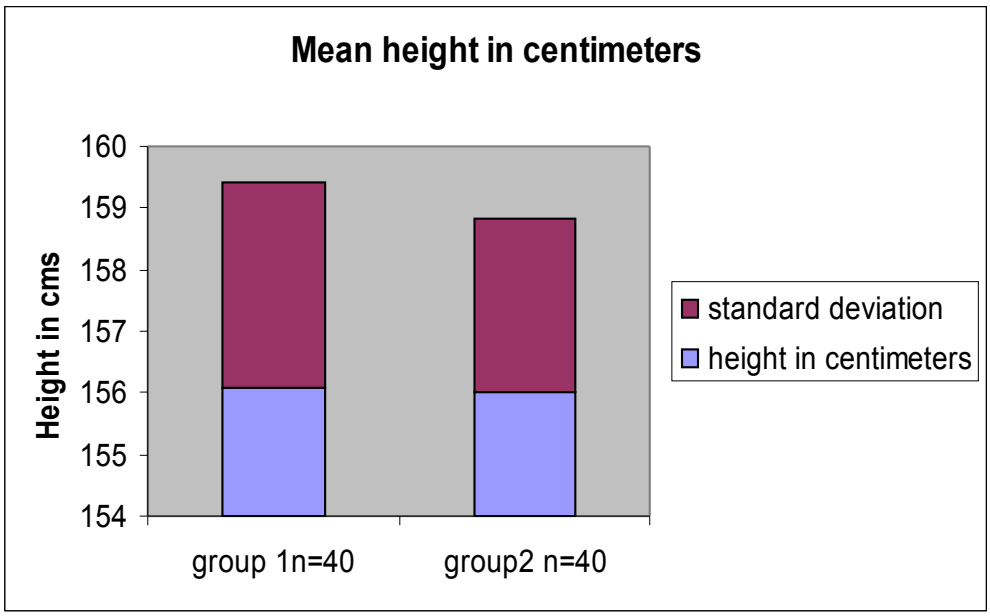


Figure -4 Mean Duration of Surgery in Hours

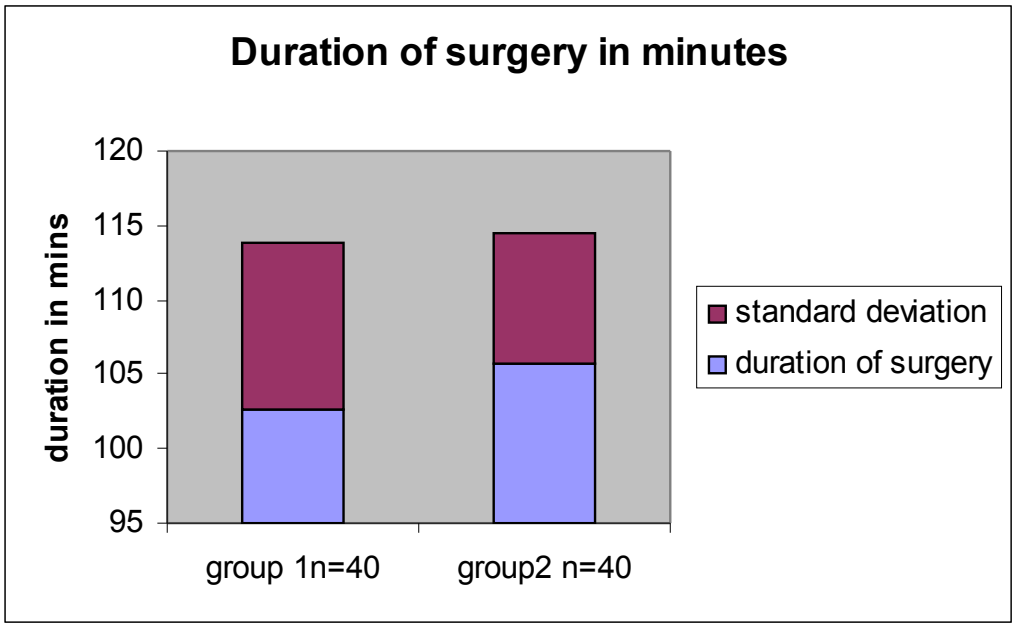


Table 3 Mean Height in CMS

Variable	Group A n=40	Group B n=40
Height in CMS	156.1 ± 3.31	156.02 ± 2.80

The mean height in group A is 156.1 ± 3.31 SD and in group 'B' is 156.02 ± 2.80 SD.

There is no statistically significant difference in height between the two groups.

Table – 4 Mean Duration of Surgery

Variable	Group A n=40	Group B n=40
Duration of Surgery in Minutes	102.7 ± 11.14	105.75 ± 8.73

Duration of surgery in Group A is 102.75 minutes ± SD 11.148 and in Group B is 105.75 minutes ± 8.737.

There is no statistically significant difference in duration of surgery between the two groups.

Figure -5: Duration of Analgesia in Hours

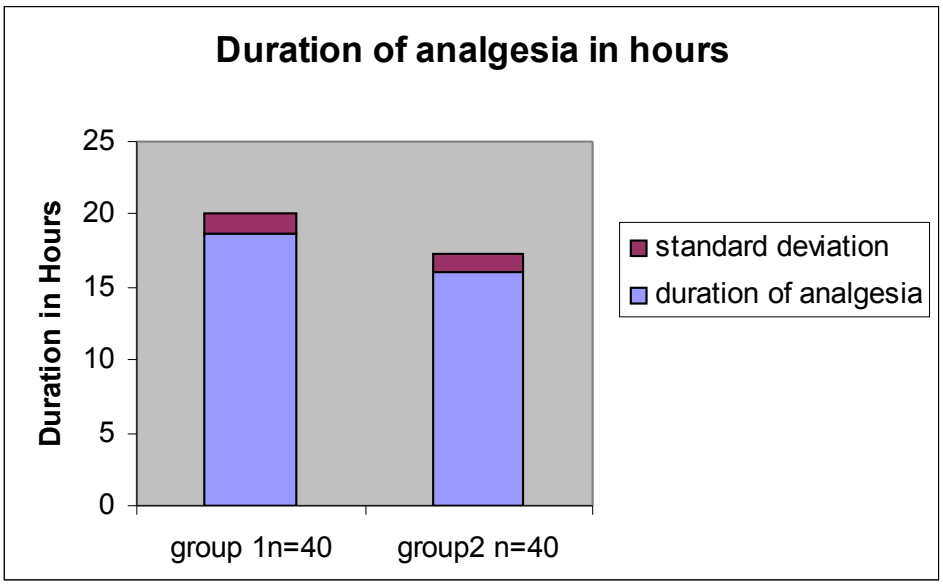


Figure -6: Nausea

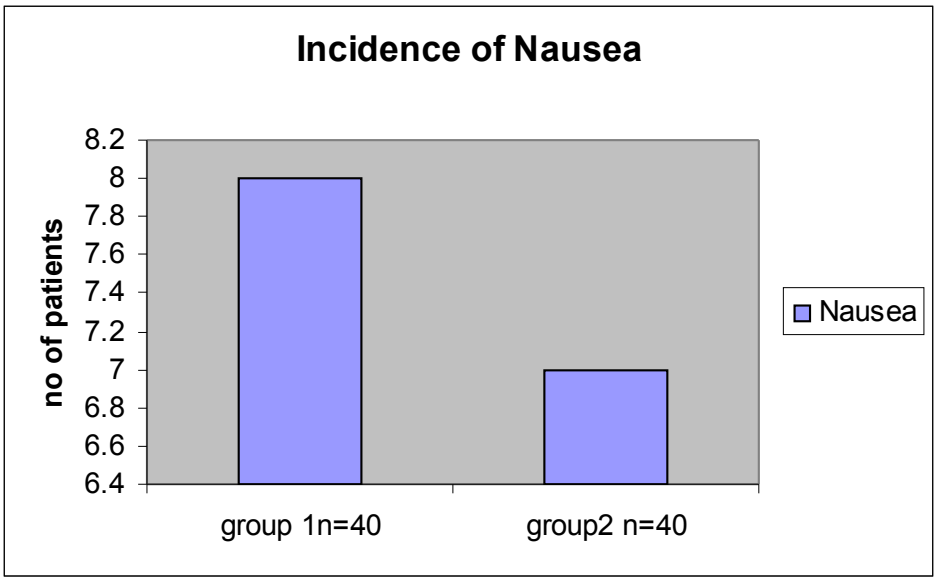


Table-5. Mean Duration of Analgesia

Variable	Group A n=40	Group B n=40	P-Value
Duration of Analgesia	18.725 ± 1.37	16.075 ± 1.22	<=0.001

Duration of analgesia was taken as time to the first dose of rescue analgesia. In group A it is 18.725 ± 1.38 and in Group B 16.075 ± 1.23

There is statistically a significanct difference in the duration of analgesia between the two groups with a 'p' value of < 0.001.

Table-6 Nausea

Variable	Group A	Group B
Nausea	8 (20%)	7 (17.5%)

20% of patients in Group A [8/40] and 17.5% of patients in Group B [7/40] had nausea; there is no statistical difference between Group A and Group B.

Figure-7: Vomiting

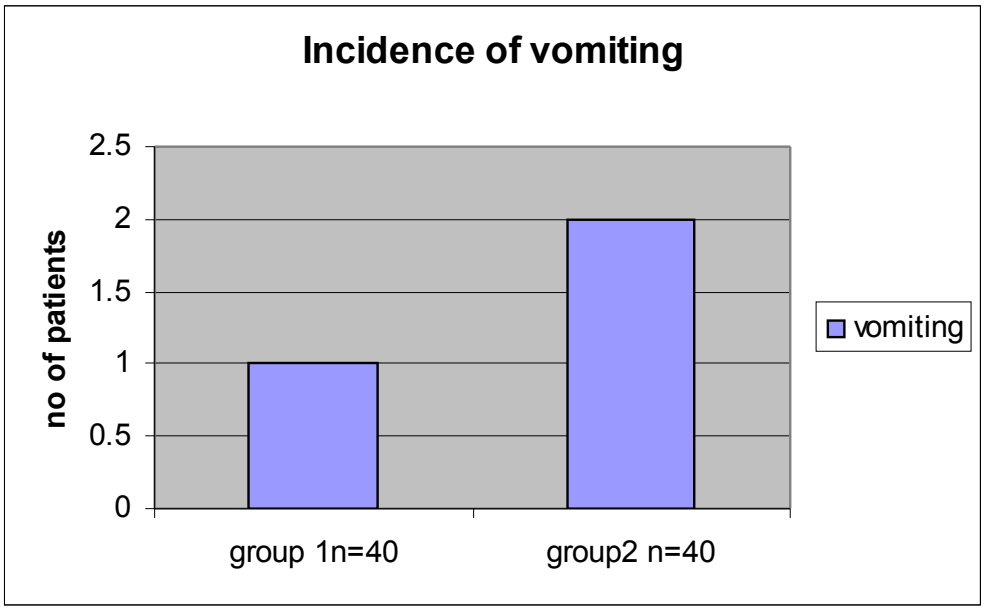


Figure-8 Pruritus

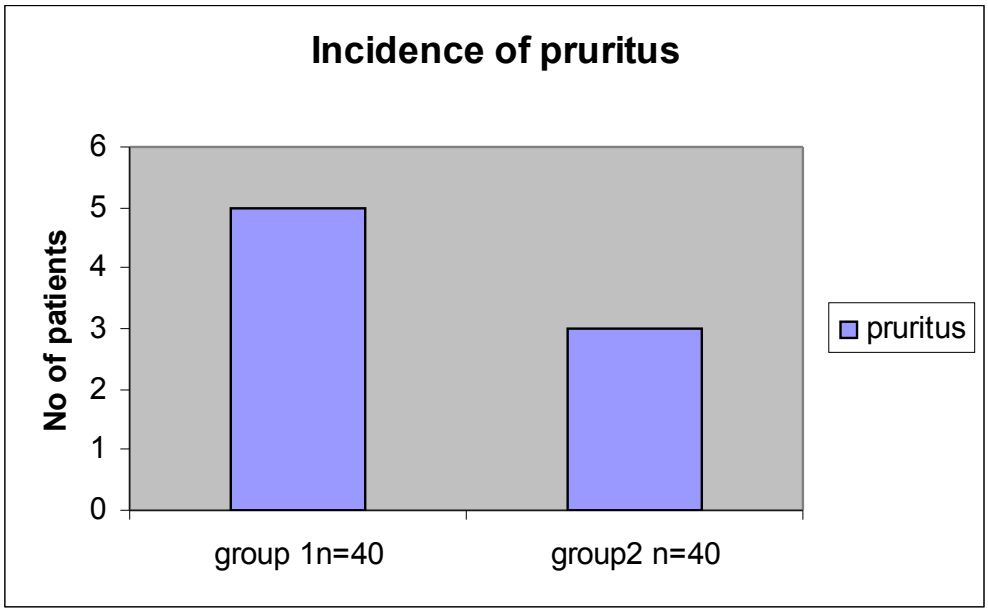


Table-7 Vomiting

Variable	Group A n=40	Group B n=40
Vomiting	1 (2.5%)	2 (5)

The incidence of vomiting in group A is 2.5% (1/40) and 5% (2/40) in group 'B'. There is no statistically significant difference in the incidence of vomiting between the two groups.

Table-8 Pruritus

Variable	Group A n=40	Group B n=40	P-Value
Pruritus	5 (12.5%)	3 (7.5%)	0.808

The incidence of pruritus in Group A is 12.5% (5/40) and group B 7.5% (3/40). There is no statistically significant difference in the incidence of pruritus among the 2 groups.

Figure -9 Additional Dose of Ondansetron

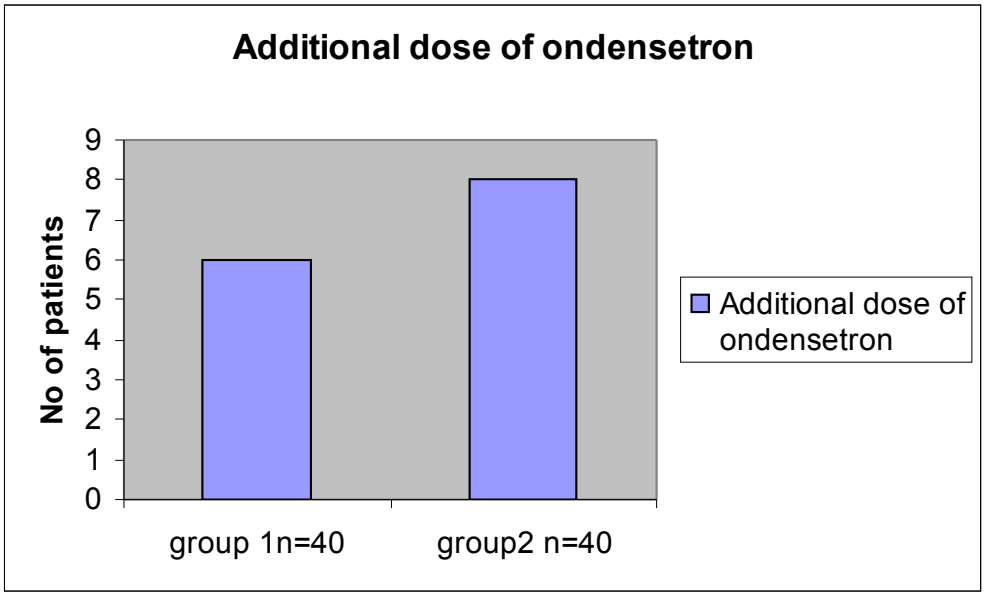


Figure-10 Chlorpheneramine Maleate

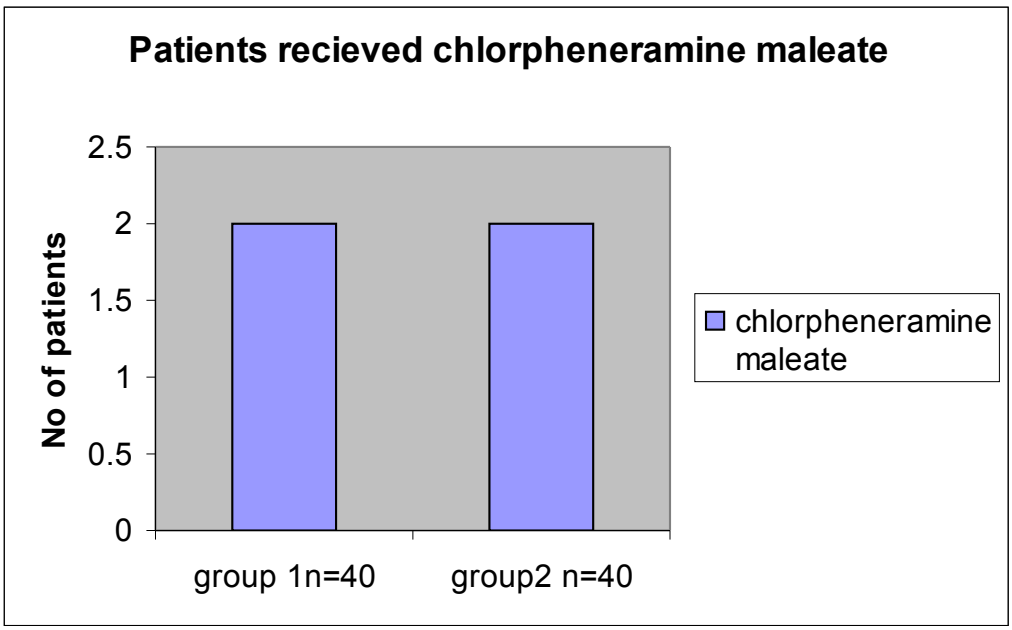


Table-9 Additional Dose of Ondansetron

Variable	Group A n=40	Group B n=40	P-Value
Additional Dose of Ondansetron	6 (15 %)	8 (20%)	0.556

15% (6/40) of patients in group A 20% and (8/40) of patients is group B required additional doses of ondansetron in addition to the 8th hourly doses. There is no statistically significant difference is the consumption of additional ondensetron between the two groups.

Table-10 Chlorpheneramine Maleate

Variable	Group A n=40	Group B n=40	P-Value
Chlorpheneramine Maleate	2 (5%)	2 (5%)	1.00

Two patients received T-Chlorpheneramine maleate in each group, there is no statistical difference between the two groups

Figure-11 T. Ketorolac 10mg.

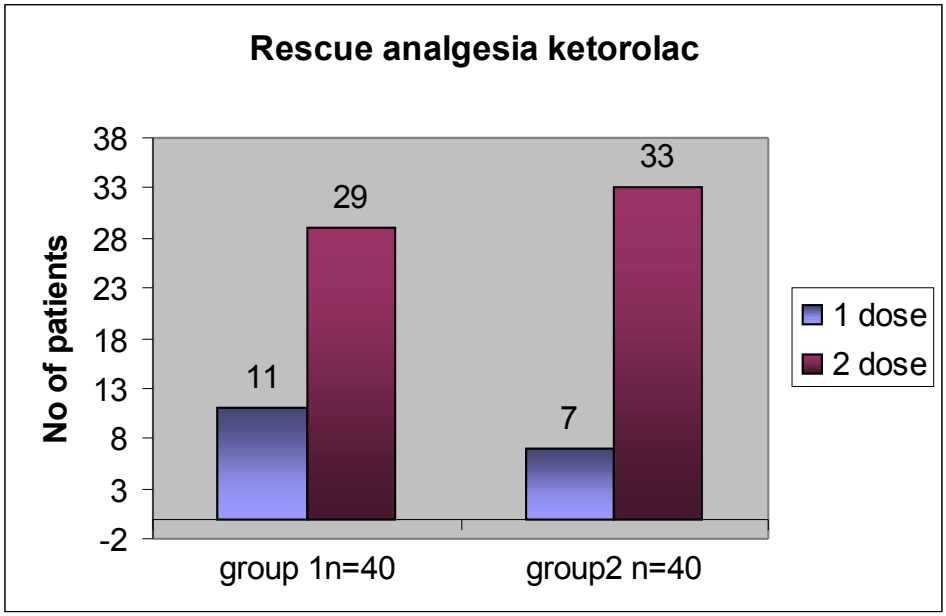


Figure-12 Sedation Score

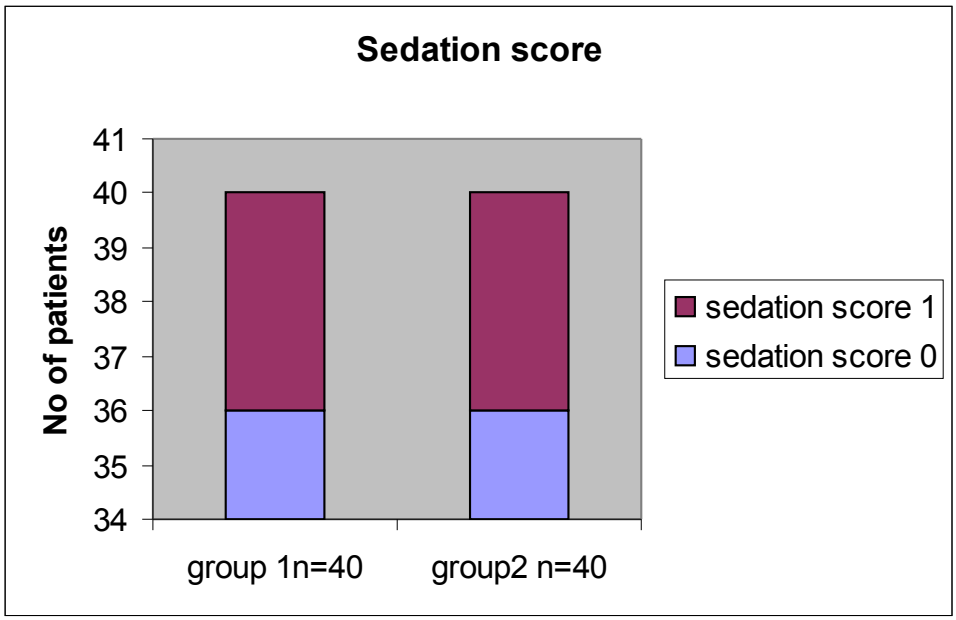


Table-11 Rescue Analgesia

Variable	Group A n=40	Group B n=40
1 Dose	11 (27.5%)	7 (17.5%)
2 Dose	29 (72.5%)	33 (82.5%)

27.5% (11/40) patients in group A, 17.5% (7/40) patients in group B received one dose of rescue analgesia (ketorolac 10mg),during the 24 hours for pain relief while 29 patients is group A (72.5%) and 82.5% (33/40) patients in group B received 2 doses of rescue analgesia. Even though there is no statistically significant difference in the rescue analgesia, all patients in the study groups required some oral NSAIDs for the first 24 hours as in both groups the duration of analgesia was less than 24 hours even with the higher dose of intrathecal morphine.

Table-12 Sedation Score

Variable	Group A n=40	Group B n=40
Sedation Score 0	36	36
Sedation Score 1	4 (10%)	4 (10%)

10% patients in Group A (4/40) and 10% patients in Group B (4/40) had a sedation score of 1(drowsy and arousable). There is no statistically significant difference between the two groups. None of them had sedation scores more than 1.

Figure-13 Pethedine Injection

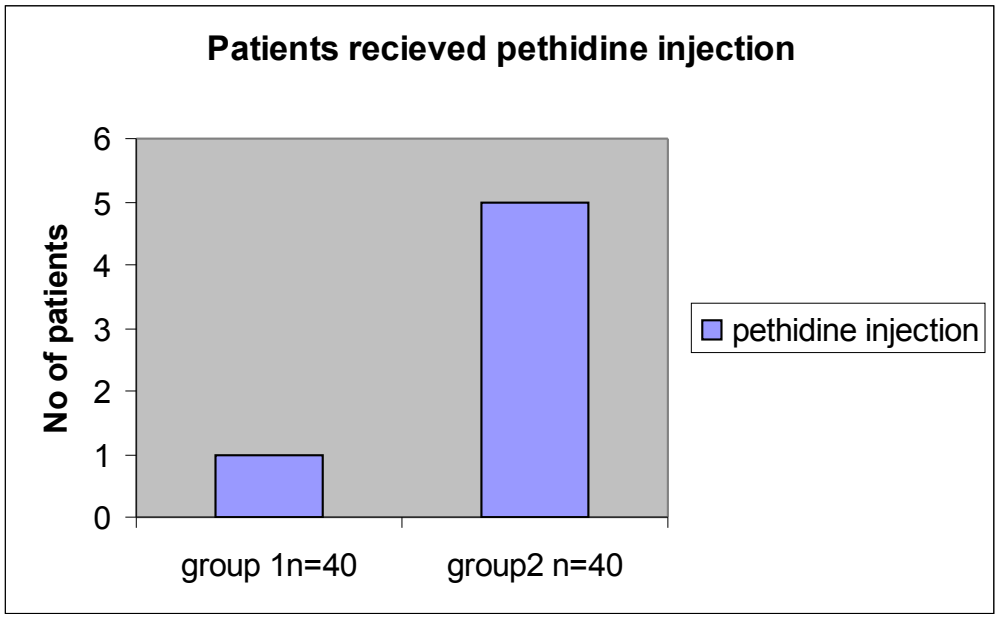


Table -13 Pethedine Injection

Variable	Group A n=40	Group B n=40	P-Value
Pethedine Injection	1 (2.5%)	5 (12.5%)	0.090

1 patient (2.5%) in group A received injection pethedine and 5 patients (12.5%) in group. Even though there is no statistically significant difference ($p < 0.09$), clinically a few patients' required parenteral opioids, necessitating additional prescription and nursing time.

Respiratory Depression

None of the patients in both study groups had clinically significant respiratory depression.

Post dural Puncture Head Ache

None of the patients in both study groups had complaints suggestive of post dural puncture headache (PDPH)

DISCUSSION

Spinal Anesthesia continues to be one of the commonest regional anesthetic techniques because of its rapid onset, safety and simplicity. More and more anesthesiologists are administering drugs intrathecally to provide both intra-operative anesthesia and postoperative analgesia for various surgical procedures.

Adequate postoperative pain management relieves suffering and leads to earlier mobilization, shortened hospital stay, reduced hospital costs and increased patient satisfaction. Pain control regimens should not be standardized; they should be tailored to the needs of the individual patient taking into account his/ her age, medical, physical, psychological condition and the level of fear or anxiety. But the general goal in all post-surgical patients is to minimize exposure to side effects of prolonged or relatively high doses of systemic narcotics or analgesics while providing adequate analgesia.

Transabdominal hysterectomy is a frequently performed operation with moderate to severe postoperative pain. The aim of our study is to compare the efficacy of two different doses of intrathecal morphine, i.e 250 μgm and 150 μgm along with a local

anesthetic in terms of duration of analgesia, time to the first dose of rescue analgesic, total dose of rescue analgesic and the incidence and severity of side effects in patients undergoing transabdominal hysterectomy.

In our country most of the transabdominal hysterectomies are done under spinal anesthesia. Intrathecal morphine has proved useful in the treatment of post operative pain in various surgical populations. However, there are only few studies in literature studying its efficacy in gynecological procedures. Moreover no study is available regarding the use of intrathecal morphine in the Indian population. Hence we thought this study would benefit this group because of the excellent analgesia it is thought to provide for the first 16-24 hours following surgery with minimal side effects as seen from Taeko Fukuda et al and others study. It is also a cost-effective option (Jeff Gadsen et al`s study[45]) Preservative-free intrathecal morphine has recently been made available in this part of the country and it is less expensive compared to other opioids or analgesia.

Various additives are added intrathecally to improve

analgesia and prolong the duration of analgesia, commonly used drugs being Fentanyl, Pethedine, Morphine, Clonidine, Neostigmine, Ketamine, Butrophenol. Among the opioids, morphine has more advantages[38-43] compared to others because it is a highly ionizable and hydrophilic drug having a prolonged effect as a result of its rostral CSF spread and slower disappearance from the C.S.F and spinal tissue Chadwick et al, have shown this to be true from their studies[43].

Various doses of intrathecal morphine have been tried ranging from 0.075 mgs to 0.5 mgs for providing high quality postoperative analgesia[39,43] lasting up to 24hrs.[46] The most commonly used doses are between 100 -300 micrograms. Palmar et al describes a ceiling effect[49,50] in the analgesic dose of morphine, after which side effects increase more than analgesia.[37,]

The results for the 80 patients allocated to the two groups were analyzed

There is no statistically significant difference between the two groups in terms of age, height, weight. There is no significant difference in duration of surgery. So the groups were comparable in terms of demographic variables.

The mean duration of analgesia in patients who received 250µgms of intrathecal morphine was 18.725 ±1.38 hours while in patients who received 150µgm it is 16.075 ±1.23 hours. In the post operative period, pain was assessed using the "Visual Analog Scale". Whenever the patient had VAS more than 4 or when patient complained of pain, Tab Ketorolac 10mgs was given per orally. Our results are comparable with the studies by Hiroshi yamaguchi et al [46]

Even though there was a statistically significant difference in the duration of analgesia between the two groups, clinically 2 more hours of duration of analgesia may not be significant. But the number of patients who had complete analgesia during the first day was more in the 250µgm group compared to the 150µgm group. Jeff Gadson et al describe pain of hysterectomy as two components, visceral and somatic, visceral pain arises from the uterus which is best taken care of by NSAIDs and the somatic pain best taken care by opioid[45]. We wanted to asses the efficacy of intrathecal morphine as a sole analgesic in the treatment of post operative pain relief. Soute etal has shown that very low doses like 40µgm or 80µgm of intrathecal morphine along with NSAIDS

provide good post operative analgesia after caesarian section.

Prolonged postoperative analgesia doesn't come with out side effects. Cousins M J et al, describes nausea, vomiting, pruritius, sedation, urinary retention and respiratory depression as side effects of intrathecal morphine.[45,47,] These side effects are mostly "nuisance factors" rather than life threatening.[48]

Review of literature shows the incidence of nausea and vomiting with intrathecal morphine as 35 to 45%,[56,61] In our study the percentage of PONV is 22.5% which is less when compared to the previous studies done by Jhi Joung Wang et al and others. Patients in our study belong to the high risk category of PONV, the risk factors being female sex, gynecological surgery, non smoker and parental opioids. All the patients in our study received 8 mgs T. ondensetron preoperatively as prophylaxis for PONV and pruritus. In addition to that, all the patients received 4mgs ondansetron intravenously eighth hourly and whenever required. This was due to ethical concerns. Despite this, 8 patients in group A and 7 patients in group B had nausea and 1 patient in group A and 2 patients in group B had vomiting. 6 patients in group A and 8 patients in group B required additional doses of ondensetron.

The fact that there was no significant difference in the incidence of PONV between the 2 groups with the increased intrathecal morphine dose of 250 µgm is in contrast to earlier studies by Dahl et al. This may be due to differences in surgical techniques and then ethnical population.[31,44,65,71] Study by Jhi-Joung Wang et al, have shown that a single dose of dexamethasone can prevent intrathecal morphine induced nausea and vomiting[56]. So it may be worthwhile to combine preoperative dexamethasone and ondansetron for prevention of postoperative nausea and vomiting after intrathecal morphine administration.

Even though a lot of patients had mild pruritis, only five patients from Group A and 3 patients in Group B had severe pruritis This is in contrast to the previous studies. Choi et al have shown that reducing the dose of intrathecal morphine in LSCS patients from 200 mcg to 50 mcg did reduce the incidence of pruritus to half[63]. In our study, 25% patients from each group had mild pruritius, which settled without treatment. This is much lesser compared to previous studies [57,63] This may be due to addition of prophylactic ondansetron[56]. Naloxone has been shown to be effective by Chang Jong Jeong et al[74] but none of our patients

required naloxone and we were able to treat the pruritius adequately with a single dose of chloropheneramine maleate[75]. Heni Ming Yeng et al have shown that a single dose of ondansetron reduced the incidence of intrathecal morphine induced pruritis.[62]

Regarding breakthrough pain and parental opioid consumption, there was statistically no significant difference between the two groups, but when this was required additional nursing time also came into play.

None of our patients showed sedation scores more than one i.e, [drowsy and arousable] and none of our patients required treatment. Sedation can sometimes be considered an advantage. It allows a calm intra operative and post operative course without other side effects. This sedation can sometimes cause profound drowsiness, which is undesirable for patients.

Urinary retention is the commonest side effect of intrathecal opioids. The incidence varies widely from 0-80% and the incidence is higher when intrathecal morphine is used. Rawal et al observed[67] that this is most likely related to interaction with opioid receptors located in the sacral spinal cord. This

interaction promotes inhibition of sacral parasympathetic nervous system outflow which causes detrusor muscle relaxation and an increase in maximum bladder capacity leading to urinary retention. Urinary retention may last for 20-24 hours. Urinary retention was not a problem in our patients as these patients are routinely catheterized as a part of surgery.

There is a lot of concern about delayed respiratory depression associated with intrathecal morphine. Delayed respiratory depression occurs 6-12 hours following intrathecal administration of morphine, and may persist for 24 hours, Wide ranges of intrathecal morphine from 0.05mgs-0.5mgs have been tried[66] and from the available literature it has been shown no respiratory depression occurred with doses less than 0.3 mgs [35-38]

In many of the earlier studies and case reports respiratory depression was not objectively quantified or defined.[55] In our study respiratory depression was defined as respiratory rate less than 10 /minute and Spo2 less than 90%. None of our patients had any respiratory depression including delayed respiratory depression. The incidence of delayed respiratory depression requiring intervention following conventional doses of intrathecal and epidural opioids is shown to be less than 1% by Jacobson K, et

al[68]. However the incidence of respiratory depression in obstetric population is less due to the effect of progesterone, which is a respiratory stimulant. Detection of respiratory depression induced by intrathecal and epidural opioids may be difficult. Classical bradypnoea may or may not be present and hypercarbia may develop despite a normal respiratory rate. Pulse-oximeter may be valuable but must be interpreted with caution if supplemental oxygen is being administered. Respiratory rate is an insensitive means of monitoring respiratory depression though it is highly used. In fact the response to CO_2 stimulation may be decreased in the face of a normal respiratory rate and apparently normal state of consciousness. Gustfson et al found the incidence of delayed respiratory depression to be 0.33% in their study.

Spinal Anesthesia is often associated with postdural puncture headache [PDPH]. In our study, none of the patients had PDPH. This may be due to older age group and intrathecal morphine masking the incidence of PDPH. Kang SB et al[69] and Brad Youngerman et al[72] have shown that lesser number of attempts and use of intrathecal morphine can reduce the incidence of PDPH. In a recent randomized trial by Lavir et al the

incidence of PDPH was 36% in cutting needle group and 3% in pencil point spinal needle group[73]

Over the last three years, the practice of spinal anesthesia has changed in our institution with the availability of 25 G pencil point needle and preservative free morphine.

The incidence of PDPH in our institution in 2004 was 12.4%; and in 2007 it was 7.9%. Many patients had mild to moderate PDPH in both the studies. However none of them required epidural blood patches. In our institution studies conducted with the use of Whitacre needle the incidence of PDPH was 4.6% vs 10.9% with Quincke 25G needles. The lesser incidence of PDPH in caesarian sections during 2007 when compared to 2004 is probably due to the use of Whittacre needles and intrathecal morphine. Studies by Balestrieri PJ[77] has shown that use of intrathecal morphine reduces the incidence of PDPH.

CONCLUSION

Our study showed that addition of 150µgms and 250µgms of preservative free morphine as adjuncts to bupivacaine local anesthetic for subarachnoid block prolonged the duration of analgesia after transabdominal hysterectomy. 250µgms morphine with local anesthetic resulted in a statistically significant longer duration of analgesia compared to 150µgms. However, there was no statistically significant increase in side-effects in this group either. Urinary retention was not a problem as these patients are routinely catheterized as part of surgery. There was no evidence of life-threatening problems like delayed respiratory depression, the dreaded PDPH or any other complication that increased morbidity. Adverse effects were similar in both groups.

All the patients in both groups reported good surgical analgesia for the first 16-18 hours. Thereafter all patients in both the groups required only one or two doses of Ketorolac as rescue analgesic for the first 24 hours. Incidence of PDPH was nil despite the spinal Anesthesia, probably due to the intrathecal analgesia

and this is definitely an advantage as far as the patient and costs are concerned. Morphine being less expensive compared to other analgesics and since very minimal doses are required via the intrathecal route, this is also a less costlier method of post-operative analgesia compared to continuous analgesic infusions and PCA while involving only the same amount of monitoring too. The incidence of pruritus in our study was found to be significantly lesser than in other studies. This may have been due to the administration of ondansetron prophylactically before the onset of action of intrathecal morphine which is thought to reduce the incidence and intensity of PONV and pruritis in patients receiving intrathecal opioids.

Nearly one-fourth of the patients in both groups still had PONV despite injection ondansetron prophylactically and 8th hourly. Since our group of patients are high risk for PONV, addition of steroids like injection dexamethasone along with ondansetron with the first dose may probably help.

We conclude that 250µgms of preservative-free intrathecal morphine provides longer duration of analgesia when compared to 150µgms morphine, with hardly any additional adverse effects.

Since preservative free morphine is now freely available in India, 250µgms intrathecal morphine pre-emptively along with local anesthetics and oral NSAIDs thereafter round the clock as required, is a good cost-effective option for complete post-operative analgesia in patients undergoing Transabdominal hysterectomy under subarachnoid block.

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APPENDIX 1:

PATIENT INFORMATION SHEET

STUDY NO:

TITLE OF THE STUDY:

Evaluation of the efficacy of 150 mcgs of intrathecal morphine with bupivacine compared to 250 mcgs for post operative analgesia following abdominal hysterectomy a double blinded randomized control study.

INSTITUTION:

Department of Anesthesia, Christian Medical College & Hospital.

NATURE AND PURPOSE OF STUDY:

The purpose of this study is to compare the efficacy of 150 mcgs of Intrathecal morphine vs 250 mcgs of the same for post operative pain relief following abdominal hysterectomy and asses the magnitude of side effects. You are going to undergo abdominal hysterectomy. This operation will be performed through a transverse incision in the lower abdomen. To ensure that your

operation is pain free, we will be giving you medicines [local anesthetics] in to the spinal space through a small needle, so that the nerves are anesthetized and you don't feel any pain or sensation through out the operation.

Normally recovery of sensation occurs after 3-4 hrs and patient will need additional drugs to ensure pain free in the immediate post operative period. However the addition of preservative free morphine to the local anesthetic drug should provide adequate analgesics for 16-24 hours after the surgery although recovery of motor function is achieved after 4 hours. This means that patients will not need other additional pain killers after the operation and can be mobile.

How ever with intrathecal morphine has occasional side effects like itching, nausea, vomiting, urinary retention and decreased rate of breathing can occur. Available literature has shown these to be mainly nuisance side effects. You will be catheterised during the first 24 hours as a part of surgical requirement, so that urinary retention is not a concern. Respiratory depression is very rare and can be readily treated, PONV and itching will be taken care to a certain extent by preoperative

ondansetron, if at all these side effects occur you can ask for rescue medicines. Hence the purpose of the study is to compare the efficacy of 150mcgs of intrathecal morphine Vs 250mcgs morphine.

If you are willing to participate in the study you will be randomly allocated to one of the 2 groups and will receive either 150mcgs of intrathecal morphine or 250mcgs of intrathecal morphine, The efficacy of the analgesic effect will be measured using visual analogue scales [VAS] this will be explained to you during the preoperative visit and on the next day the quality of analgesia will be assessed using visual analogue scale This will be recorded and compared. You may have itching, nausea, vomiting, delayed respiratory depression and urinary retention. Rescue medication for the treatment of all these conditions will be available in the ward at all times with no additional expenses involved.

EXPECTED DURATION OF INVOLVEMENT

On the day of surgery and one day post operatively

BENEFITS OF THE STUDY

The outcome of the study will help us to know if 150mcgs of intrathecal morphine is as efficacious as 250mcgs and decrease the complication and will provide the same quality of analgesia with lesser side effects when compared to 250 mcgs of morphine.

CONFIDENIALITY

All personal details identifying you will be kept confidential and only data relevant to the study will be stored and analysed.

CONSENT FORM FOR THE STUDY:

I am _____and my hospital number is_____.

The details of this study have been explained to me. I understand that this is voluntary and I am aware of the purpose of the proposed study conducted by _____. I give my consent to be enrolled in this study.

Signature of the Patient / Guardian

Signature of the Anesthetist

Name of the patient :

Signature of the witness

Hospital no. :

Name of the witness

Date :

APPENDIX 2:

PROFORMA

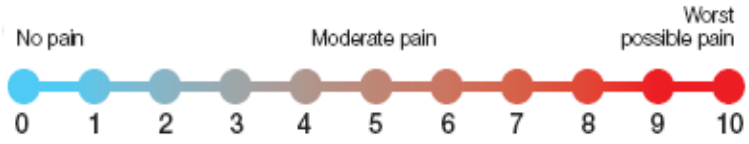
Intrathecal morphine in Abdominal hysterectomy for post operative pain relief- study

Group: Time of spinal
Indication for surgery: Rescue Analgesia:
Hospital no:
Age:
Intra op events: hypotension/ arrhythmia/ bradycardia / pruritus/ nausea & vomiting/

time	VAS	PONV	pruritus	Resp depress	sedation	antiemetic	antipruritic
0							
1							
2							
4							
8							
12							
24							

Patient satisfaction excellent/ good/ fair/ poor

Troublesome side effects (patient)



PONV
0 no nausea or vomiting
1 nausea
2 vomiting

SEDATION SCORE

0 awake

1 mild (occ. Drowsy)
2 moderate (freq drowsy)
3 difficult to arouse

If respiratory rate is < 10 / min, check SpO2, if < 90% O2 by face mask @ 6L/min

Prophylaxis for nausea or vomiting – ondansetron 8 mg IV q8h

In c/o severe pruritus-T Chlorpheniramine maleate 25 mg

Inclusion criteria

ASA I and II patients

Exclusion criteria: Morbidly obese, contra indication for spinal anesthesia, allergy to any study drug, age>60 yrs

Premedication: tablet ondansetron 8 mgs tablet diazepam 10 mgs

L 2-3, 3-4, 25G Whitacre spinal needle.

In case of hypotension SBP < 100 mmHg or < 80% of base line value, Rx with fluid bolus, i/v ephedrine

APPENDIX 3:
MASTER CHART

Sl no	Group	Hosp no	Age	Wt	Ht	dur surg m	VAS	ANALH	Sed score	side eff	drug 1	drug2	drug3	drug4	drug5	Resc anal	pdph	pethedine
1	B	201288D	45	49	150	110	4	15	0	0	0	0	0	0	0	2	0	0
2	A	197894D	37	72	157	90	5	20	0	1	0	0	0	0	0	1	0	0
3	A	199309D	43	45	153	145	5	19	0	0	0	0	0	0	0	1	0	0
4	A	984473A	45	55	155	125	5	18	0	0	0	0	0	0	0	1	0	0
5	B	185694D	41	52	156	130	4	16	0	0	0	0	0	0	0	1	0	0
6	B	176400D	48	60	156	110	4	16	0	0	0	0	0	0	0	2	0	1
7	B	933260D	52	55	154	95	4	20	1	2	1	0	0	0	0	1	0	0
8	A	180194D	55	50	152	115	5	19	0	0	0	0	0	0	0	2	0	0
9	B	196584D	38	52	155	120	5	18	0	1,2,3	1	2	0	0	0	1	0	1
10	B	240678D	42	58	156	100	5	15	0	0	0	0	0	0	0	2	0	0
11	A	163753D	45	55	150	95	5	21	1	1,3	1	2	0	0	0	1	0	0
12	A	853650C	48	52	152	90	5	19	0	1	0	0	0	0	0	2	0	0
13	B	222296B	52	56	154	105	4	16	0	0	0	0	0	0	0	2	0	0
14	A	146555D	39	52	155	110	4	20	0	0	0	0	0	0	0	2	0	0
15	A	151538D	41	55	158	110	4	18	0	0	0	0	0	0	0	2	0	0
16	B	055272C	54	52	154	100	4	16	0	0	0	0	0	0	0	2	0	0
17	A	157827D	46	51	153	90	5	20	0	1,3	1	0	0	0	0	1	0	0
18	A	949468C	39	55	156	95	5	21	1	0	0	0	0	0	0	2	0	0
19	B	117922D	45	59	158	110	4	16	0	1	1	0	0	0	0	2	0	0
20	B	176558D	46	60	160	115	4	15	0	0	0	0	0	0	0	2	0	0
21	B	176511D	48	59	158	100	5	14	0	0	0	0	0	0	0	2	0	0
22	A	175627D	40	62	160	90	4	18	0	0	0	0	0	0	0	2	0	0
23	A	181601D	56	55	155	95	5	19	0	0	0	0	0	0	0	2	0	1
24	B	178196D	46	54	152	100	4	15	0	1	1	0	0	0	0	1	0	0
25	B	447525B	42	58	158	105	5	16	0	0	0	0	0	0	0	2	0	0
26	A	101217D	54	56	154	100	4	20	0	1	0	0	0	0	0	2	0	0
27	B	128682D	39	55	156	110	5	18	0	1,3	1	2	0	0	0	1	0	0
28	B	183631D	45	52	154	110	5	16	0	0	0	0	0	0	0	2	0	0
29	B	084204D	43	54	158	120	5	17	1	0	0	0	0	0	0	2	0	0
30	A	144424C	54	56	159	110	5	19	0	0	0	0	0	0	0	2	0	0
31	A	185694D	41	59	154	105	4	19	0	0	0	0	0	0	0	2	0	0
32	A	198057D	45	55	158	110	4	20	1	1,2	1	0	0	0	0	1	0	0
33	A	203429D	39	55	157	105	4	17	0	0	0	0	0	0	0	2	0	0
34	B	174333D	45	60	158	100	5	15	0	0	0	0	0	0	0	2	0	1
35	B	077587B	52	55	157	120	5	15	0	0	0	0	0	0	0	2	0	0
36	B	234147D	45	52	154	110	5	16	1	1	0	0	0	0	0	2	0	0
37	A	078874d	46	50	152	100	5	20	0	1,3	1	0	0	0	0	1	0	0
38	A	689225C	48	55	155	110	4	18	0	0	0	0	0	0	0	2	0	0
39	B	191999D	38	52	154	100	4	17	0	1	0	0	0	0	0	2	0	0
40	A	194749D	45	50	155	110	5	18	0	0	0	0	0	0	0	2	0	0
41	A	177981D	40	55	158	100	5	19	0	0	0	0	0	0	0	2	0	0
42	B	192468D	41	50	154	90	4	18	1	1	0	0	0	0	0	2	0	0

Sl no	Group	Hosp no	Age	Wt	Ht	dur surg m	VAS	ANALH	Sed score	side eff	drug 1	drug2	drug3	drug4	drug5	Resc anal	pdph	pethedine
43	A	201467D	45	55	159	95	4	15	0	0	0	0	0	0	0	2	0	0
44	B	143531D	40	54	154	100	5	16	0	0	0	0	0	0	0	2	0	0
45	B	237021D	38	59	157	105	5	17	0	0	0	0	0	0	0	2	0	0
46	A	250801D	43	62	160	100	4	19	0	0	0	0	0	0	0	2	0	0
47	A	243807D	49	64	162	110	5	18	0	1	0	0	0	0	0	2	0	0
48	B	220903D	48	60	159	115	4	15	0	0	0	0	0	0	0	2	0	0
49	B	195408D	39	59	157	100	5	16	0	1,2	1	0	0	0	0	1	0	0
50	A	193110C	42	54	155	105	5	19	0	0	0	0	0	0	0	1	0	0
51	B	257773D	55	50	154	90	5	17	0	0	0	0	0	0	0	2	0	1
52	A	945473A	50	48	152	95	5	20	0	1,2,3	1	0	0	0	0	1	0	0
53	A	9905004C	56	50	154	90	5	19	0	1	0	0	0	0	0	2	0	0
54	B	320046B	52	48	152	95	4	17	0	0	0	0	0	0	0	2	0	0
55	B	182913D	48	45	154	100	4	15	0	0	0	0	0	0	0	2	0	0
56	B	386910B	46	52	158	110	5	16	0	0	0	0	0	0	0	2	0	0
57	A	258518D	55	56	156	100	5	20	1	1	0	0	0	0	0	2	0	0
58	A	256842D	46	54	154	105	5	21	0	0	0	0	0	0	0	1	0	0
59	B	684299C	48	50	156	100	4	16	0	0	0	0	0	0	0	2	0	0
60	A	752122A	42	49	154	90	4	19	0	0	0	0	0	0	0	2	0	0
61	B	067883D	54	50	155	100	5	17	0	0	0	0	0	0	0	2	0	0
62	B	053006D	48	59	158	110	5	15	0	0	0	0	0	0	0	2	0	1
63	A	173335B	39	62	160	100	4	19	0	1	0	0	0	0	0	2	0	0
64	A	172976C	45	65	162	120	4	20	0	1,2,3	1	2	0	0	0	1	0	0
65	B	267744D	42	60	160	110	5	18	0	0	0	0	0	0	0	2	0	0
66	A	212954D	55	56	158	105	5	17	0	0	0	0	0	0	0	2	0	0
67	A	275297D	55	56	154	100	5	16	0	0	0	0	0	0	0	2	0	0
68	A	356628C	45	52	156	90	4	18	0	0	0	0	0	0	0	2	0	0
69	B	869074C	38	50	154	105	4	14	0	0	0	0	0	0	0	2	0	0
70	B	075597D	42	45	152	100	5	16	0	1	0	0	0	0	0	2	0	0
71	B	090479D	45	59	163	100	4	15	0	0	0	0	0	0	0	2	0	0
72	A	051558D	42	55	159	110	5	18	0	1	0	0	0	0	0	2	0	0
73	B	380002B	45	52	154	100	4	17	1	3	1	0	0	0	0	1	0	0
74	A	045167D	41	50	152	105	5	16	0	0	0	0	0	0	0	2	0	0
75	A	001188D	48	58	160	100	4	17	0	0	0	0	0	0	0	2	0	0
76	B	089335D	43	65	162	110	4	16	0	1	1	0	0	0	0	2	0	0
77	A	589075B	49	66	165	100	5	18	0	0	0	0	0	0	0	2	0	0
78	B	114206D	52	62	160	120	5	15	0	0	0	0	0	0	0	2	0	0
79	B	115066D	42	55	156	100	4	15	0	0	0	0	0	0	0	2	0	0
80	A	113920D	45	50	154	90	5	18	0	0	0	0	0	0	0	2	0	0

APPENDIX-4

GLOSSARY

Hospital No	:	Hospital number
Age	:	Age in years
Weight	:	Weight in Kgs
Height	:	Height in Cms
Duration of surgery	:	Duration of surgery in Minutes
VAS	:	Visual Analog Scale
ANACH	:	Duration of analgesia in hours
Sed. Score	:	Sedation score
Resc anal	:	Rescue analgesia
Pdph	:	Post dural puncture headache

Side Effects

0 – No Side Effect
1 – Nausea
2 – Vomiting
3 – Pruritus
4 – Hypotension
5 – Shivering
6 – Bradycardia
7 – Respiratory Depressin

Sedation Score

0 – Awake
1 – Mild (occasionally drowsy)
2 – Moderate (Frequently drowsy)
3 – Difficult to arouse

Drugs

Drug-1 Ondansetron
Drug-2 Chlorphenramine maleate
Drug-3 Ephedrine
Drug-4 Pethedine
Drug-5 Atropine

Rescue Analgesia

0 – Nil
1 – One dose
2 – Two dose