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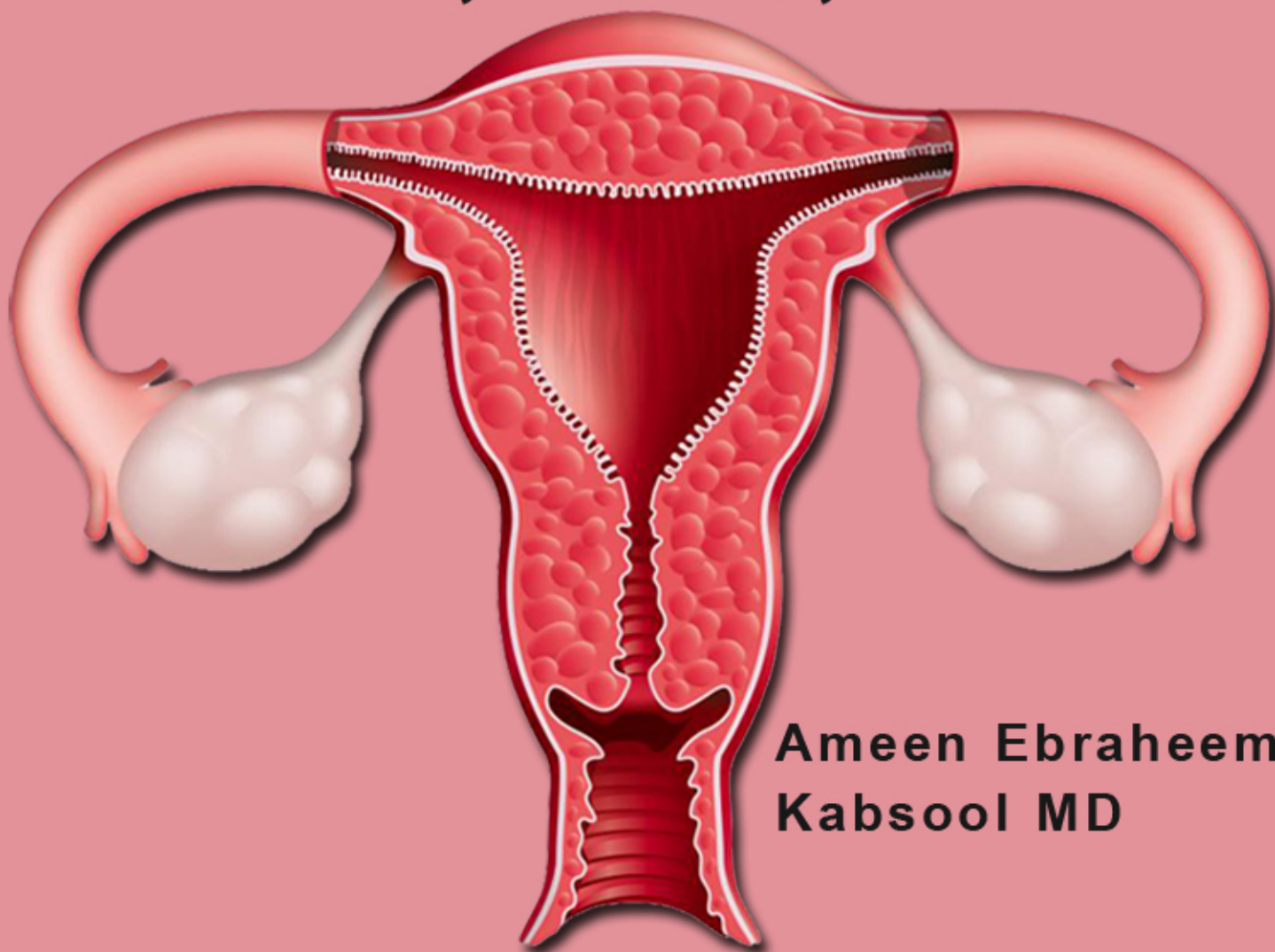
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General Versus Spinal Anesthesia with Difference Form of Sedation for Patient Undergoing Elective Hysterectomy

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Dedication

To my Beloved Madam
Dear Family
Faithful friend and dignified teachers
To the anesthetic staff at Omdurman
Military Hospital for the kind and generous support

Contents

Abstract

To assess the impact of spinal anesthesia combined with three different form of conscious sedation on intraoperative and post operative outcome in patients undergoing elective hysterectomy in Omdurman Military Medical Hospital in the period from the 1st of April 2007 to the 30th of April 2008.

All patients of ASA grade 1 and 2 within the age group between 3 0-80 yrs of patients in a total of 80 Sudanese ladies. The first group 20 patient received GA combined with 25mg pethdine intraoperative. The second group 20 patients received SPA lumber-subarachnoid puncture with bupivacine hydrochloride 0.5% plus diazepam i.v 2.5mg as a sedative agents plus 02 by adult mask. The third group 20 patients received SPA with bupivacine plus midazolam i.v as sedative agents, (0.5-1mg i.v) in bolus and 02 by adult mask. The 4th group 20 patients received SPA with bupivacine plus propofol 4-5mg/kg per h. in continuous infusion and 02 by adult mask.

Data was collected using questionnaire parameters were colleted results the present study showed that muscle relaxation throughout hysterectomy was not different in all groups: bleeding was significantly lower with spinal anaesthsia with regardless of the form of sedation. Group four reported the best postoperative oxygen saturation percentage by pulse-oximetry and sedation score- the shortest waiting time in the postoperative holding area, the lowest pain on postoperative day, and the highest frequency the first flatus passage. A higher number in group 4 patients were able to carry out the assisted ambulation.

In this study we can concluded that conscious sedation coupled with SPA is safe, reliable and effective procedure for patients undergoing hysterectomy. The use of propofol as sedative agents offers several advantages both over the types of conscious sedation and GA.

Abbreviations

ASA: American Society of Anesthesiology

SPA: Spinal Anesthesia

GA: General Anesthesia

GABA: Amine Butyrine System- Gama – Amino Butyric Acid

ITU: Intensive Therapy Unit

ICU: Intensive Care Unit
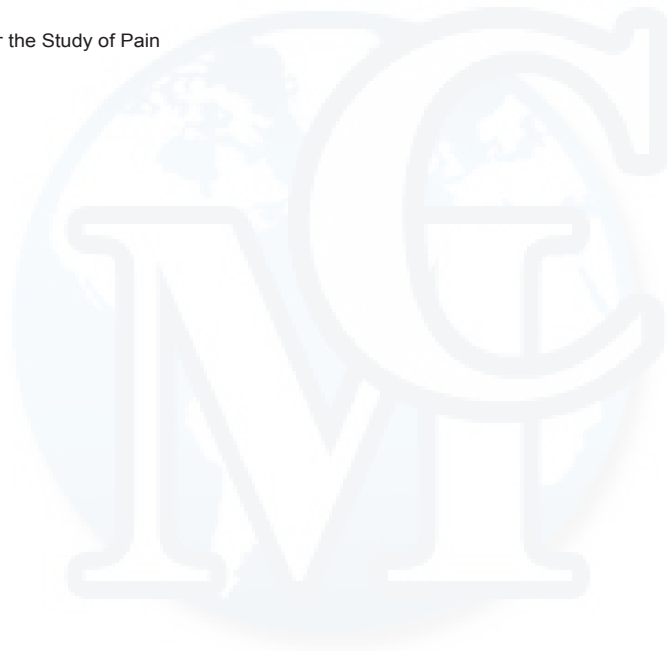
IV: Intra Venous

CBF: Cerebral Blood Flow

LMA: Laryngeal Mask Airway

CSF: Cerebro Spinal Fluid

IASP: International Association for the Study of Pain

NMDA: N-methyl-D-Aspartate

Chapter 1: Introduction

Introduction

Several studies suggest that both SPA and (GA) combined with postoperative analgesia can be used effectively and safely for hysterectomies. We have recently showed that spinal anaesthsia (SPA) combined with adequate sedation might be an attractive alternative to standard general anesthesia for patients undergoing hysterectomies. Spinal anesthesia is associated with significantly reduced blood loss and good control of hemodynamics and respiratory parameters both intra operatively and peri operatively, and results in reduced pain and a faster post-surgical recovery. Sedation plays a major role during the surgical procedure; however, to our knowledge, the impact of different types of sedation on overall reliability and patient acceptance of this procedure has not been assessed to date.

The aim of this prospective, blinded, randomized controlled study was to assess intraoperative and postoperative outcomes in patient undergoing general anaesthsia versus spinal anaesthsia with three different forms of sedation (diazepam, propofol, and midzolam) during hysterectomies against GA control group.

Literature Review

Hystrprectomy is a gynecological operations associated with increased risk of mortality and morbidity as it is done Usually in elderly ladies. The anesthetist may face both the problems of ageing of all body systems and of the specific disease which become more prevalent with increasing age.

Choosing the type of appropriate anesthesia is really important in dealing with this kind of surgery.

Problems

Cardiovascular: Decreasing vessel elasticity leads to, a lesser complaint vascular tree (a raised SVR) with systemic hypertension, left ventricular. Strain and hypertrophy cardiac conduction time and stroke volume are reduced. Cardiac output falls and arm-brain circulation time is increased affecting the drug circulation. Baroreceptor sensitivity, sympathetic tone and the ability to increase the heart rate when required are reduced.

Disease: Hypertension, heart failure IHD, valvular disease (especially mitral regurgitation and aortic stenosis and peripheral disease.

Respiratory: Pulmonary elasticity, lung and chest wall compliance, FEy. FVC, vital capacity and inspiratory reserve are all reduced. The closing volume exceeds FRC in the supine position after the age of 43 years with resultant V/Q mismatch and hypoxaemia, the residual volume is increased. There is a reduced response to hypoxaemia and hypercarbia and protective airway reflexes decrease in old age. Diseases: Chronic obstructive airflow and emphysema.

Renal: Renal blood flow, GFR and concentrating ability are all reduced. This leads to reduced renal clearance of drugs, a raised blood urea but a stable blood creatinine.

Metabolic endocrine: Adipose tissue increases whilst muscle bulk and total body water arc reduced. The BMR falls by 1% per year after and thermo regulation is impaired.

Diseases: Diabetes, thyroid, osteoporosis and nutritional disorders.

Pharmacology: Lateral drug absorption, protein binding, metabolism and excretion in combination with aging body systems make drug effects more variable in the elderly.

Anesthetic Management

Assessment and premeditation: History and examination is followed by a FBC, U + E and ECG in all over 60 yrs, and a small dose of anxiolytic may be helpful.

Conduct of anesthesia: Monitoring is as indicated by low systems pathology and planned surgery. Regional anesthesia avoids the problems of the general anaesthesia. Hypotension is common and will control by fluids and vasopressors. All patients should receive supplementary 0_2. For general anesthesia consider pre oxygenation intravenous agents should be given slowly with care and in small dose being worry of a slow arm/brain circulation time. IPPV may cause a marked fall in blood pressure special care should be taken with respect to pressure points when positioning the patient. Hyperthermia should be prevented and surgery should not be prolonged.

Postoperatively:

a) The majority of elderly systemic disease patient's should admit in the high intensive care unit.

b) Supplementary 0_2.

c) Analgesia is filtrated to effect when using opioids.

d) P.C.A. or regional techniques may also be used.

Spinal anesthesia

The subarachnoid (spinal anesthesia is obtained if a local anesthetic solution is injected through a spinal needle into a patient's subarachnoid space, it will anaesthetize the spinal nerves as they pass through the spinal canal, which of this spinal herves are anaesthetized depends on how, the drug flows and diffuses in the C.F.F before it is fixed, during the first 10 mm after the injection [1]. Hyperbaric spinal anesthesia has been the standard method for many years. It provides good conditions for surgery, blood loss is reduced, the gut is well contracted and the muscles of the lower part of the body are relaxed. The hyperbaric (heavy) solution is made up and mixed with 5 to 10% of dextrose without adrenaline

or preservatives. The solution is heavier than the C.S.F and tends to settle down. By varying the patient's position, the extent of the block can be varied.

Spinal anesthesia - a practical guide:

a. Spinal anesthesia is induced by injecting small amounts of local anaesthetic into the cerebro-spinal fluid (CSF).

b. The injection is usually made in the lumbar spine below the level at which the spinal cord ends (L2).

c. Spinal anesthesia is easy to perform and has the potential to provide excellent operating conditions for surgery below the umbilicus.

d. If the anesthetist has an adequate knowledge of the relevant anatomy, physiology and pharmacology, safe and satisfactory anaesthesia can easily be obtained to the mutual satisfaction of the patient surgeon and anesthetist.

The advantages of spinal anesthesia:

Cost: Anesthetic drugs and gasses are costly and the latter often difficult to transport. The costs associated with spinal anesthesia are mineral.

Patient satisfaction: Anesthetic and surgery are performed skillfully; the majority of patients are very happy with the technique and appreciate the rapid recovery and absence of side effects.

Respiratory disease: Spinal anesthesia produces few adverse effects on the respiratory system as long as unduly high blocks are avoided.

Patent airway: There is reduced risk of airway obstruction or the aspiration of gastric contents. The advantage may be lost with too much sedation.

Diabetic patients: There 'is a little risk of unrecognized hypoglycemia in an awake patient. Diabetic patients can usually return to their normal food and insulin regime soon after surgery as there is less sedation, nausea and vomiting.

Muscular relaxation: Spinal anesthesia provides excellent muscle relaxation for lower abdominal and lower limb surgery.

Bleeding: Blood loss during operation is less than when the same operation is done under general anesthesia. This is as a result of a decreased blood pressure and heart rate, and improved venous drainage, which result in oozing.

Splanching blood flow: Increasing the blood flow to the gut, spinal anesthesia reduces the incidence of anastomotic dehlscenc.

Visceral tone: The bowel is contracted by spinal anesthesia sphincters relaxed although peristalsis continues. Normal gut function rapidly returns following surgery.

Coagulation: Post-operative deep vein thromboses ad pulmonary emboli are less common following spinal anesthesia.

Disadvantages of spinal anesthesia:

a) When learning a new technique, it will take longer to perform than when more practicing and it would be wise to let the surgeon know that induction of anesthesia may be longer than usual. Once competent, however, spinal anesthesia can be very swiftly performed.

b) Occasionally, it is impossible to locate the dural space, and obtain CSF, the technique has to be abandoned. Rarely despite.

c) An apparently faultless technique, anesthesia is not obtained.

d) Hypotension may occur with higher blocks and the anesthetist, must know how to manage this situation with the necessary resuscitative drugs and equipments. As with, general anesthesia, continues, close monitoring of the patient is mandatory.

e) Even if a long-acting local anesthetic is used, a spinal is not suitable for surgery lasting longer than approximately 2 hours. If an operation unexpectedly lasts longer than this, it may be necessary to convert to a general anesthetic.

f) There is a risk of introducing infection into the sub arachnoids space leading to meningitis. It shouldn't happen if equipments are sterilized properly and an aseptic technique is used.

Indications for spinal anesthesia:

a. Spinal anesthesia is best reserved for operations below the umbilicus e.g. hernia repairs, gynecological and urological operations and any operation on the perineum or genitalia.

b. All operations on the leg are possible, but an amputation, through painless, may be an unpleasant experience for an awake patient. In this situation it may be kinder to supplement the spinal with generous sedation of light general anesthetic.

c. Spinal anesthesia is especially indicated for order patients and those with systemic disease such as chronic respiratory disease, hepatic, renal and endocrine disorders such as diabetes.

d. Most patients with mid cardiac disease benefit from vasodilatation that accompanies spinal anaesthesia except those with stenotic valvular diseases or uncontrolled hypertension.

e. It is suitable for managing patients with trauma if they, have been adequately resuscitated and are not hypovolaemic.

f. In obstetrics, it is ideal for 'manual removal of

a retained placenta (again, provided there is no hypovolaemia). There are definite advantages for both mother and baby in using spinal anesthesia for Caesarean section. However, spinal considerations should be applied to manage spinal anesthesia in pregnant patients.

Contraindications to spinal anesthesia:

A. V Most of the contra-indications to spinal anaesthesia 'apply equally to other forms, of regional anesthesia. These include:

   a. Inadequate resuscitative drugs and equipment.

   b. No regional anesthetic technique should be attempted if drugs and equipments for resuscitation are not immediately available.

Clotting Disorders

i. If bleeding occurs into the epidural space because an epidural vein has been punctured by the spinal needle, a hematoma could form and compress the spinal cord.

ii. Patients with a low platelet count or receiving anticoagulants drugs such as heparin or warfarin are at risk.

iii. Patients with liver, disease may have abnormal clotting profiles whilst low platelets count as well as abnormal clotting can occur in pre-eclampsia.

   a. Hypovolaemia: Patients with hypovolaemia from whatever cause e.g. bleeding dehydration due to vomiting, diarrhoea or bowel obstruction must be adequately re-hydrated or resuscitated before spinal anaesthesia.

   b. Any sepsis on the back: near the site of lumbar puncture.

   c. Patient refusal.

   d. Uncooperative patients.

   e. Spinal anesthesia is not given to children or uncooperative patients, if it is needed it is given after general anesthesia.

Septicaemia

Due to the presence of infection in the blood there is a possibility of such patients developing; meningitis if a hematoma forms at the site of lumbar puncture and becomes infected.

a) Anatomical deformities of the patient's back: This is relative contraindication, as it will probably only serve to make the dural puncture more difficult.

Neurological Diseases

The advantages and disadvantages of spinal anaesthesia in the presence of neurological diseases and careful assessment. Any worsening of the disease postoperatively may be blamed erroneously on the spinal anesthetic. Raised intracranial pressure, however, is an absolute contraindication as a dural puncture may precipitate coning of the brain stem.

   A. Reluctant surgeon:

      a) If a surgeon is unhappy operating on an awake patient he is relatively unskilled, spinal anesthesia may be better avoided.

I. Physiology of spinal anesthesia:

i. Local anesthetic solution injected into the subarachnoid space blocks conduction of impulses along all nerves with which it comes in contact, although some nerves are more easily blocked than others.

ii. Classes of nerves are three: motor, sensory and automatic.

iii. The motor convey messages for muscles to contract and when they are blocked, muscle paralysis results.

iv. Sensory nerves transmit sensations such as touch and pain to the spinal cord and from there to the brain.

v. Whilst automatic nerves control the caliber of blood vessels, heart rate, gut contraction and other functions not under conscious control.

vi. Generally, automatic and pain fibers are blocked first and motor fibers last. This has several important consequences. For example, vasodilatation and a drop in blood pressure may occur when the automatic fibers are blocked and the patient may be aware of touch and yet feel no pain when surgery starts.

vii. There are practical implications associated with these physiological phenomena.

viii. The patient should be well hydrated before the local anesthetic is injected and should have an intravenous infusion in place so that further fluids or vasoconstrictors can be given if hypotension occurs.

ix. The site to be operated on should not be repeatedly touched and the patient asked: can you feel? as this increases the patient anxiety. It is better to pinch the skin gently either with artery forceps or fingers and ask if it is painful. If it is not then surgery can begin.

Anatomy

The spinal cord usually ends at the level of L2 in adults and L3 in children. Dural puncture above these levels is associated with a slight risk of damaging the spinal cord and is best, avoided. An important landmark to

remember is that a line joining the top of the iliac crests is at L4 to L45.

Remember the structures that the needle will pierce before reaching the CSF.

The skin

It is wise to inject a small bleb of local anesthetic into the skin before inserting the spinal needle.

a) **Subcutaneous fat:** This, of course, is of variable thickness, identifying the intravertebral spaces is far easier in thin patients.

b) **Interspinous ligament:** It is a thin band of ligament running between the spinous processes.

c) **Ligmentum flavum:** It is quite thick, up to about 1cm in the middle and is mostly composed of elastic tissue. It runs vertically from lamina to lamina. When the needle is within the ligaments it will feel griped and a distinct "give can often be felt as it passes through and into the epidural space.

d) **Epidural space:** Contains fat and blood vessels. If blood comes out of the spinal needle instead of CSF when the stylet is removed, it is likely than an epidural vein has been punctured. The needle should simply be advanced a little further.

e) **The dural:** After feeling a "give as the needle passes through the ligarnentum flavum, a similar sensation may be felt when the needle is advanced a short distance further and pierces the dural sac.

f) **Subarachnoid space:** This contains the spinal cord and nerve roots surrounded by CSF. An injection of local anesthetic will mix with the CSF and rapidly block the nerve roots with which it comes in contact.

Pain

Pain is an extraordinary complex sensation which is difficult to define and to measure in an accurate objective manner. The international Association for the study of pain (LASP) defines pain as 'unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [2-8].

It is not only a physical sensation but also, ultimately, a subjective physiological event which can occur in spite of negative physical findings and investigations. Pain has sensory, cognitive and motivational - effect dimensions and has been described as a biopsychosocial experience as in the following Figure 1.

Pain can be broadly divided into:

A. Acute pain

B. Chronic pain

Acute pain: Lasts less than week. It tends to have an identifiable cause, and is often relieved following the removal of the cause. Examples of acute pain are: post surgical pain, sports-related injury, trauma, lower back pain, as well as acute headache.

Chronic pain: Lasts more than 6 months. It is more complex and tends to have less identifiable causes. Therefore, the focus of the management has been to improve symptoms and preserve functionality as well as psychological function. Examples of chronic pain include musculoskeletal pain, pain from malignancy, chronic infections, osteoarthritis, rheumatoid arthritis, lower back, pain and chronic headache. Post operative pain is a type of acute pain; it requires planning, patient and staff education to the type of surgery. It is usually transitory, with progressive improvement over a relatively short time course. Typically, the affective component tends towards an anxiety state associated with diagnosis of the condition and fear of delay in provision of analgesic therapy by attendants [8-11].

The Venn diagram below shows the interrelationship between emotional rational and physical components of pain: the shaded area represents the quantum of suffering experienced by the patient (Figure 2).

Figure 1: Pain has sensory, cognitive and motivational - effect dimensions and has been described as a biopsychosocial experience.

1: Physical problem

2: Psychological distress

3: Illness behavior

4: Social interaction

Classification of pain

Nociceptive pain: This is the pain that we experience in our every day lives in. response to a noxious stimulus. It acts as an early warning system. It is an essential

protective mechanism that prevents tissue damage by alerting the body to the presence of an intense, potentially damaging stimulus in the environment. It can be either:

a) Somatic pain: It results from activation of nociceptors in cutaneous and deep tissues. It is well localized and described as aching, throbbing or gnawing.

b) Visceral pain: It arises from internal organs, often described as deep, dull, dragging pain. The mechanisms include abnormal distention or contraction of smooth muscle, stretching of the capsule of solid organs, hypoxia or necrosis and irritation by allergic substances.

Figure 2: The Venn diagram below shows the interrelationship between emotional rational and physical components of pain: the shaded area represents the quantum of suffering experienced by the patient.
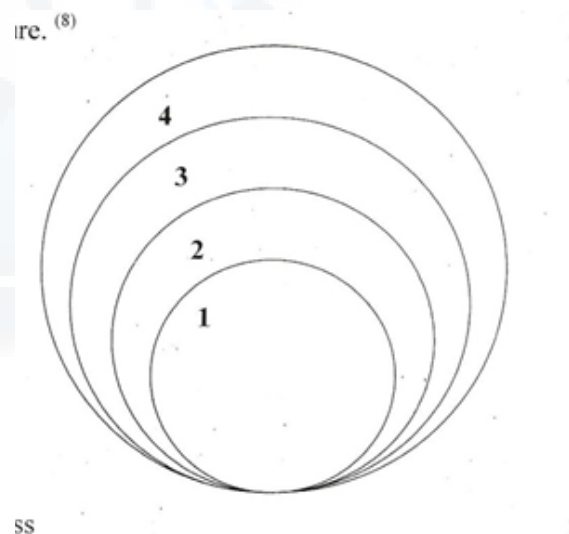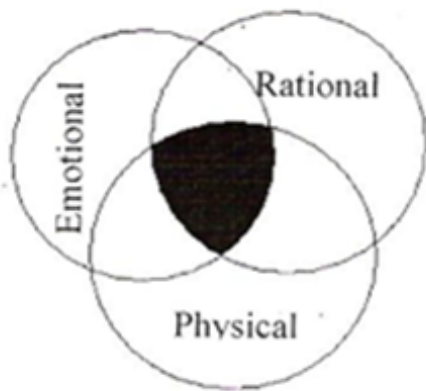
Inflammatory pain: Inflammatory pain has a number of different manifestations. Obviously one of them is a situation where the early warning nociceptive pain has been overwhelmed and instead of preventing tissue damage by a withdrawal response, severe trauma occurs. So post-traumatic pain includes tissue damage and an inflammatory response.

Neuropathic pain [12]: It is caused by functional abnormality of the peripheral and or CNS. Some examples of this would be compression of the median nerve with carpal tunnel syndrome; pain associated with the after effects of acute herpes zoster, post therapeutic neuralgia and damage to the spinal cord producing a central pain.

Basic anatomy of pain

Nociceptors: There are specific sensory nerve terminals activated by a sufficient intensity stimulus such as mechanical, chemical or thermal stimulus. The initial stimulus for activation is probably mechanical distortion of the nerve terminal followed by increase in local concentration of K and H which lead to a reduction in the threshold for stimulation.

Primary afferent fibers: There are two types:

a. **Alpha-delta fibers:** Small myelinated fibers with a conduction velocity of<2ms-1.

b. **C-fibers:** Small unmyelinated fibers with conduction velocity of (10-40ms'). Following a noxious stimulus, an immediate sharp pain is experienced "due to activation of alpha-delta fibers", followed by persistent burning pain (due to activation of C fibers). The first sharp pain allows rapid reflex and behavioral mechanism to remove the individual from the source of pain. The second pain persists to prevent further injury and tissue damage.

The spinal cord

70% of afferent fibers enter in the dorsal root, the remaining enter the ventral motor root. A cross section of the spinal cord shows 10 anatomically and physiologically distinct layers, termed Rexed Laminae.

The most important are:

a) Lamina I: (outer marginal zone).

b) Lamina II: Substantia gelatinosa, which responds to noxious stimuli only.

c) Lamina Vil-Vill: Represents the motor horn.

Ascending tract and supraspinal systems

Dorsal horn neurons project to higher centers in the brain by one of three major spinal systems.

a. Spinothalamic tract: It is the most important for the pain transmission. It projects to several nuclei in the thalamus.

b. Spinorecticular tract: Terminates in the reticular nuclei in the brain stem.

c. Spinomesencephalic tract: Terminates in the mesencephalic reticular formation and periaqueductal grey. These tracts project to:

a) Somatosensory cortex: Associated with the sensory aspect of pain.

b) Limbic system: Associated with the affective aspect of pain.

Descending systems

The two most important areas in the brain associated with descending inhibitory pathways are:

A. Periaqueductal grey in the midbrain.

B. Rostral ventromedial medulla.

They contain high concentrations of endogenous opioids and opioids receptor. Activation of these receptors increases the activity in the descending monoamine pathways (serotonin and norepinephrine which project to the dorsal horn.

Pain and neurotransmitters:

Excitatory neurotransmitters: The most important ones are glutamate and tachykinins. These act at various neurokinin receptors including substance P, neurokinin A and B. Other substances that transmit pain impulses from incoming nerves in dorsal horn calcitonin gene related peptide (CGRP), vasoactive intestinal polypeptide and somatostatin.

Inhibitory neurotransmitters: Gamma amino-butyric acid (GABA) in the main inhibitory neurotransmitters.

Descending pain regulation neurotransmitters: Noradrenalin, serotonin and opioids relief pain by stimulating t and a receptors at the host of sites. Specific neurotransmitters: The most important ones are:

I. Glutamate: NMDA receptors mediate a host of spinal responses to severe stimulation. These receptors are inactive, due to Mg present on its ion chemicals. For this to be removed, adjacent peptide receptors have to be stimulated Mg is removed and painful stimuli occur. Glutamate receptors activation results in production of prostanoids and nitric oxide.

II. GABA: is spread in the brain and the spinal cord, along with glycine. Interneurons in plasma I, II are GABA rich, and mediate gate control by synapse on neurons that contains substances.

III. Tachykinins: Neurokinin receptor mediates pain in the spind cord substances P binds to NK- 1 receptor, while neurokinins A and B bind respectively to NK-2 and NK-3 receptors. These substances are "tachykinins". The tachykinin receptors are G protein triggering gene transcription.

Effects of pain

Cardiovascular system: Tachycardia, hypertension, vasoconstriction and may end with angina and myocardial infraction. Respiratory system: painful abdominal and thoracic wounds restrict inspiration leading to tachypnoea, small tidal volume, inhibition of the patient affective coughing and mobilization.

Endocrine system: Surgery and pain generate a catabolic state with increased secretion of anabolic hormones. They affect alternations in the blood flow, coagulation and fibrinolysis. V Some methods of treating post-operative pain:

a) Administration of opioids: It has a lot of side effect such as ventilatory depression, sedation, constipation, cough suppression and tolerance.

b) Non-steroidal anti-inflammatory drugs: Effective after minor surgeries and outpatient surgeries.

c) c- Neural blockade.

Pharmacology

Sedatives [13]

Sedation may be defined as the use of pharmacological agents to produce depression of the level of consciousness sufficient to result in drowsiness and anxiolysis without loss of verbal communication. The difference between sedative and anaesthetic drugs is largely one of usage. Many anaesthetic drugs may be used at reduced dosage to produce sedation. Drugs more usually used as sedatives produce a form of anaesthsia if given in high enough doses. There exists a seamless progression from so-called 'conscious' sedation to deep sedation where verbal contact and protective reflexes are lost, a state indistinguishable from general anaesthsia. The ability of the patient to maintain a patent airway independently is one characteristic of conscious sedation, but even at this level of sedation it cannot be assumed that protective reflexes are intact.

Indication for the use of sedative drugs

Pre-medication: 'Sedo-analgesia' this term describes the use of combination of a sedative drug with local anaesthsia, e.g. in dental surgery or surgical procedures performed under regional blockade. The recent expansion in the development of minimally invasive surgery makes this technique more widely applicable.

Radiological procedure: Some patients, particularly children and anxious individuals are unable to tolerate long and uncomfortable imaging procedures without sedation. Developments in the use and scope of interventional radiology have further increased the demand for sedation in the radiology department.

Endoscopy: Sedative drugs are commonly used to provide anxiolysis and sedation during endoscopic examination and interventions. In gastrointestinal endoscopy, local analgesia is usually inappropriate, necessitating co-administration of systemic opioids. This significantly increases the risk of airway obstruction and ventilatory depression.

Invasive therapy: Most patients require sedation to facilitate mechanical ventilation and other therapeutic interventions. With the increasing sophistication of mechanical ventilators, the modern approach is to combine adequate analgesia with sufficient sedation to maintain the patient in a tranquil but rousable state. A system of sedation scoring should be used and the pharmacokinetic profiles of individual drugs considered, as sedatives are inevitably given by infusion for prolonged periods in patients with potential organ dysfunction and impaired ability to metabolize or excrete drugs.

Supplementation of general anaesthesia: Use is made of the synergy, between sedative drugs and intravenous induction agents in the technique of co-induction. The administration of a small dose of sedative may result in a significant reduction in the dose of induction agent required, and therefore in the frequency of side-effect.

Benzodiazepines

Those drugs were developed initially for their anxiolytic and hypnotic properties and largely replaced oral

barbiturates in the 1 960s. As parentral preparations become available, they rapidly become established in anaesthsia and intensive care. All benzodiazepines have, similar pharmacological effects; their therapeutic use is determined largely by their potency and the available pharmaceutical preparations. Benzodiazepines are often classified by their duration of action as long acting (e.g. diazepam medium acting (e.g. temazepam) or' short-acting (e.g. midazolam) (Table 1).

Mechanism of action: Benzodiazepines exert their actions by specific high affinity binding to the benzodiazepine receptor, which is part of the amino butyric acid (GABA) receptor complex. GABA is the major inhibitory neurotransmitter in the central nervous system (CNS), with most neurons undergoing GABA ergic modulation. The benzodiazepine receptor is an integral binding site on the GABA receptor subtype. Binding of the agonist facilitates the entry of chloride ions into the cell, resulting in hyper polarization of the postsynaptic membrane, which makes the neuron resistant to excitation. Benzodiazepine receptors are found throughout the brain and the spinal cord, with the highest density in the cerebral cortex, hippocampus and cerebellum.

The clinical CNS effects of benzodiazepines have been shown to correlate with receptor occupancy (Table 1). The binding of other compounds to the benzodiazepine receptor explains the synergism seen with some other drugs, including propofol. The benzodiazepine antagonist flumazenil occupies the receptor but produces no activity, resulting. Benzodiazepine compounds have been developed which are V ligands at the receptor but have inverse agonist activity, resulting in cerebral excitement. These compounds are also antagonized by flumazenil and exacerbated by increasing the dose of the original drug. Other more sinister causes of restlessness, such as hypoxaemia and local anaesthetic toxicity, V should always be excluded first. Chronic administration of benzodiazepines results in receptor down regulation, with decreased receptor binding and function explaining, at least in part, the development of tolerance.

CNS effects: The characteristic CNS effects seen with all benzodiazepine are as follows:

Anxiolysis occurs at low dosage and these drugs are used extensively for the treatment of acute and chronic anxiety states. Longer acting oral drugs V such as diazepam V and chlordiazepoxide have a place in the management of acute alcohol withdrawal states. Anxiolysis is very V useful in premedication and during unfamiliar or unpleasant procedures. V Sedation occurs as a dose-department depression of cerebral activity with mild sedation at low receptor occupancy progressing to a state similar to general anaesthsia when most receptor V sites are occupied. Midazolam is firmly established as safe intravenous sedative. Benzodiazepines have a high therapeutic index (ratio of effective to lethal dose) because, in over dosage, differences in modularly depression. However, upper airway V obstruction and loss of protective reflexes occur before profound sedation ensues, and are a major hazard to the patient following inadvertent over sedation and self-poisoning.

Amnesia is a common sequel to intravenous administration of benzodiazepine and is useful for patients undergoing unpleasant or repeated procedures. Retrograde amnesia has not been demonstrated. Prolonged periods of amnesia have been reported in association with the use of total lorazepam, making it potentially dangerous in the day-case setting. Anticonvulsant activity is the result of prevention of the sub cortical spread of seizure activity. Intravenous diazepam is used to terminate seizures and clonazepam is used as an adjacent in chronic anticonvulsant therapy. Benzodiazepines increase the threshold to seizure activity in local anaesthsia toxicity but may also make the early signs.

Muscle relaxation: Benzodiazepines produce a mild reduction in muscle tone, which can be advantageous, e.g. during mechanical ventilation in the intensive care unit, when reducing articular dislocations or during endoscopy. However, muscle relaxation is not related to any effect at the neuromuscular junction, but results from suppression of the inter-nuncial neurons of the spinal cord and depression of polysynaptic transmission in the brain.

Respiratory effects: Benzodiazepines produce dose-related central depression of ventilation. The ventilatory response to carbon dioxide is impaired and hypoxic ventilatory responses are markedly depressed. It follows the patient with hypoventilation syndromes and type 2 respiratory failure are particularly sensitive to the respiratory depressant effects• of benzodiazepines. Ventilatory depression is exacerbated by airway obstruction and is more common in the elderly. Synergism occurs when both opioids and benzodiazepines are administrated. If both types of drug are to be given intravenously, the opioid should be given first and its effect assessed. A dose reduction of benzodiazepine of up to 75% should be anticipated. It should be standard practice to provide supplemental oxygen and to monitor oxygen saturation by pulse oxirnetry during intravenous sedation.

Cardiovascular effects: Benzodiazepines produce modest haemodynamic effects, with good preservation of homeostatic reflex mechanisms and a much wider margin of safety than intravenous anesthetic agents. A decrease in systemic vascular resistance results in a small decrease in arterial pressure. Significant hypotension may occur in hypovolaemic or vasoconstricted patients.

Pharmacokinetics: Benzodiazepines are relatively small lipid-soluble molecules, which are readily

absorbed orally and which pass rapidly into the CNS. After intravenous bolus administration, termination of action occurs largely by redistribution. Elimination takes place by hepatic metabolism followed by renal excretion of the metabolites. There are two main pathways of metabolism involving either microsomal oxidation or glucuronide conjunction. The significance of this is that oxidation is much more likely to be affected by age, hepatic disease, drug interactions and other factors which alter cytochrome P450. Some of the benzodiazepines, including diazepam, have active metabolites, which greatly prolong their effect. Renal dysfunction results in the accumulation of metabolites, and this is an important factor in delayed recovery from prolonged sedation in the intensive therapy unit (ITU).

Diazepam [13]

Diazepam was the first benzodiazepine available for parental use. It is insoluble in water and was formulated initially in propylene glycol, which is very irritant to veins and which is associated with a high incidence of thrombophlebitis. A lipid emulsion (diazemuls) was developed later. Both formulations are presented in 2ml ampoules of 5mg m11. Diazepam is also available orally as tablets or a syrup which a bioavailability of 100% and as a rectal solution and suppositories. The elimination half-life is 20-50 h, but active metabolites are produced, including desmethyl-diazepam, which has a half-life of 36-200h. Clearance is reduced in hepatic dysfunction.

Dosage:

Premedication 10-15mg orally l-l.5h preoperatively.

Sedation 7-15mg i.v. slowly; incremental bolus of 1-2mg.

Status epilepticus - 2mg, repeated every minute until seizure ends, maximum dose 20mg.

Intensive therapy - not suitable for infusion; i.v. bolus dose 5- 10mg 4-hourly.

Midazolam [13]

Midazolam is an imidazo- benzodiazepine derivative and it is the imidazole ring which impairs water solubility at pH less than 4. At blood pH, the drug becomes highly lipid-soluble and penetrates the brain rapidly with onset of sedation in 90 s and peak effect at 2-5 mm it is available in 2ml (5mg mF') and 5ml (2mg mF') ampoules and, unlike diazepam, may be diluted. It is also available as a 15mg tablet with an oral bioavailability of 44%. Midazolam undergoes hepatic oxidative metabolism and has an elimination half-life of 2h. The major metabolite, hydroxy-midazilam, has a half-life of around Ih, and although it is biologically active, it is only clinically important after prolonged infusion in patients with renal impairment. Midazolam is 1.5-2 times more potent than diazeparn and has much more favourable pharmacokinetics for use as a short-term intravenous sedative.

Dosage:

Premedication 15mg orally or 5mg i.m.

Sedation - 2-7mg i.v. (elderly less than 4mg); incremental bolus of .0.5-1mg.

Status epilepticus - not recommended.

Intensive therapy - i.v. infusion 0.03-0.2mg kg' h'.

Intravenous anesthetic agents [14]: Intravenous anaesthesia agents are used commonly induces anaesthesia, as induction is usually smoother and more rapid than that associated with most of the inhalation agents. Intravenous anaesthsia may also be used for maintenance, either alone or in combination with nitrous oxide; they may be administered as repeated bolus doses or by continuous i.v. - infusion. Other uses include sedation during regional anaesthesia; sedafion is the intensive therapy unit (ITU) and treatment of status epileptics.

Properties of the ideal intravenous anaesthetic agent:

a) Rapid onset.

b) Rapid recovery.

c) Analgesia at subanaesthetic concentrations.

d) Minimal cardiovascular and respiratory depression.

e) No emetic effects.

f) No excitatory phenomena (e.g. coughing, hiccp, involuntary movement) on induction.

g) No emergence phenomena (e.g. nightmares).

h) No interaction with neuromuscular blocking a\ drugs.

i) No venous sequelae.

j) Safe if injected inadvertently into an artery.

k) No toxic effects on other organs.

l) No release of histamine.

m) No hypersensitivity reactions.

n) Water-soluble formulation.

o) Long shelf-life.

p) No stimulation of porphyria.

Pharmacokinetics of intravenous anesthetic drugs: After i.v. administration of drug, 'there is an immediate rapid, increase in plasma concentration followed by a slower decline. Anaesthesia is produced by diffusion of drug from arterial blood across the blood brain,' and therefore the anesthetic effects are regulated by the following factors:

I. Protein binding: Only unbound drug is free to across the blood brain barrier. Protein binding may be reduced by low plasma protein concentration of displacement by other drugs resulting 'in higher concentrations of free drug and an exaggerated anesthetic effect. Protein binding is also affected by changes' in blood pH. Hyperventilation increases protein binding and increases the anaesthetic effect.

II. Blood flow to' the brain: Reduced cerebral blood flow (CBF), e.g. carotid artery stenosis, results, in reduced delivery of drug to the brain. However, if CBF is reduced because of low cardiac output, initial blood concentrations are higher than normal after i.v. administration and the anaesthetic effect may be delayed but enhanced.

III. Extracellualr pH and pKa of the drug: Only the non ionized fraction of the drug depends on the degree of ionization at the pH of extracellular fluid' and the pKa of the drug.

IV. The relative solubilities of the drug in lipid and water: high lipid solubility enhances transfer into the brain.

V. Speed of injection: Rapid i'.v. administration results in high initial concentrations of drug. This increases the speed of induction, but also extent of cardiovascular and respiratory

VI. Side-effects: In general, any factor which increases the blood concentration of free drug, eg. reduced protein binding or low cardiac output, also increases the intensity of side-effects.

Propofol (non-Barbiturate intravenous anesthetic agent

The phenol derivative was identified as a potentially useful intravenous anesthetic agent. In 1980, and become available commercially in 1986. it is more expensive than thiopental or methohexial, but has achieved great popularity because of its favorable recovery characteristic and its antiemetic effects.

Chemical structure: 2,6-Di-isopropyiphenol (Figure 3).

Physical properties and presentation: Propofol is extremely lipid-soluble, but almost insoluble in water. The drug was formulated initially in Cremophor El-. However, several other drugs formulated in these solubilizing agents were associated with release in histamine and an unacceptability high incidence of anaphylactoid reaction, and similar reactions occurred with his formulation of propofol. Consequently the drug was formulated in a white, aqueous emulsion containing soybean oil and purified egg phosphatide. Ampoules of the drug contain 200mg of propofol in 20mg (l0 mg ml') and 50ml bottles containing 1% (l0 mg kg') or 2%

(2omgm[') solution and 100m1 bottles containing 1% solution, are available for infusion. In addition, 50m1 per-filled syringes of 1% and 2% solution are available and are designed principally for use in target-controlled infusion techniques.
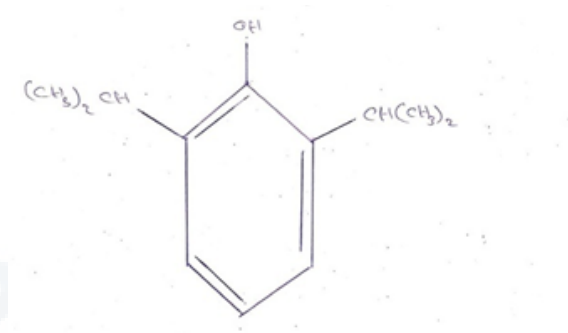

Figure 3: 2,6-Di-isopropyiphenol.

Pharmacology

Central nervous system: Anaesthesia is induced within 20-40s after i.v. administration in otherwise healthy young adults. Transfer from blood to the sites of action in the brain is slower than with thiopental, and there is a delay in disappearance of the eyelash reflex, normally used as a sign of unconsciousness after administration of barbiturate anaesthetic agents. Over dosage of Propofol, with exaggerated side-effects, may result if this clinical sign is used; loss of verbal contact is better endpoint EEG frequency decrease, and amplitude increases. Propofol reduces the duration of seizures induced by ECT in humans. However, these have been reports of convulsions following the use of Propofol to epileptic patients. Normally cerebral metabolic rate, CBF and intracranial pressure are reduced. Recovery of consciousness is rapid and there is a minimal 'hand over' effect in the immediate post anesthetic period.

Cardiovascular system: In healthy patients, arterial pressure to a greater degree after induction of anaesthsia with propofol than with thiopental; the reduction results predominantly from vasodilatation although there is a slight negative isotropic effect. In some patients, large decrease (>40%) occur. The degree of hypotension is substantially reduced by decreasing the rate of administration of the drug and appreciation of the kinetics of transfer from blood to brain. The pressor response to tracheal intubation is attenuated to a greater degree by propofol than thiopental. Heart rate may increase slightly after induction of anaesthsia with propofol. However, there have been occasional reports of sever bradycardia and a systole during or shortly after administration of Propofol, and it is recommended that a vagolytic agent (e.g. glycopyrronium or atropine) should be considered in a patient with a pre-existing bradycardia or when propofol js used in conjunction with

other drugs which are likely to cause bradycardia.

Respiratory system: After induction, apnoea occurs more commonly, and for a longer duration, than after thiopental. During infusion of propofol, tidal volume is lower and respiratory rate higher than in the conscious state. There is decreased ventilatory response to carbon dioxide. As with other agents ventilatory depression is more marked if opioids are administered. Propofol has no effects on bronchial muscle tone and laryngospasm is particularly uncommon. The suppression of laryngeal reflexes in a low incidence of coughing or laryngospasm when a laryngeal mask airway (LMA) is introduced, and Propofol is regarded by most anesthetists as the drug of choice for induction of anaesthesia when the LMA is to be used.

Skeletal muscles: Tone reduced, but movements may occur in response to surgical stimulation.

Gastrointestinal system: Propofol has no effects on gastrointestinal motility in animals. It is used associated with a slow incidence of postoperative nausea and vomiting.

Uterus and placenta: Propofol has no effects extensively in patients undergoing hynaecological surgery, and it does not appear to have any clinically significant to the neonate has not been established and its use in pregnancy (except for function tests are not deranged after infusion of propofol for 24hrs).

Endocrine: Plasma concentrations of cortisol are decreased after administration of propofol, but a normal response occurs to administration of synacthen.

Pharmacokinetics: In common with other i.v. anaesthesia drugs, propofol is distributed rapidly, and blood concentrations decline exponentially. Clearance of the drug from plasma is greater than would be expected if the drug was metabolized only in the liver, and it is believed that extrahepatic sites of metabolism exists. The kidneys excrete the metabolites of propofol (mainly glucuronoids); only 0.3% of the administered dose of propofol is excreted unchanged. The terminal elimination half-life of propofol is 3-3.8h, although its effective half- life is much shorter (3060min). The distribution and clearance of propofol are altered by concomitant administration of fentanyl. Elimination of propofol remains relatively constant even after infusions lasting for several days.

Dosage and administration: In healthy, unpremedicated adults, a dose of 1.5 - 2.5mg kg1 is required to induce anaesthesia. The dose should be reduced in the elderly, an initial dose of 1.25mg kg' is appropriate, with subsequent additional doses of 10mg until consciousness is lost. In. children, a dose of 3-3.5mg kg' is usually required; the drug is not recommended for use in children less than 1 month of age. Cardiovascular side-effects are reduced if the drug is injected slowly.

Lower doses are required for induction in prernedicated patients. Sedation during regional analgesia or endoscopy can be achieved with infusion rates. of up to 15mg kg 'h' are required to supplement nitrous oxide / oxygen for surgical anaesthesia, although these may be reduced substantially if an opioid drug is administered. The average infusion rate is approximately 2mg kg 'h1 in conjunction with a slow infusion of morphine (2mg kg') for sedation of patients in ICU.

Adverse effects

a) Cardiovascular depression: Unless the drug is given very slowly, cardiovascular depression following a bolus dose Propofol is greater than that associated with a bolus dose of barbiturate and is likely to cause profound hypotension in hypovelaemic or untreated hypertensive patients in those with cardiac disease. Cardiovascular depression is modest if the drug is administered slowly or by 'infusion.

b) Respiratory depression: Apnea is more common and of longer duration than after barbiturate administration.

c) Excitatory phenomena: These are frequent on induction than with thiopental, but less than with methohexial. There have been occasional reports of convulsions and myocolnus during recovery from anesthesia in which propofol has been used. Some of these reactions are delayed.

d) Pain on injection: This occurs in up to 40% of patients. The incidence is greatly reduced if a large vein is used, if a small dose (10mg) of lidocaine is injected shortly before propofol, or if lidocaine is mixed with propofol in the syringe (up to 1 ml of 0.5 oi 1% lidocaine per 20ml of Propofol). Accidental extravasation or intra-arterial injection dose not appear to result in adverse effects.

e) Allergic reactions: skin rashes occur occasionally. Anaphylactic reactions have also been reported, but appear to be no more common than with thiopental.

Indications

Indications of anesthesia: Propofol is indicated particularly when rapid early recovery of consciousness is required. Two hours after anaesthsia, there is no difference in psychomotor functioning between patients who have received propofol and those given thiopental or methohexial, but the former enjoy loss drowsiness in the ensuring 1-2h. The rapid recovery characteristics are lost if the induction is followed by maintenance by inhalation agents for longer than 10-15mm. The rapid redistribution of non-depolirizing muscle relaxants, or at the start of surgery, unless the lungs are ventilated with an appropriate mixture of inhaled anaesthesia, or additional doses or an infusion of propofol administered.

Sedation during surgery: Propofol has been used

successfully for sedation during regional analgesia techniques and during endoscopy. Control of the airway may be lost at any time, and patients must be supervised continuously by an anesthetist.

Total i.v. anesthesia: Propofol is the most suitable of the agents currently available. Recovery time is increased after infusion of propofol compared with that after a single bolus dose.

Sedation in ICU: Propofol has been used successfully by infusion to sedate adult patients for several days in ICU. The level of sedation is controlled easily, and recovery is rapid (usually >30mm).

Absolute contraindications: Airway obstruction and known hypersensitivity to the drug are probably the only absolute contraindications. Propofol appears to be safe in prohyric patients. Propofol should not be used for long-term sedation of children in ICU because of a number of reports of adverse outcome.

Precautions: There are similar to those listed for thiopental. The side-effect of propofol makes it less suitable than thiopental or methohexial for patients with existing cardiovascular compromise unless it is administered with great care. Propofol is more suitable than thiopental for outpatient anesthesia, but its used dose not obviate the need for an adequate period of recovery before discharge. Solutions of propofol do not possess any antibacterial properties, and they support the growth of microorganisms. The drug must be drawn aseptically into a syringe and any unused solution be discarded if not administered promptly. Propofol must not be administered via a microbiological filter.

Bupivacaine

Is a long acting, arnide type local anesthetic chemically related to lignocaine and mepivacaine. It is approximately four times as potent as lignocaine.

Physical properties:

a) Bupivacainc is presented in different concentrations. It is a clear, colorless, particle-free solution, with pH 4.0-6.5.

b) Bupivacaine adrenaline is a clear, colorless, particle-free solution containing metabisuphite, with pH 3.3-5.0, metabisuphite may cause allergic-type reaction including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

c) Bupivacaine should be stored at 25°C or below. I)o not freeze.

d) The ampoules are designed for a single use only; any unused portions of solutions should be discarded.

Pharmacokinetics:

a. Bupivacaine has pKa of 8.1 and a high degree of lipid solubility with an oil/water partition coefficient of 27.5. It is mainly bound to alpha-i-acid glycoprotein in plasma with binding of 96%.

b. These factors contribute to its prolonged duration of action.

c. The rate of absorption and plasma concentration of bupivacaine depends upon the dose, the route of administration and the vascuairity of the injection site Absorption may be slowed by the addition of adrenaline. In concentration of 5mg/ml it has a long duration of action, from 2-5 hours following a single epidural injection and up to 12 hours after peripheral nerve blocks.

d. When used in low concentration (2.5mg/ml or less) there is less effects on motor nerve fibers and the duration of action is shorter.

e. Low concentrations may, however, be used with advantage for prolonged pain relief, e.g. in labour or postoperatively.

f. Absorption of bupivacaine from the epidural space occurs in 2 phases, the first phase is in the order of 7 minutes and the second is 6 hours. The slow absorption is rate limiting in the elimination of bupivacaine, which explains why the apparent elimination half-life after epidural administration is longer than after intravenous administration.

g. Bupivacaine has a total plasma clearance of 0.58L/min, a volume of distribution at steady state of 37 L, an elimination half- life of 2.7 h and an intermediate hepatic extraction ratio of 0.4 following experimental IV administration in adults. The terminal elimination half-life is prolonged in the new born to approximately 8 hours. In children over 3months the elimination half-life is similar to than in adults. Bupivacaine readily crosses the placenta and is excreted in breast milk in concentrations lower than the maternal plasma concentration.

Metabolism of Bupivacaine: Bupivacaine is metabolized in the liver and excreted via the kidneys, the possibility of bupivacaine accumulation should be considered in patients with hepatic and / or renal impairment. Bupivacaine is excreted in the urine principally as metabolites with about 6% as unchanged medicine and approximately 5% as the N-dealkylated metabolite, pipecolylxlidine (PPX). Following epidural administration, the urinary recovery of unchanged bupivcaine is about 0.2% of pIpecolylxlidine (PPX) about 1% and of Llhydroxy bupivacaine about 0.1 of the administered dose.

Mode of action: Bupivacaine, like other local anesthetics, causes a reversible blockade of impulse propagation along nerve fibers by preventing the inward movement of sodium ions through the nerve membrane.

Local anesthetics of the amide type are though to act within the sodium channels of the nerve membrane. Given as a spinal anesthetic, bupivacaine has a rapid onset and a medium to long duration. The duration in dose dependent. It is approximately four times more potent and toxic than lignocaine.

Indications:

a. Analgesia in labour.

b. Post-operative analgesia and

c. Other therapeutic pain blocks, particularly where long acting anaesthesia is required.

d. Surgical anesthesia.

Contraindications:

A. Allergy or hypersensitivity to amide type local anesthetics or sodium metabisuiphite in adrenaline-containing solutions.

B. Obstetric paracervical block, intravenous regional anesthesia (Bier's block) and all intravenous infusion.

C. The following are additional contraindications for solutions with adrenaline.

D. Adrenaline is contraindicated in conditions where the production or exacerbation of tachycardia could prove fatal, such as:

a) Thyrotoxicosis or

b) Severe heart disease or

c) In obstetrics when maternal blood pressure exceeds 130/80mm hg.

d) Adrenaline-containing solutions must not be used for analgesia in parts of the body with compromised blood supply oi supplies by end arteries, such fingers, toes, nose, ears or penis. There is a possibility of producing arterial vasoconstriction and subsequent ischemic gangrene distal to the site of injection.

Side effects: Cardiovascular, hypotension, bradycardia, arrhythrnias and cardiac arrest may occur respiratory, difficulty in breathing, apnoea and respiratory failure may be precipitated. Central nerve, CNS manifestations are excitatory and / or depressant and may be characterized by light-headedness, tinnitus, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, agitation, difficulty in swallowing slurred speech, tremor, convulsions, and unconsciousness. Allergy, it may be presented as allergic dermatitis, bronchospasm or anaphylaxis. Acute systemic toxicity, it occurs in accidental intravascular injections and over dosage. The early features are circumoral para anesthesia, numbness of the tongue, light headedness, hyperacusis [16] and tinnitus followed by cardiovascular and respiratory failure.

Precautions: Caution in the presence of hepatic insufficiency, impaired cardiovascular function (severe bradycardia conduction disturbances, severe shock and heart block), epilepsy and preexisting abnormal neurological or neuromuscular disease. Reduction of the dosage in elderly, debilitated patients and in pediatric patients. .

Precaution:

Marcain ± Adrenaline:

Bupivacaine hydrochloride with and without adrenaline.

a. 0.125% infusion - a clear, colorless, particle-free solution containing 1.25mg/mi bupivacaine HCL, 8.5mg/mi sodium chloride, with pH 4.0-6.5.

b. 0.25% injection and infusion a clear, colorless, particle-free solution containing 2.5mg/mi bupivacaine HCL, 8mg/mi sodium chloride, with pH 4.0-6.5.

c. 0.375% injection and infusion a clear, colorless, particle-free solution containing 3.75mg/mi bupivacaine HCL, 8mg/mi sodium chloride, with pH 4.0-6.5.

d. 0.5% injection and infusion a clear, colorless, particle-free solution containing 5mg/ml bupivacaine HCL, 8mg/rnl sodium chloride, with pH 4.0-6.5.

e. 0.25% injection plus adrenaline 1:400,000 a clear, colorless, particle-free solution containing 2.5mg/mi bupivacaine HCL, 8mg/mi sodium chloride 4.5mcg/ml adrenaline acid tartrate, 0.5mg/mi sodium metabisuiphite with pH 3.3-5.0.

f. 0.5% injection plus adrenaline 1:200,000 a clear, colorless, particle-free solution containing 5mg/mi bupivacaine HCL, 8mg/mi sodium chloride 9.lmcg/ml adrenaline acid tartrate, 0.5mg/mi sodium metabisulphite with p11 3.3-5.0.

Pethidine (meperidine) hydrochloride:

a) Pethidine (meperidine) hydrochloride is the hydrochloride of the ethyl ester of 1 -methyl-4phenyl-piperidine-4-carboxylic acid.

b) Pethidine use is diminishing because of multiple disadvantages, of which the accumulation of norpethidine is the most significant. Norpethidine toxicity is associated with a variety of neuroexcitatory effects, ranging from nervousness to convulsions.

Pharmacodynamics:

I. Analgesia: Pethidine relieves most types of pain, especially those associated with plain muscle spasm. It depresses the respiratory centre and

cough reflex, and is also a local analgesia. It has no effect on the ciliary body or iris. It raises the cerebrospinal fluid pressure and can cause addiction.

II. Smooth muscle: Pethidine has a direct papaverine-like effect on the smooth muscle of the bronchioles, intestine, ureters and arteries. It will often relive bronchospasm. Vasodilatation may be unwelcome in trauma patients and uncontrolled hypertensives. Cholinergic effects:. Pethidine has an atropine-like effect on cholinergic nerve endings.

III. Histamine release:

i. Pethidine may release histamine from tissues.

ii. Side-effects: Side-effects of pethidine include sweating hypotension, vertigo and limb tingling.

iii. Postoperative nausea is similar to that following morphine, but comes on earlier. It is worse after intravenous than after intramuscular injection.

iv. Like morphine, pethidine may cause hypotension if the head of the patient is raised, or with sudden movement. Because of its circulatory depressant effects it is probably not the ideal drug for the relief of pain in myocardial infraction.

v. Norpethidine can produce nervousness, tremors,' twitches, myoclonus and seizures.

vi. Phenobarbital enhances the production of toxic metabolites of pethidine. These two drugs should not be given together.

vii. Precautions: The administration of pethidine to patients receiving monoamine oxidase inhibitors may cause severe reactions and even death. There is restlessness, hypertension, convulsions and coma, with absent tendon jerks and an extensor plantar response; hypotension may also be seen. The reaction is said to be due to serotonin reuptake inhibition.

IV. Pharmacokinetics:

i. The routes of administration of pethidine are the same for morphine. Oral bioavailability is 45-75% and 64 is bound to plasma protein.

ii. Pethidihe is metabolized at the rate of 17%h. The biological half-life is 3-4hours in man, and 80% is hydrolyzed in liver. About 5-10% is excreted unchanging by the kidneys. One metabolite, norpethidine, may cause convulsions or hallucinations if pethidine is given in large doses, for prolonged periods or with monoamine axidase inhibitors. Patients in renal failure are at increased risk of norpethidine toxicity.

iii. The dose of pethidine is 0.5mg/kg intravenously and 1.5mg/kg intramuscularly. Its onset of action is 2-5 minute, and its duration 5 hours.

Table 1: Relationship between the effects seen with benzodiazepine and receptor occupancy.

Midazolan Dose	Effect	Receptor Occupancy %	Flumazenil Dose to Reverse
Low dose	Anticonvulsant	20-25%	Low dose
	Anxiolysis	20-30%	
	Slighr sedation		
	Reduced attention	25-50%	
	Amnesia		
	Intensive sedation	60-90%	
	Muscle relaxation		
High dose	Anaesthsia		High dose

Chapter 2: Objectives

Chapter 2: Objectives

To assess the spinal anesthesia combined with three different form of conscious sedation on intraoperative and postoperative outcome in patients undergoing elective hysterectomy. Special objective:

1. Muscle relaxation.
2. Bleeding reduce it.
3. Best postoperative Spo2 percentage by pulse oximetry.
4. Shortest waiting time in the postoperative holding area.
5. Lowest pain on postoperative day.
6. Highest frequency of first platus passage c.

Patients and Methods

This study was carried out on eighty Sudanese patients' ladies for elective hysterectomies in Omdurman Military Hospital during the period from April 2007 to April 2008.

Study Design

This is prospective blinded randomized controlled study on the role of general versus spinal anesthesia with difference form of sedation for patients undergoing elective hysterectomies (diazeparn, midazo lam, propofol).

Study Population

80 Sudanese patients' ladies undergoing for elective hysterectomies (age 30-80 yrs).

Inclusion Criteria

Patient with ASA I and II

Exclusion Criteria

a) Females with ASA more than II.
b) Patient with psychological problem.
c) Blind patient.
d) Patient on anticoagulant.
e) Patient with CNS problem, spinal deformation.
f) Patient refusing of spinal anesthesia.

Preoperative Analysis

a) Hb%.
b) Urine general.
c) Renal function test.
d) Random blood sugar.
e) ECG.
f) Chest x-ray.

Methodology

I.   After excluding all above patients were putting in list table from 1- 80 according to their arriving to the theatre

II. Patients were divide into four groups as follows:

   i.   20 patients of the control group received GA.

   ii. 20 patients received SPA with diazepam i.v as sedation.

   iii. 20 patients received SPA with midazolam i.v as sedation.

   iv. 20 patients received SPA with propofol infusion as sedation.

III. An (2) intravenous lines were putted on the both dorsum of the hands using two canulae size 18 and size 16 fluid normal saline was started to run in the one of them.

IV. The first patient from GA group controlled was induced with atropine 1mg, propofol (2.5mg/kg) or thiopentone (5.7mg/kg) according to the anesthesiologist preference. Before tracheal intubation succinyicholine chloride (1-1.5mg/kg) was administrated, GA was maintained by pancrounium (0.01mg/kg) in bolus eventually replaced, supplied by halothane (0.3-0.5%) nitrous oxide (60) oxygen. Neuromuscular blood was antagonized at the end of the surgery with atropine 1mg and neastigmine 2.0mg.

V.   The second, patient from the second group received SPA which induced with bupivicane hydrochloride 1% (0.23mg/kg) and diazepam i.v as a sedative agent (2.5mg in bolus) and nasal oxygen with Fio_2 of 0.04% were given as needed.

VI. The third patient from the third group received SPA and midazolam as sedation agent (0.5-1.5mg) per hr and added as need and oxygen mask.

VII. The fourth patient from group four received SPA and propofol 4-5mg/kg per hr infusion as a sedation agent and oxygen mask.

VIII. The following surgical outcome parameters were assessed: surgical time (defined as time between the initial skin incision and the complete of wound closure) and degree quality of patients muscle relaxation or 1-4 scale (1 poor muscle relaxation during surgery as judged by the surgeon.

IX. Estimated intraoperative blood loss as well as autologous or homologous Tran perfusion were accurately assessed fluid suctioned from the women was collected and surgical sponges also collected after used.

X.   Total volume was calculated by combining the sectional volume and sponges. Furthermore occurrence (defined as systolic blood pressure

<90 may or alternatively as a 20% decreased from the baseline in patients with baseline BP<90nmhg and any other complications were assessed.

XI. The following post-surgical outcome parameters were then carefully assessed in both groups, hemodynamics parameters, Spo_2, preoperative sedation, time in the holding area, and any eventual postoperative complications.

XII. In the post-surgery holding area patients completed a 10 point visual analog scale (VSA; 0, no pain worst pain imaginable for pain.

XIII. Urine output and drainage output were also assessed until the first day after surgery.

XIV. On postoperative day, patients were specifically questioned about the occurrence of complications, pain, assisted ambulation and first flatus passage with first oral intake.

XV. Ethical consideration: A brief explanation of the procedures SPA and GA was given to the patient and their consent was taken verbally before entering the study.

Chapter 3: Result

Chapter 3: Results

Age and Weight

a. Eighty patients undergoing gynaecological operations hysterectomies were under the study.

b. The four group did not differ regarding age, weight, ASA score (Table 2 & 3).

c. The mean age of the GA group was 54,50 years and 59, 17 years

d. SPA group (Table 2).

e. The mean weight of GA group was 73.25 and 74.12kg for the (SAP Table 2).

f. The mean ASA score 54.5% class I for both GA and SPA and 47.5% class II for both GA and SPA.

Surgeon Comment about the Relaxation of the Patients

a) There were no significant differences in the four groups of patients in terms of quality of muscle relaxation during hysterectomies.

b) 96.7% from SGA groups were relax and 3.3 from SPA groups relaxation.

Blood Loss Transfusion

Overall blood loss was significantly less with SPA, regardless of the time of sedation. Moreover, patients treated with SPA combined with propofol had significantly lower intraoperativc blood loss ((P 0.03) as compared with those who received diazeparn and inidzolam even GA as known is a bloody operation.

Shortage of Waiting Time in the Postoperative Holding Area

The mean time for holding area postoperative was significantly high in the GA group (2.5hrs) compared with the SPA groups propofol groups 1.8h, Diazepam 2h GA group 2.5hrs (Figure 4).

Best Postoperative SPO$_2$%

In four groups, baseline air SPO$_2$ 99% was similar in all of them. Postoperative SPO$_2$ was best significantly better in each SPA group, with the groups that received SPA combined with propofol had a highest postoperative SPO$_2$% value. Similarly, SPA with propofol was associated with the lowest sedation and shortest time in the postoperative holding area (Figure 5).

Postoperative One Day

Lowest pain

The pain scores measured in postoperative holding area and one day were lower in all SPA group. The GA groups in particular patients who received SPA combined with midazolan reported that lowest value compared with patients in all the other groups. However group propofol patients had significantly lower pain postoperatively one day (Table 4-6).

Highest frequency of first flatus passage

Spinal anesthesia with propofol was associated with the greatest frequency of the postoperative first flatus passage in comparison with other GA group after 24hrs, Diazepam group within 24.7 h midazolan 5.5h propofol group 4.2h (Figure 6).
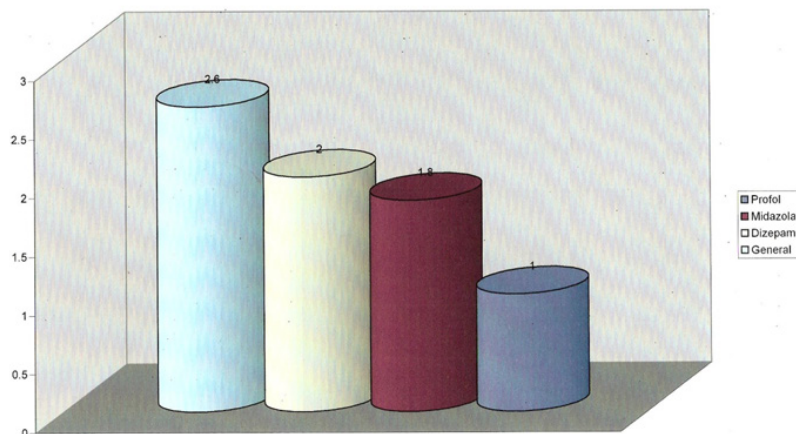

Figure 4: The mean of Weating Time in post oparattive Holding Area in hours.
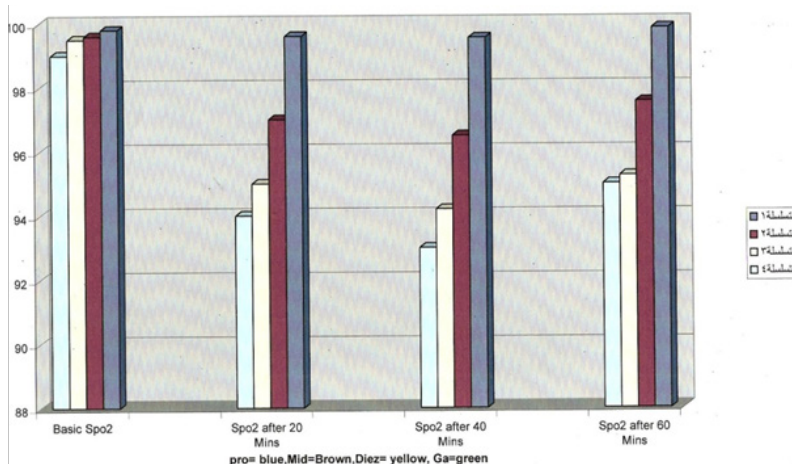
(P = 0.03).

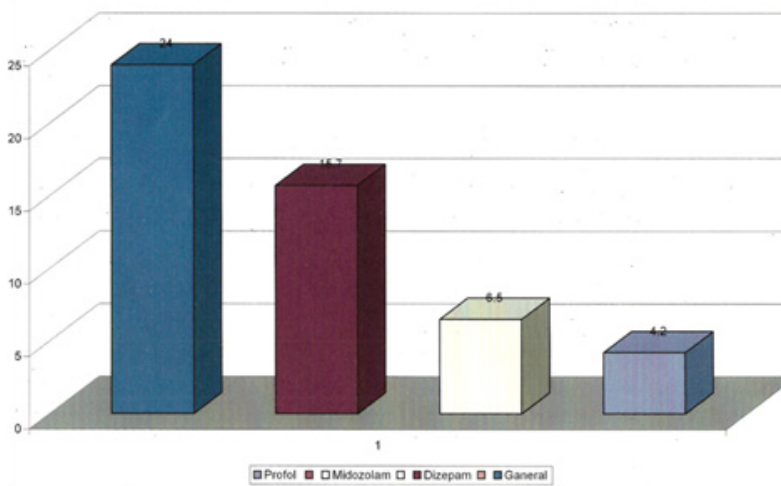**Figure 5:** The means of spo$_2$ post operative.

(P = 0.02)

Figure 6: The mean of the frequency first flatus passage in hours.

(P=0.0001).

Table 2: Average age and weight of the patient under study.

Groups	No of Patients	Average Age (year)	Average Weight(kg)
SPA	60	59.17	74.12
GA	20 P = 64.5	59.5 P = 0.832	73.25

Table 3: Surgeon comment about the Relaxation.

Groups	Relax	Not Relax	Total
SPA	58 96.7%	2 3.3%	60
GA	17 85%	3 15%	

P= .00097

Table 4: Blood loss and Transfusion.

Type of Anesthesia GA	No 12 60%	Yes 8 40%	Total
SPA	Type of drugs used		
	Propofol 90.09 18	2 10%	20
	Midozolom 16 80%	4 20%	20
	Diazepam 14 70%	6 30%	20

(p=0.03)

Table 5: Waiting time in post operative Holing area.

Type of Anesthesia		
SPA	N0	60
	mean	1.582
GA	N0	20
	mean	2.6316
Total	N0	80
	mean	1.8442

p=0.004

Table 6: Post operative one day lowest pain.

Drugs which used as Sedation	Yes	No	Total
Propofol	2 %10	18 %90	20
Midozolom	11 %55	9 %45	20
Diazpam	13 65%	7 %35	20
	46.60%	53.40%	60

P=0.0001

Chapter 4: Discussion

Chapter 4: Discussion

I. Hysterectomies are a procedure that is widely carried out in Sudanese patient's ladies.

II. Anesthesia procedures might impact the early postoperative recovery of patients, also influencing 'the length of hospitalization stay after surgery.

III. The result of this prospective, 'randomized study suggested that SPA combined with sedation is an attractive alternative to standard GA for patients undergoing elective hysterectomy.

IV. Several studies have reported SPA might be considered a safe, reliable, and effective anesthetic modality for patients undergoing gynaecological operations [14-18].

V. SPA is cheaper, technically easier to carry out, and significantly faster to induce compared with GA.

VI. Furthermore GA is also associated with a delayed onset of effect as a compared to SPA and this lightens to overall duration of surgery.

VII. In the present study, surgical time was significantly shorter for every SPA group than GA group. In addition the surgeons about opinions abdominal muscle relaxation, through surgery.

VIII. Both in terms of overall value and continuity during surgery was adequate and not significantly different in the four groups. In agreement with former observations, the surgeons considered both GA and SPA to be inadequate only when procedure did not allow achievement of good and continuous muscle relaxation.

IX. Postoperative (BP) and heart rate (HR) values were significantly lower in patients treated with SPA and diazepam and midazolan.

X. Propofol use resulted in the highest postoperative (HR) several pieces of data have shown that propofol might induce a compensatory increase in HR [9] although this issue is controversial after SPA, which was promptly treated with ephedrine (0.1- 0.3mgkg), with incidence of 15% to 33% is one of the most frequent complications of SPA [20].

XI. However recently concluded that patients developing relevant hypertension during SPA will probably also tend to develop hypotension during GA; thus, the anesthesiologist should not necessarily retain from using SPA in patients with independent risk factors for hypotension, but should certainly increase vigilance in this patients.

XII. Overall bleeding was less with SPA, regardless of the type of sedation moreover, patients treated with SPA combined with propofol had a significantly lower intraoperative. Blood loss as compared with those who received diazepam and midazolarn.

XIII. Several studies have also shown that SPA result is less in the introspective bleeding when compared with GA [21].

XIV. After SPA patients showed a better SPO_2% and lower sedation score, for both these clinical parameters, Propofol showed, the best profile confirming data previously reported [22,23].

XV. SPA also was associated with a significantly shorter stay in the post-surgery holding area, to minimize this time with the' objective of improving patient, comfort and reducing casts, patients were taken to their rooms in the, gynaecological department after their motor a sensory recovery was fully achieved SPA allowed a complete recovery of leg mobility.

XVI. All patients received a similar amount of analgesic drug during the first 24hr after surgery. However, pain during the immediate postoperative period was significantly less after SPA regardless the type of sedation. According to their pharmacokinetics profile, midazolam should the best effect on pain after surgery, while propofol was associated with the lowest pain score 24h later over all patients, subjective feelings of well being were higher and postoperative pain scores were significantly better with SPA than GA.

XVII. Our results showed a significant difference between the postoperative first flatus passage during the first 24h after surgery in patients who underwent a GA and SPA.

XVIII. The observation suggest that intraoperative regardless of type of sedation SPA might enhance postoperative recovery of bowel function compared with GA. Depend to anesthetic and surgical 1242 protocol that can diseases time to recovery of bowel function, with an acceptable cost in terms of risks, side effects, and time, is an attractive, alternative to current standard anesthetic and surgical protocols [26].

XIX. SPA was associated with a higher mobilization and an assisted ambulation rate during the first day after surgery.

XX. Several authors have showed that early mobilization together with a day prophylaxis with subcutaneous heparin might allow the reduction of the risk of thromboembolism 27 in addition, earlier ambulation and overall mobilization helps to reduce the risk of respiratory depression and psychological mood deflection [27] (Appendix).

Conclusion

Although the number of patients enrolled in each group was small, these results confirm that spinal anesthesia combined with different types of sedation is an attractive alternative to general anesthesia for patients undergoing elective hysterectomy. Spinal anesthesia is easy to carryout and allows the operation to be done under the best possible conditions regardless of the form of sedation. Finally spinal anesthesia combined with propofol seems to offer several clinical advantages as compared with spinal anesthesia with diazepam and midazolam.

Recommendation

a) More studies should be done concerning different type of sedation with GA.

b) All anesthiologist should be encouraged the practice S.A with sedation for different type of hysterectomy.

c) The benefit of S.A during hyterectorny cone. Blood the surgical field should be explained to the surgeons.

d) Every patient undergoing hysterectomy should be informed about spinal anesthesia and its beneficial effect, in comparison with general anesthesia.

e) Paramedical staff '(assistant) should know more about spinal with sedation.

f) This sedative drugs especially midazolam and propofol should be encouraged to be available in the hospitals.

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