INTRATHECAL TRAMADOL VERSUS INTRATHECAL FENTANYL FOR VISCERAL PAIN CONTROL DURING BUPIVACAINE SUBARACHNOID BLOCK FOR APPENDICECTOMY.

BY

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DECLARATION

I hereby declare that this study was conducted in the University of Benin Teaching Hospital, Benin City Edo State. No part of this book has been presented to any academic body or college for a fellowship, neither has it been submitted elsewhere for presentation or publication.

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Afolayan, Jide Michael.
CERTIFICATION

THE STUDY REPORTED IN THIS DISSERTATION WAS PREPARED BY THE AUTHOR UNDER OUR SUPERVISION. WE ALSO SUPERVISED THE WRITING OF THIS DISSERTATION.

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DEDICATION

This project is dedicated to God Almighty through our Lord Jesus Christ. Also to my precious wife, Funmi and our lovely children, Esther, Favour and Goodnews.
ACKNOWLEDGEMENT

I must recognize and appreciate Almighty God’s unconditional contributions towards overall successes of my training in anaesthesia in general and this project in particular.

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<tr>
<td>µg</td>
<td>microgram</td>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
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<tr>
<td>Bp</td>
<td>blood pressure</td>
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<tr>
<td>bpm</td>
<td>beats per minute</td>
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SUMMARY

Background

Traditionally, appendicectomy is performed under general anaesthesia. Recently, addition of opioids to heavy bupivacaine for sub-arachnoid block is taking the centre stage of anaesthetic practice. The reliable measurement and treatment of pain intensity have assumed an important dimension in the face of recent knowledge demonstrating the detrimental effects of untreated pain. Any untreated pain intra-operatively during appendicectomy may not only be distressing to the patients, it will also be distressing to both the anaesthetist and the surgeon. Although it has been shown that addition of fentanyl to hyperbaric bupivacaine could produce profound intra-operative and immediate post-operative analgesia, its effectiveness with equipotent dose of intrathecal tramadol has not been compared. In this study, the effectiveness and duration of intra-operative and post-operative analgesia produced by intrathecal fentanyl were compared with that of intrathecal tramadol during bupivacaine spinal anaesthesia for appendicectomy.

Study Design

This was a prospective, randomized, double blinded, controlled trial. Approval was obtained from the University of Benin Teaching Hospital research and ethics committee. One hundred and ninety five ASA 1 or 11 patients aged between 18 and 60 years scheduled for emergency appendicectomy at the University of Benin Teaching Hospital were recruited into this study. Informed written consent was obtained.

The patients were randomized into three groups. Group A received intrathecal fentanyl 25µg plus 3ml of 0.5% hyperbaric bupivacaine, Group B received 0.5ml normal saline plus 3ml of 0.5% hyperbaric bupivacaine and Group C received intrathecal tramadol 25mg plus 3ml of 0.5% hyperbaric bupivacaine. The preoperative vital signs
(pulse rate, systolic blood pressure, diastolic blood pressure, arterial oxygen saturation and respiratory rate) were obtained and recorded.

Intravenous access was secured using a 16 or 18G cannula and normal saline 15 ml/kg was administered for preloading. Visual Analogue Scale (VAS) score was used to assess both intraoperative and post-operative pain score. Visual Analogue Scale 0mm indicated no pain, 100mm showed worst pain, 1mm to 39mm showed mild pain, 40mm to 69mm showed moderate pain, 70 and above showed severe pain. Visual Analogue Scale scores and frequency of subjective symptoms of chest tightness, dragging sensation, vomiting, nausea and retching from manipulation of peritoneum or abdominal viscera recorded for patients in the three groups formed the measurement of primary outcome of this study.

The data obtained were analyzed using statistical package for social sciences (SPSS) 16.0 software (Chicago Illinois, USA.) All parametric data were analyzed with one way ANOVA. Non-parametric data were analyzed with chi square, Fisher’s exact, Kruskal-Wallis or Mann-Whitney test where applicable. Probability values <0.05 were considered significant.

**Results**

Effective intraoperative sensory block was achieved in 100% of patients in group A and C. Thirty three patients (53.2%) had effective sensory block in group B while 29 (46.8%) others in the group had ineffective sensory block. The incidence of ineffective sensory block in Group B was significant statistically (P-value=0.0001) when compared with Groups A and C. The difference between Groups A and C was not significant.

The pain free period was significantly longer in patients in Group A than Group B and C. Mean time for Group A with regard to first analgesic request was 304±67.91min,
Group B was 146.59±36.62 and Group C was 238.39±61.8min. Intergroup comparison of time to first analgesic request showed that the difference was statistically significant between Groups B and C (P-value=0.001); between Groups B and A (P-value=0.001) and between Groups A and C (P-value=0.001.)

Incidence of complications were comparable among the three groups. Fifteen (24.2%), 13 (20.9%) and 15 (24.5%) patients in Groups A, B, and C respectively had hypotension. The difference in incidence of hypotension was not significant (P-value=0.88.) No patient in Groups A and C had any complaint of pain, chest tightness, vomiting, retching or nausea, but 5 patients (8.1%), 7 patients (11.1%), and 3 patients (4.8%) in Group B reported pain, chest tightness and vomiting respectively. Three patients (4.8%) had episodes of nausea and another three (4.8%) had retching.

Shivering occurred in 3 patients (4.8%) in Group B none in Group A or C which was not significant (P-value=0.108.) Itching was significantly higher in Group A compared with Groups B and C (P-value=0.035.) Four patients (6.5%) had pruritus in Group A, none in the other groups. One (1.6%) had headache in Group A but none in the other groups, the difference did not achieve any statistical significance (P-value=1.000.) The difference in the incidence of post-operative vomiting was significant statistically (P-value=0.016) when vomiting episode (16.1%) in Group C was compared with Groups B and A.

The degree of both surgeon’s and doctor’s satisfactions were comparable. They were more satisfied with the anaesthesia administered to fentanyl and tramadol groups than that administered to placebo group (P-values=0.0001 and 0.0001 respectively.)
Conclusion

This study showed that intrathecal tramadol can safely replace intrathecal fentanyl in the management of visceral pain and discomfort during subarachnoid block for appendicectomy. Tramadol (25mg) is equipotent with intrathecal fentanyl (25µg) and like intrathecal fentanyl, it has profound and prolonged post operative analgesia.
CHAPTER ONE

INTRODUCTION

Appendicectomy is commonly performed under general anaesthesia worldwide. Presently, regional techniques are gaining widespread popularity for surgeries below the umbilical region. The pressing need to change from general anaesthesia to regional anaesthesia for appendicectomy poses a major health burden. The most favoured amongst the regional technique is subarachnoid block which is also known as spinal anaesthesia. This is due to its simplicity, reliability and safety.

The first spinal analgesia was administered in 1885 by Leonard Corning (1855-1923), a neurologist in New York. He was experimenting with cocaine on the spinal nerves of a dog when he accidentally pierced the dura mater. The first planned spinal anaesthesia for surgery in man was administered by August Bier (1861-1949) on 16 August 1898 in Kiel, when he injected 3ml of 0.5% cocaine solution into a 34 year old labourer. After using it on 6 patients, he and his assistant each injected cocaine into the other's spine. They recommended it for surgeries of the legs but gave it up due to the toxicity of cocaine.

Attempts at using appropriate safe dose of local anaesthetic agent intrathecally without additive while managing pain associated with appendicectomy had proved abortive in the past. Spinal anaesthesia with 0.5% hyperbaric bupivacaine is commonly administered nowadays for lower abdominal and major gynaecological surgery. Its advantage includes the simplicity of the technique, its rapid onset and usefulness during absolute contraindication to general anaesthesia. Kezaala in 1997 reported that spinal anaesthesia was cheap, simple and safe. He recommended that it should be more frequently and widely used in rural Ugandan hospitals.
In the past and up till now, world anesthesiologists are faced with the herculean task of mitigating visceral pain and discomfort associated with surgical removal of the appendix under subarachnoid block. To increase the intensity and duration of intra-operative and post operative analgesia, a number of adjuvants have been added through the central neuraxial route. Experimental studies have shown that addition of opioids to local anaesthetic agent intrathecally was able to relieve visceral pain.

Visceral pain is mediated by sympathetic nerve fibres in the wall of hollow organs such as the appendix. It is caused by surgical stimulation or stretching of these fibres causing ischaemia and the release of inflammatory mediators.

The early experience with addition of large doses of opioids to local anaesthetic agents for subarachnoid block produced not only prolonged duration of anaesthesia, but also side effects; such as delayed emergence, respiratory depression, nausea and pruritus, which dampened the early enthusiasm of using spinal opioids. Sudarshan et al. demonstrated that intrathecal fentanyl with 0.5% heavy bupivacaine provided excellent surgical anaesthesia with few side effects. Lack of side effects is related to the dose of fentanyl used. Gielen et al. also reported that intrathecal fentanyl is one of the safest opioids that was not associated with any troublesome side effect. Techanivate et al. reported that spinal anaesthesia with intrathecal fentanyl is commonly employed for appendicectomy in Thailand.

Among other things, ideal intrathecal opioids should be cheap, readily available, effective and with minimal side effects. In most developing countries like Nigeria, opioids like fentanyl, morphine, pethidine, sufentanil, alfentanil are expensive and not readily available. Moreover, the problem of getting fentanyl or pethidine by most hospitals in Nigeria contributes to its under-utilization. Recently, the search for less expensive, readily available opioids drew attention to intrathecal tramadol. Researchers have
demonstrated the usefulness of tramadol in both appendicectomies and major gynaecological surgeries.\textsuperscript{10,11}

There is general paucity of reports on intrathecal opioids as adjuvants to local anaesthetic agents during management of pain of appendicectomy in Africa. This is more marked in Nigeria where spinal anaesthesia for appendicectomy is still relatively under-utilized. Tramadol is commonly available in pharmaceutical stores in Nigeria. It is therefore necessary to evaluate its usefulness among the Nigerian population undergoing appendicectomy. Intrathecal tramadol if found useful, could be recommended as a substitute for fentanyl and other scarce opioids amongst this Nigerian population and this will encourage further research.
AIMS

To compare the effectiveness and duration of intraoperative and post-operative analgesia produced by intrathecal tramadol and fentanyl during bupivacaine spinal anaesthesia for appendicectomy

OBJECTIVES

(1) To determine the efficacy of analgesia produced by bupivacaine spinal anaesthesia for appendicectomy

(2) To evaluate the effectiveness of intrathecal tramadol added to bupivacaine spinal anaesthesia for appendicectomy

(3) To evaluate the effectiveness of intrathecal fentanyl added to bupivacaine spinal anaesthesia for appendicectomy

(4) To determine whether intrathecal tramadol and fentanyl are equipotent in mitigating visceral pain and discomfort during bupivacaine spinal anaesthesia for appendicectomy.

(5) To assess both patients’ and surgeons’ satisfaction following the use of spinal anaesthesia with or without intrathecal tramadol or fentanyl.
CHAPTER TWO
LITERATURE REVIEW

Studies have been carried out to evaluate the safety of spinal anaesthesia for appendicectomy.\textsuperscript{2,10} These studies looked at the prevention and elimination of the major complications, like visceral pain, and discomfort from nausea, vomiting and chest tightness.\textsuperscript{2} In most cases, these complications arise when local anaesthetic agents are used alone intrathecally. The local anaesthetic agents that are used for spinal anaesthesia include lidocaine, bupivacaine, mepivacaine and ropivacaine. In order to prevent toxicity and complication that will result if high doses of these local anaesthetic agents are used, adjuvants like ketamine, sufentanil, fentanyl, pethidine, morphine and tramadol have been used during subarachnoid block.\textsuperscript{12,13}

Subarachnoid block is a form of regional anaesthesia involving administration of a local anaesthetic into the cerebrospinal fluid (CSF), through a fine needle (spinal needle), usually 9cm long.\textsuperscript{14} For extremely obese patients, some anaesthesiologists are known to prefer spinal needles which are 18cm long. Bupivacaine is the local anaesthetic most commonly used for subarachnoid block because it has a longer duration of action than lidocaine, tetracaine, procaine, ropivacaine or cinchocaine.\textsuperscript{14}

Bupivacaine is a local anaesthetic agent which reversibly blocks the transmission of peripheral nerve impulse by inhibiting voltage-gated sodium channels in the spinal cord.\textsuperscript{15} It is usually injected as an acid solution of the hydrochloride salt (pH < 5). In this form, the amine group is ionized and the drug becomes soluble in water.\textsuperscript{16} After injection, tissue buffering raises the pH and a percentage of the drug dissociates to become free base, the amount depending upon the “dissociation constant” of the drug. Being lipid-soluble, the free base is able to penetrate both the nerve coverings and the lipid cell membrane to reach the interior of the axon, where a portion re-ionizes. The re-ionized
portion enters the sodium channels and plugs these channels so that ions cannot enter the cell. As a result, action potentials are neither generated nor propagated and conduction block occurs.\textsuperscript{16}

Hyperbaric solution of bupivacaine is preferred during subarachnoid block, as its spread can be effectively and predictably controlled by the anaesthetist by tilting the patient. Baricity refers to the density of bupivacaine compared to the density of human cerebro-spinal fluid. Baricity is used in anaesthesia to determine the manner in which a particular drug like bupivacaine will spread in the intrathecal space. There are hyperbaric and hypobaric solutions of bupivacaine.

Hyperbaric bupivacaine is made heavy by adding dextrose to the mixture. The desired effect of bupivacaine is to block the transmission of nerve signals to and from affected area.\textsuperscript{17} Sensory signals from the site are blocked, thereby eliminating pain, and motor signals are also blocked to eliminate movement. In the effect, the result is total numbness of the area and impaired motor function. This allows surgical procedures to be performed with little or no sensation whatsoever to the person undergoing the procedure and provides a still patient or area for the surgeon to work on.

Surgery is always stressful for the patients, some sedation is sometimes provided to help the patient relax and pass the time during the procedure, but with a successful spinal anaesthetic, the surgery can be performed with the patient wide awake.\textsuperscript{17} In the event of an inadequate subarachnoid block, it is much better to administer a light general anaesthesia and safeguard the airway, than to over-sedate a patient with benzodiazepines or narcotics.

Opioids work in the intrathecal space by activating opioid receptors in the dorsal gray matter of the spinal cord, which modulates the function of afferent pain fibres.\textsuperscript{5} Numerous studies support the combination of local anaesthetics with opioids to provide
safe anaesthesia and analgesia while reducing the required doses and adverse effect of each agent.\textsuperscript{2,10,11,18}

Extreme cephalad spread of bupivacaine may affect the ability to breathe by paralyzing the intercostal respiratory muscles, or diaphragm in extreme cases (high spinal or total spinal with which consciousness is lost) as well as the body’s ability to control the heart rate via the cardiac accelerator fibers.\textsuperscript{18}

Opioid added to local anaesthetic for spinal anaesthesia was first introduced into clinical practice in 1979 with intrathecal morphine as a forerunner.\textsuperscript{19} Fentanyl has a rapid onset of action following intrathecal administration. It does not tend to migrate to the fourth ventricle in sufficient concentration to cause delayed respiratory depression when administered intrathecally.\textsuperscript{19}

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine with a dual mechanism of action.\textsuperscript{20} It stimulates the $\mu$- receptor and to a lesser extent $\delta$- and $\kappa$-opioid receptors. Like tricyclic antidepressants, it also activates spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin. This produces a non-opioid basis of analgesia.\textsuperscript{20,21} A report suggesting that tramadol may have a direct serotonin-releasing action has been documented.\textsuperscript{22} Analgesic doses of tramadol may produce less respiratory depression in part because of its non-opioid receptor mediated actions.\textsuperscript{21,23} Seizures have been reported in patients taking the drug orally or intravenously, therefore caution should be exercised when combining tramadol with monoamine oxidase inhibitors, neuroleptic agents and other drugs that lower the seizure threshold. It was suggested that tramadol may have local anaesthetic effects on peripheral nerve when used alone.\textsuperscript{24} Side effects of tramadol include nausea, vomiting, dizziness, dry mouth, sweating and confusion. The multimodal action may be responsible for its decreased depressant effect on respiration.\textsuperscript{25,26} Kezaal et al\textsuperscript{4} advocated the use of spinal anaesthesia
for lower abdominal surgeries, being a cheap, safe and simple form of anaesthesia. He recommended that it should be frequently and widely used in rural Ugandan hospitals.4

Until recently, the use of spinal anaesthesia for appendicectomy was discouraged by earlier proponents of the procedure. This was due to profound side effects following use of local anaesthetics as the sole drugs of choice intrathecally.2 These side effects were as a result of visceral pain and discomfort leading to nausea, vomiting, chest tightness and dragging sensation from intestinal manipulations.2

Experimental studies have shown that opioids administered intrathecally were able to relieve visceral pain and discomfort during spinal anaesthesia for appendicectomy.5 In the last few years, intrathecally administered opioids with local anaesthetics with its advantages of simplicity and reliability, have gained popularity in visceral pain management during appendicectomy. The clinical efficacy of intrathecal opioids to relieve visceral pain has also been demonstrated.27

Opioids are the other groups of drugs widely used neuraxially, in particularly, to provide analgesia alone or more commonly in combination with local anaesthetic agents. The physico-chemical properties of the various opioids explain the main differences in efficacy and safety between these drugs when used intrathecally of which morphine, fentanyl and sufentanil are most commonly used. Fentanyl is a lipophylic opioid similar to pethidine which is easily metabolized from cerebrospinal fluid than hydrophilic opioids such as morphine. However, opioids that are lipophilic have a potential of a short duration of action. Duration of action of fentanyl may be dose dependent.28

Drugs such as clonidine, dexmedetomidine and epinephrine provide neuraxial analgesia via alpha-adrenergic receptors and are used as adjuvant to local anaesthetic agent.21
Furthermore baclofen is in routine clinical use to treat spasticity in a number of neurological conditions. Besides these established approaches, a wide range of other drugs have been assessed for neuraxial administration to provide analgesia however most are not used routinely. These drugs include neostigmine, ketamine, midazolam, adenosine, propofol and even muscle relaxants.\textsuperscript{21}

Studies investigating appropriate, safe and effective doses of intrathecal fentanyl, during bupivacaine sub-arachnoid block, had been reported and the results varied. Belzarena et al.\textsuperscript{29} reported that the dose of 0.25µg/kg intrathecal fentanyl provided excellent surgical anaesthesia with short-lasting postoperative pain relief. This clinical effect of spinally administered fentanyl was assessed in 120 healthy women who underwent Caesarean section with spinal anaesthesia using 0.5% hyperbaric bupivacaine. Group O received 2ml of normal saline, Group 25 received 0.25µg/kg of fentanyl, Group 50 received 0.50µg/kg of fentanyl and Group 75 received 0.75µg/kg of fentanyl. Surgical anaesthesia was 100% in the treated groups and was 87% in Group O. Effective postoperative analgesia lasted longer and significantly increased with the dose of the fentanyl administered. Group O = 197±77min, Group 25, 305±89min, Group 50, 640±142min, and Group 75, 787±161min (P< 0.001.)

Techanivate et al\textsuperscript{2} observed that spinal anaesthesia was commonly employed for appendicectomy in Thailand. He discovered that some patients complained of pain and discomfort when the appendix and intestine were retracted and when the intestine was returned to the abdomen, with the use of intrathecal bupivacaine or lidocaine only.\textsuperscript{2} To prove that opioid especially fentanyl could obtund these complications, he recruited 60 patients in a prospective randomized double-blinded study. Patients were randomly assigned into three groups: 20 in each group. Subjects in group 20 received 0.4ml (20µg) of fentanyl; group 10 received 0.2ml (10µg) of fentanyl
and 0.2ml of normal saline and group 0 received 0.4ml of normal saline (placebo). In addition, each group received 4ml of 0.5% bupivacaine. At the end of the study it was observed that all patients who had intrathecal fentanyl had complete intraoperative analgesia, whereas only 13 patients (65%) in the placebo group had no pain.

The first request of post-operative analgesics was also extended in the group that was administered with 20µg of fentanyl compared with the other two groups. Time to first request of post-operative analgesics in 20µg fentanyl group was longer than in the other two groups [11.0hr vs, 5.25hr, 4.7hr; P < 0.05]. Eight patients [40%] in group 20, 6 patients (30%) in group 10 and 7 patients (35%) in group 0 had episodes of hypotension (P> 0.05.) Two patients in both fentanyl groups and 6 patients in group 0 had vomiting (P< 0.05.) Four patients (20%) in group 20, 3 patients (15%) in group 10 and 12 patients (60%) in group 0 experienced severe shivering (P< 0.05.) The result revealed an improvement of analgesia without increase in side effects with the addition of fentanyl 10µg or 20µg to bupivacaine in spinal block for appendicectomy. The addition of 20µg of fentanyl intrathecally however prolonged analgesic effect.

Goel and colleagues added intrathecal fentanyl to intrathecal bupivacaine for day case surgery, in a prospective single blind randomized study conducted in 45 adult males scheduled for minor urological procedures. The patients were randomly assigned to one of three groups (n = 15 each). Patients received 5mg of 0.17% bupivacaine with either fentanyl 7.5µg, 10µg or 12.5µg intrathecally in a total volume of 3ml. It was concluded that fentanyl 12.5µg added to low-dose bupivacaine 5mg intrathecally provided better surgical anaesthesia and increased reliability of block than intrathecal fentanyl 7.5µg or 10µg. Haemodynamic stability was the same for all dose combinations.

Seewal and colleagues conducted a study on sixty patients planned for elective inguinal hernia repair who were randomized to receive a spinal anaesthetic with 2.2ml of
bupivacaine (0.5% hyperbaric) and saline (control group) or fentanyl 10, 20, 30 or 40 μg. Significant improvement in quality and duration of analgesia occurred in groups treated with intrathecal fentanyl and bupivacaine compared with control group (P < 0.05). However no improvement in analgesia occurred when the dose of fentanyl added was increased from 10 to 20, 30 or 40. They concluded that addition of 10 μg fentanyl to bupivacaine 0.5% hyperbaric significantly improved the quality and duration of analgesia during superficial lower abdominal surgery. No further advantages occurred if the dose of fentanyl is increased to 40 μg.

Singh and colleagues\textsuperscript{12} conducted a clinical trial to investigate the effect of intrathecal fentanyl on the onset and duration of hyperbaric bupivacaine – induced spinal block in forty three patients undergoing lower extremity or genitourinary surgery. Patients were randomized into two groups. Patients in Group I received 13.5 mg hyperbaric bupivacaine 0.75% plus 0.5 ml of cerebrospinal fluid and Group II received 13.5 mg bupivacaine 0.75% plus 25 μg fentanyl. The time required for two sensory segment regression and sensory regression to L1 dermatome was 74±18 min and 110±33 min vs 93±22 min and 141±37 min in Groups I and II respectively (P < 0.05).

It was found that intrathecal fentanyl did not enhance the onset of sensory or motor block. Fewer patients demanded pain relief in the fentanyl treated group than in the control group in the early post-operative period (19% vs 59% P < 0.05.) Episodes of hypotension were more frequent in the fentanyl-treated group than in the control group (43% vs 14%; P<0.05). They concluded that fentanyl 25 μg intrathecally, did not accelerate onset of action of spinal anaesthesia but prolonged the duration of bupivacaine induced sensory block and reduced the analgesic requirement in the early postoperative period.
Evidence suggesting that intrathecal fentanyl improved both intra and postoperative analgesia with surgeries involving visceral pain was supported by researchers\textsuperscript{2,12,29,30} in different studies. They demonstrated that there was significant increase in duration of analgesia with increasing dose of fentanyl. Although Seewal et al\textsuperscript{31} demonstrated no advantage in regards to duration and quality of analgesia with increasing dose of fentanyl but this might be due to the fact that much less visceral pain is involved in the repair of uncomplicated inguinal hernia.

Kuusniemi and co-workers\textsuperscript{32} carried out a clinical trial on the use of bupivacaine and fentanyl for spinal anaesthesia for urological surgery. Eighty men ASA I or II undergoing urologic surgery were randomized into four groups. Group I received bupivacaine 10mg; Group II received bupivacaine 10mg plus fentanyl 25µg; Group III received bupivacaine 7.5mg plus fentanyl 25µg and group IV received bupivacaine 5mg plus fentanyl 25µg. They concluded that the addition of 25µg of fentanyl to 5mg of bupivacaine resulted in short-acting motor block. When 25µg of fentanyl was added to 10mg of bupivacaine, it increased the intensity and duration of motor block.

Varrassi and colleagues\textsuperscript{33} conducted a study to evaluate the ventilatory effects of different doses of subarachnoid fentanyl in 28 elderly patients scheduled for urological surgery. Patients were randomized into 4 groups. Group A received bupivacaine 15mg plus 50µg fentanyl, Group B received bupivacaine 15mg plus 25ug fentanyl, Group C received bupivacaine 15mg plus 12.5µg fentanyl. Group D received bupivacaine 15mg plus 1ml normal saline. It was found that 2 patients in group A had prolonged analgesia and respiratory depression. The researchers\textsuperscript{33} recommended 25µg fentanyl as the ideal dose that provided prolonged analgesia without respiratory depression.

Biswa et al\textsuperscript{19} evaluated forty healthy women of ASA grade I scheduled for elective Caesarean section by randomizing them into two groups. Group A received 2ml of 0.5%
bupivacaine with 0.25ml of normal saline (group A, n=20). Group B received 0.25ml (12.5µg) fentanyl with 2ml of 0.5% bupivacaine (n=20.) Complete analgesia (time from injection to first report of pain) lasted longer in Group B (183±9min) than Group A (129±9.5min.) The duration of effective analgesia (time from injection to first parenteral analgesic) was increased with the dose of intrathecal fentanyl 12.5µg (248±11.76min.) Four patients (20%) in Group A had hypotension as compared to six (30%) in Group B. Four patients (20%) in Group A had shivering episode as compared with one patient (5%) in Group B. Eight patients (40%) and one patient (5%) in Groups A and B had emetic episodes (nausea and vomiting) respectively. No patient had pruritus in either group. It was concluded that addition of fentanyl to bupivacaine improved the quality of spinal anaesthesia.

Techanivate demonstrated that the addition of intrathecal fentanyl to bupivacaine during sub-arachnoid for appendicectomy was necessary in order to have complete sensory block in all the patients. In support of Techanivate were works of Biswas et al, Bezarena et al, Goel et al and Varrasi et al which showed that intrathecal fentanyl was required to abolish visceral pain. According to Techanivate et al, time to first analgesic request was significantly prolonged in fentanyl group compared with placebo. This was in agreement with the studies of other researchers.

High dose of intrathecal fentanyl can result in respiratory depression. This was supported by Varassi who reported that the group that received 50µg of intrathecal fentanyl had respiratory depression whereas groups that received 25µg or less did not have respiratory depression. No respiratory depression was observed by Techanivate et al and other different workers. This was due to low dose of intrathecal fentanyl administered (10-25µg). Shivering incidence was high (70%) in the placebo group as observed by Techanivate et al. This was probably due to the sympatholytic effect of
intrathecal hyperbaric bupivacaine used in their study. Biwas et al\textsuperscript{19} and Bogra et al\textsuperscript{34} found no significant difference in the episodes of shivering because 2mls of intrathecal bupivacaine was used as against 4mls used by Techanivate.\textsuperscript{2}

In a bid to reduce the incidence of side effects associated with high dose of bupivacaine, Goel et al\textsuperscript{30} concluded that fentanyl 12.5µg added to low-dose bupivacaine 5mg intrathecally provided better surgical anaesthesia than intrathecal fentanyl 7.5µg or 10µg. The effect of minidose bupivacaine-fentanyl spinal anaesthesia for surgery of hip fracture in the aged was investigated by Ben-David et al.\textsuperscript{35} Twenty patients aged seventy years and above were randomized into two groups of ten patients. Group A received spinal anaesthetic bupivacaine 4mg plus fentanyl 20µg and Group B received 10mg bupivacaine. They concluded that a minidose of 4mg bupivacaine in combination with 20µg fentanyl provided anaesthesia for surgical repair of hip fracture in the elderly. It was also found that minidose combination caused dramatically less hypotension than 10mg bupivacaine and nearly eliminated the need for vasopressor support of blood pressure.

Ben-David et al\textsuperscript{36} also investigated the effect of intrathecal fentanyl with small dose of dilute bupivacaine. Fifty patients that were scheduled for ambulatory surgical arthroscopy were randomized into two groups. Group 1 received 3ml of 0.17% bupivacaine in 2.66% dextrose and Group II received 3ml of 0.17% bupivacaine in 2.66% dextrose with addition of fentanyl 10µg. They observed that the addition of fentanyl made the block reliable and effective. The low-dose of fentanyl (12.5µg)\textsuperscript{19,30} and low-dose bupivacaine (5mg)\textsuperscript{30,35,36} may be useful and effective intra-operatively in short procedures, ambulatory anaesthesia or patients with intercurrent ailments but produce short duration of analgesia, hence 25µg of fentanyl\textsuperscript{12,32,33} with 15mg of hyperbaric
bupivacaine\textsuperscript{37,38} had been found to have prolonged post-operative analgesia and less side effects.

Tramadol is presented in a sterile intravenous preparation with water for injection and sodium acetate, it does not contain preservatives like sodium metabisulphite, methylparaben, chlorocresol which are neuro-toxic agents. It is usually produced preservative-free.\textsuperscript{39} It is a centrally acting analgesic agent. Both animal and human studies have confirmed its safety and efficacy intrathecally.\textsuperscript{11,40} Tsai et al.\textsuperscript{40} carried out a study on the effects of intrathecal tramadol on spinal somatosensory evoked potentials and motor-evoked responses in rats.\textsuperscript{40} The results indicated that tramadol exerts a dose-related central neural blockade, if it is given intrathecally.\textsuperscript{40}

Barret et al\textsuperscript{39} reported an inadvertent intrathecal injection of tramadol in a 57 year old female with a widely spread metastatic squamous cell carcinoma of unknown primary. Intrathecal injection of tramadol (about 25 mg) was inadvertently given on day 21 of her admission for palliative management. Within 10 min of the injection, it was noted that she was diaphoretic and hypotensive with a systolic blood pressure of 70-80\textsuperscript{mmHg}. In the preceding days, her systolic blood pressure was approximately 100-130\textsuperscript{mmHg}. Her heart rate was unchanged at 110-130 beats per minute in a regular rhythm. She developed severe central back pain associated with back arching spasms and myoclonic jerks in both lower limbs. Her sensorium was unchanged. The myoclonus and hypotension persisted until her death 48 hours later.\textsuperscript{39}

Barret et al\textsuperscript{39} were not sure whether it was intrathecal tramadol or other drugs that caused the constellation of signs and symptoms that followed the intrathecal injection of tramadol in the case reported. They postulated possible synergistic effect of intrathecal tramadol with intrathecal morphine in producing an intractable hypotension, since morphine was known to cause hypotension. Moreover, the patient was ASA IV but
the safety of tramadol in ASA I and II patients was documented by Parthasarathy et al\textsuperscript{10} and Alhashemi et al\textsuperscript{41} in different studies. In Tunisia, Frikha et al\textsuperscript{42} compared intrathecal tramadol with sufentanil in a combined spinal epidural analgesia in labour. He discovered that though sufentanil had a rapid onset and profound analgesia, tramadol had longer lasting analgesia\textsuperscript{42}.

Brijesh et al\textsuperscript{43} evaluated the extent of surgical analgesia by conducting a study on 130 patients. Patients were divided into two groups. Group I comprised of 100 patients scheduled for lower segment Caesarean section and Group II comprised of 30 patients scheduled for major gynaecological surgeries. The patients in Group I were administered 1.3ml of 5\% lidocaine (heavy) and 0.5ml tramadol (25mg) intrathecally and the patients in Group II received 3.5ml of 0.5\% bupivacaine (heavy) and 0.5ml of tramadol (25mg) intrathecally. They reported that excellent surgical analgesia and an extended analgesia was observed in postoperative period with the given dose of intrathecal tramadol and side effects were negligible.

Frickha et al\textsuperscript{44} studied forty pregnant women undergoing Caesarean section, randomized to receive bupivacaine 0.5\% (2ml) with fentanyl 10\(\mu\)g intrathecally plus either tramadol 50mg (tramadol group) or saline 1ml (saline group.) There were no differences between the groups for postoperative VAS scores (mean was 26mm in every group), post-operative morphine requirements (mean 37.5 vs 35.5mg, \(P = 0.13\)), times to first analgesic request (mean 23 vs 18min, \(P = 0.07\)) and sedation scores (0 for all the pregnant women). Nausea, vomiting and itching were more frequent in the tramadol group. No case of respiratory depression or neurological complication occurred in any of the patients. Spinal tramadol did not influence intra-operative haemodynamic profile and had no effect on the fetus. They concluded that spinal tramadol in the dose of 50mg was
not different from saline in its effect on post-operative morphine requirement after Caesarean section.

Fifty patients ASA I and II scheduled for Wardmayo’s operation and Fothergill’s operation were randomly allocated to two equal groups by Susmita et al. Group B (n = 25) received 3ml of 0.5% hyperbaric bupivacaine and 0.2ml (20mg) tramadol by intrathecal route at L₃-L₄ interspace. Group A (n=25) received 3ml of 0.5% hyperbaric bupivacaine and 0.2ml of normal saline. In group B patients, the VAS score was significantly lower than Group A patients. The duration of analgesia was 210±10.12min in Group A; whereas in Group B, it was 380±11.81min, which was found to be significant (P<0.05). None of the patients had post operative complication like pruritus, vomiting, respiratory depression and lower limb weakness.

In 2002, Parthasarathy et al studied post-appendicectomy pain management using single dose intrathecal tramadol. He studied 50 patients scheduled for appendicectomy. In a randomized double blind trial, tramadol group (group T) received 1.8ml of lidocaine 5% with 10mg of preservative free tramadol, while the control group (group C) received 1.8ml of lidocaine 5% with normal saline intrathecally.

No patient required general anaesthesia or additional sedatives/narcotics due to inadequate block and the intraoperative period was uneventful in all the fifty patients. The appendicectomy performed was completed within 30 minutes in all patients. In the postoperative period, the mean time for first analgesia (TFA) was significantly prolonged in the tramadol group (310 ± 127.49 vs 131 ± 40.51 minutes.) The mean pentazocine requirements were significantly less in the tramadol group (46.8 ± 15mg) than placebo group (63.6 ± 19.1mg) (P < 0.05). These two factors clearly established the analgesic efficacy of low dose intrathecal tramadol. It was also noted that patients in the tramadol group were more sedated at 0 and 6 hours, while patients in the placebo group were
more sedated at 3 and 9 hours, but the sedation scores were similar at 12 hours. Only one patient had vomiting and one had urinary retention in group T. No other side effects were observed.

In an attempt to determine the efficacy of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate (TURP), Alhashemi and Kaki recruited 64 patients undergoing TURP for a double-blind, placebo-controlled study. The study populations were randomized to receive 3mls of 0.5% bupivacaine intrathecally premixed, with either tramadol 25mg (group T) or saline 0.5ml (group C). After operation, morphine 5mg i.m every 3 hours was administered as needed for analgesia. Postoperative morphine requirements, visual analogue scale for pain at rest, and sedation scores, time to first analgesic requirement and length of hospital stay were recorded by a blinded observer. The result demonstrated VAS scores of 1.6±1.2 versus 1.2±0.8 (P-value=0.18) in group C and group T respectively. Time to first analgesia was 6.3±6.3 versus 7.6±6.2 hours (P-value=0.42) for groups C and T. Sedation scores were 1.2±0.3 versus 1.2±0.2 (P-value=0.89). It was observed that there was no difference between the groups with regard to post-operative morphine requirement.

In a prospective double-blind study, Batra and colleagues studied forty children scheduled for hypospadias repair. They were allocated randomly to receive either caudal tramadol (1mg/kg) or 0.25% plain bupivacaine (0.5ml/kg). They found that total consumption of rescue analgesics was significantly higher in bupivacaine group as compared to tramadol group during the study period (P < 0.001). The result pointed toward a significantly lower pain scores with caudal bupivacaine in the immediate postoperative period, whereas caudal tramadol caused a significant lower pain score in the late postoperative period. The incidence of vomiting was more frequent with caudal
tramadol. They concluded that caudal tramadol can safely be used for postoperative analgesia with a longer duration as compared to caudal bupivacaine.

Prosser et al\textsuperscript{46} studied ninety boys, aged 13-53 months, undergoing repair of hypospadias and randomly allocated them into three groups to receive 0.8ml/kg of one of the three solutions into caudal space. Group B received bupivacaine 2mg/kg; Group T received tramadol 2mg/kg in 0.9% saline while Group BT received a mixture of both. The result showed that nine patients (30\%) in Group T required additional analgesia within one hour of surgery compared with only two (6.7\%) and three (10\%) in group B and BT respectively (P = 0.04). Mean duration before additional analgesia was required in the remaining patients was 9.3±3 hours in Group B, 10.7±2.2 hours in group T and 10.5±2.0 hours in Group BT (P > 0.20). There were no significant differences between the groups in terms of side effects. They concluded that caudal tramadol had a slow onset of action and that the addition of tramadol to bupivacaine, when both drugs were administered caudally, did not significantly prolong the duration of action of bupivacaine.

Delikan et al\textsuperscript{47} studied the efficacy of epidurally administered tramadol for the relief of postoperative pain. Sixty patients undergoing abdominal surgery were randomly allocated to three treatment groups to be given the following agents by the epidural route: Group 1 tramadol 50mg; Group 2 tramadol 100mg and Group 3 bupivacaine 25mg (10ml of 0.25\%). Pain scores (assessed using Visual Analogue Scale) were significantly less (P < 0.05) at 3,12 and 24 hours in patients receiving tramadol 100mg than in those receiving tramadol 50mg or bupivacaine. The incidence of nausea and vomiting in Group 2 was significantly higher than in group 3 (P < 0.05). There was no significant difference in the incidence of nausea and vomiting in group 1 compared to group 3 (P>0.05).

There is no study yet involving the use of intrathecal opioids in combination with bupivacaine spinal anaesthesia for the management of pain during appendicectomy in
the Nigerian surgical population. Even among several studies that were carried out in other countries, no one compared intrathecal fentanyl with intrathecal tramadol in the management of visceral pain and discomfort during appendicectomy. This comparative study is necessary, especially in Nigeria where cost of health care is unaffordable by many people. Access to tramadol is easier than fentanyl and previous studies did not also evaluate both patient’s and surgeon’s satisfaction with intrathecal fentanyl versus tramadol. This clinical trial is aimed at addressing the advantages and disadvantages of intrathecal tramadol and fentanyl with hyperbaric bupivacaine combination in the management of visceral pain in the Nigerian surgical population.
CHAPTER THREE
METHODOLOGY

Study Design

This was a prospective, randomized, placebo-controlled clinical trial, comparing intrathecal tramadol with intrathecal fentanyl and a normal saline placebo-controlled protocol for visceral pain control during bupivacaine subarachnoid block for appendicectomy.

Setting

The study was conducted at the University of Benin Teaching Hospital, Benin City. Patients were drawn from those scheduled for emergency appendicectomy requiring subarachnoid block.

Ethical approval and informed consent

Ethical clearance and approval were obtained from the institution’s ethical committee. Informed consent of every participating patient was obtained before the study was commenced.

Inclusion criteria

One hundred and ninety five ASA I or II patients scheduled for emergency appendicectomy, aged between 18 and 60 years were recruited for the study.

Exclusion

Exclusion criteria included patients unable to understand written and/or verbal information, patients with appendicular mass, rupture or any co-existing surgical procedure. Patients for elective appendicectomy were excluded because their overnight fast could affect incidence of nausea and vomiting. Patients with history of
hypersensitivity to local anaesthetic agent and opioids that were used were excluded. Patients with peripheral neuropathy or having contraindications to regional anaesthesia or patients who could not attain a minimum height block of T6 at 4 minutes following injection of spinal solution were also excluded.

Sample size estimation

The sample size was determined using the following assumption.

Proportion of interest (70%). This was based on success rate of work of Techanivate et al.\(^2\)

Sample size was calculated using the formula below\(^48\)

\[
n = \left[ \frac{U \sqrt{\Pi(1 - \Pi)} + V \sqrt{\Pi_{\text{null}}(1 - \Pi_{\text{null}})}}{(\Pi - \Pi_{\text{null}})^2} \right]^2
\]

\[
n = \text{required minimum sample size}
\]

\[
\Pi = \text{proportion of interest (0.7)}
\]

\[
\Pi_{\text{null}} = \text{Null hypothesis proportion (0.5)}
\]

\[
U = \text{one-sided percentage point of the normal distribution}
\]

\[
\text{corresponding to (100% - power) = 100% -10%. } U = 1.28
\]

\[
V = \text{percentage of the normal distribution corresponding to}
\]

\[
\text{the required (two-sided) significance level =5%. } V = 1.96
\]

\[
n = \left[ \frac{1.28 \times \sqrt{(0.7 \times 0.3)} + 1.96 \times \sqrt{(0.5 \times 0.5)}}{(0.7 - 0.5)^2} \right]^2
\]

\[
n = \frac{1.5666^2}{0.2^2} = 61.4
\]

A minimum of 61.4 patients were required for each of the three groups; hence 65 patients were recruited for each of the group A, B or C in this study. A total of 195 patients were included to allow for drop outs from the study.
Randomization

All eligible patients were randomly assigned into three groups of 65 each by opening unmarked envelop indicating the type of coded spinal solution package to be used. A second anaesthetist who was not involved in the study prepared the spinal solutions. The anaesthetist performing the block was blinded to the spinal solution administered. Each of the spinal solutions was coded A, B or C.

Group A (n=65), Group B (n=65) and Group C (n=65). Coded spinal solution A, B or C contained one of the following spinal solution packages.

First package: 0.5ml (25mg) tramadol plus 3ml (15mg) of 0.5% heavy bupivacaine.
Second package: 0.5ml (25µg) fentanyl plus 3ml (15mg) of 0.5% heavy bupivacaine
Third package: 0.5ml of normal saline plus 3ml (15mg) of 0.5% heavy bupivacaine.

Study Protocol

Preoperative assessment of the patients, including history with detailed systemic review and examination of all systems (central nervous, cardiovascular, respiratory, genito-urinary, musculoskeletal systems with assessment of airway using Mallampati score) was carried out. Routine investigations such as haemoglobin concentration, urinalysis, serum electrolytes and urea were done for every patient. Visual Analogue Scale [VAS] score for pain assessment, consisting of 100mm line with 0=no pain and 100=worst pain, was explained to all the patients during the preoperative visit. They were all informed that VAS between 1mm and 39mm indicated a mild pain; between 40mm and 69mm indicated a moderate pain, 70mm and above indicated severe pain. They were all educated on the use of VAS scores.

A routine anaesthetic equipment check was performed and three different sizes of portex endotracheal tubes (estimated size for the patient, one size above and one size below the calculated size) were made available. Curved blade and Miller laryngoscopes
were also made available. Suction machines, stilletes, laryngeal mask airway, gum elastic bougie, face mask and resuscitating drugs such as ephedrine, atropine, adrenaline, with induction agents and muscle relaxants were made available in case of conversion to general anaesthesia with muscle relaxant technique.

In the operating room, each patient had Edan multi-parameter monitor attached. Baseline pulse rate, non-invasive blood pressure, oxygen saturation and respiratory rate were obtained and recorded before induction of spinal anaesthesia and subsequently during the procedure. A venous access was secured using 16 or 18 gauge cannula and the patient was preloaded with normal saline (15ml/kg) before the induction of spinal anaesthesia. Aseptically, spinal anaesthesia was carried out in a sitting position, using 25G Quincke spinal needle at \( L_3-L_4 \) interspace. \( L_2-L_3 \) Interspace was used in some cases where it was difficult to use \( L_3-L_4 \) interspace. After a free flow of cerebrospinal fluid was confirmed, each patient received one of the spinal solutions coded A, B or C.

Maximum sensory block height was assessed at one minute, two minutes, 3 minutes and 4 minutes following injection of spinal solution, using loss of sensation to cold and gentle pin prick test. A minimum sensory block height of T6 at 4 minutes was the minimum desired level for commencement of surgery. Any patient who did not meet this minimum sensory block height was excluded from the study. The level of sensory analgesia defined as loss of sensation to pin prick test was recorded. Pulse rate, blood pressure, respiratory rate and oxygen saturation were also recorded every 3 minutes for the first eighteen minutes and then at interval of 5 minutes until the end of surgery. Time of skin incision was recorded. Following skin incision, VAS scores were recorded every 3 minutes for the first eighteen minutes and then at interval of 5 minutes until the end of surgery. Intraoperative complications such as hypotension (reduction in systolic blood pressure greater than 30% of the baseline\(^{49} \)), bradycardia (reduction in pulse rate
greater than 30%, itching, paraesthesia, vomiting and shivering were identified and treated accordingly. Any discomfort following visceral manipulation was recognized, recorded and treated accordingly. Pain and discomfort such as dragging sensation, chest tightness, nausea, vomiting and retching were documented and treated appropriately. The time surgery ended was noted and duration of surgery in minutes was calculated and recorded.

Intraoperatively, patients who experienced pain, dragging sensation and chest tightness were managed with pentazocine, 30mg intravenously as rescue analgesic. Nausea, vomiting or retching was treated with metoclopramide, 10 mg. Shivering was managed using warmed fluid, covering with more drapes. Additionally, the air conditioner in the operating room was switched off, 100mg tramadol was on stand by in case the shivering persisted despite the above mentioned management of shivering. Hypotension was treated with either rapid fluid infusion or aliquots of ephedrine, 3mg intravenously and bradycadia was treated with atropine 0.6mg intravenously. Visual Analogue Scale scores were recorded postoperatively at 30 minutes interval for the first one hour, then hourly for the next 12 hours. Postoperative complications were assessed and recorded. Time and VAS score of first analgesic requirement postoperatively were documented. Duration of pain free period was defined as the period between time of injection of spinal solution and time of first rescue analgesic administered on demand or when VAS score was equal or greater than 40mm. The effectiveness of analgesia produced by either intrathecal fentanyl, tramadol or normal saline placebo intraoperatively was judged by presence or absence of pain and discomfort-dragging sensation, chest tightness, vomiting, nausea and retching-following abdominal manipulation.
The effectiveness of post-operative analgesia produced by either intrathecal fentanyl, tramadol or normal saline placebo was assessed by the use of the duration of pain free period which was from time of injection of local anaesthetic with or without opioids to time of first analgesic requirement in the post operative period or when VAS score was greater or equal to 40mm. Degree of both patient’s and doctor’s satisfaction with the subarachnoid block for the procedure was sought and each of them responded to the different grades of satisfaction: Not satisfied, satisfied, very satisfied or excellent.
Statistical Analysis

All data were presented as means and standard deviation; numbers and percentages; median and range except where specified. The data obtained were analysed using statistical programme for social sciences (SPSS) 16.0 software (Chicago Illinois, USA). All parametric data (continous or discreet) obtained from age, height, weight and haemodynamic variations were analyzed using one way ANOVA. Evaluation of non-parametric data (norminal or ordinal) obtained from sex, ASA, onset of block, pain free period, intestinal manipulation, intra-operative or post-operative complications and inadequate sensory block were analyzed using chi square, Fisher’s exact, Kruskal-Wallis or Mann-Whitney test where applicable. Probability values <0.05 were considered significant.
CHAPTER FOUR

RESULTS

One hundred and ninety five ASA I or II patients, male 75 (38%) and female 120 (62%) aged between 18 and 60 years were recruited into the study. Sixty five patients were randomized to each group A, B and C. Patients in Group A received 3mls (15mg) of 0.5% heavy bupivacaine plus 0.5ml (25µg) fentanyl intrathecally. Group B received 3mls (15mg) of 0.5% heavy bupivacaine plus 0.5ml of normal saline whereas Group C received 3mls (15mg) of 0.5% heavy bupivacaine plus 0.5ml (25mg) tramadol.

Nine of the patients were however disqualified. The reasons for the disqualification were inappropriate documentation for two patients. One patient had appendicectomy with ovarian cystectomy. Three patients had minimum sensory block height below T6 at 4 minutes. One patient had appendicular mass, two others had high grade fever. As a result, only one hundred and eighty six patients in the three groups were analyzed.

Table I shows patient’s characteristics. There was no statistically significant difference amongst the three groups with regard to age, height and weight (P-values = 0.54, 0.17 and 0.56; respectively.) The difference in male and female distribution amongst the three groups did not achieve any statistical significance (P-value= 0.85.)The difference in ASA distribution was also not statistically significant among the study population (P-value 0.83.)

Table II shows distribution of patients according to lumbar interspace used. Subarachnoid block was performed in the patients using lumbar inter- space L3-L4 or L2-L3. Two patients (3.2%) in Group A, 6 patients (9.7%) in Group B and 3 patients (4.8%) in Group C had their lumbar puncture performed at L2-L3. (i.e a total of eleven (5.9%) out of 186 patients.) One hundred and seventy five patients (94.1%) had their lumbar puncture
performed at L$_3$-L$_4$; Group A, 60 (96.8%), Group B, 56 (90.3%) and Group C, 59 (95.2%). This showed that majority (94.1%) had their procedure performed at L$_3$-L$_4$ inter space.

The distribution of patients according to lumbar interspace used did not achieve any statistically significant difference (P-value = 0.391 for L$_2$L$_3$ and 0.391 for L$_3$L$_4$; respectively.)

Table III shows onsets of sensory block in the three groups. Following induction of spinal anaesthesia at 1 minute, patients in Group A had T$_9$ as median of maximum height of sensory block and range of T$_7$ to T$_{11}$, Group B had median of T$_{10}$ and range of T$_8$ to T$_{11}$, while Group C had median of T$_{10}$ with range of T$_8$ to T$_{11}$. Intergroup comparison did not achieve any statistical significance (P-value = 0.47.) At 2 minutes only Group A had some patients with T$_4$. Group A had median of T$_5$ and range of T$_4$ to T$_8$; Group B median was T$_7$ with range of T$_6$ to T$_9$, while Group C median was T$_8$ and range of T$_5$ to T$_{10}$. The difference in the dermatomal level attained in 2 minutes failed to achieve any statistical significance (P-value= 0.065.) At 3 minutes after spinal anaesthesia, both Group A and Group C had some patients with T$_4$ as maximum height of sensory block. The difference in the median level of dermatome reached at 3 minutes did not achieve any statistical significance (P-value= 0.059.) However, at 4 minutes, which was the cut-off point, majority of patients in Group A and C had attained T$_4$ as the maximum height of sensory block. Group A had median value of T$_4$ with range of T$_2$ to T$_6$, Group B had median value of T$_6$ with range of T$_4$ to T$_6$, while Group C had median of T$_4$ with range of T$_2$ to T$_6$. The difference in the level of dermatome reached among the three groups was highly significant (P-value= 0.002.) Despite this high height of sensory block, none of the patients studied had oxygen saturation less than 95%.

Table IV shows minimum dermatomal height of block at the 4$^{th}$ minute. Fifteen patients (24.2%) in Group A, 8 patients (12.9%) in group C and no patient (0.0%) in B
attained T2 dermatomal level at the 4th minute. The difference was statistically significant (P-value = 0.0001.) Thirty six patients (58.1%) in Group A, 12 patients (19.7%) in group B and 35 patients (56.5%) in Group C attained T4 dermatomal level at the 4th minute. The difference was also statistically significant amongst the three groups (P-value = 0.0001.) Fifty patients (80.3%) in group B as compared with 11 patients (17.7%) in Group A and 19 patients (30.6%) in Group C attained T6 dermatomal level at the 4th minute. The difference was also statistically significant (P-value = 0.0001.)

Table V shows intra-operative pain score. Patients in Groups A and C did not experience any pain intra-operatively whereas 55 patients (88.7%) in Group B reported no pain. The difference was highly significant statistically amongst the three groups (P-value = 0.001.) Two patients (3.2%), 4 patients (6.5%) and one patient (1.6%) had mild, moderate and severe pain respectively among patients in Group B and (P-values = 0.330, 0.035 and 1.000 respectively.)

The incidence of discomfort following intestinal manipulation in various groups is shown in Table VI. No patient in both Groups A and C had any form of discomfort following intestinal manipulation. Three patients (4.8%) had episode of intraoperative vomiting with difference among the three groups showing statistical insignificance (P-value = 0.108.), 3 patients (4.8%) reported nausea (P-value= 0.108) and 3 patients (4.8%) complained of retching (P-value= 0.108.)

However, 8 patients (12.9%) had dragging sensation in group B, the difference in Group B as compared with Groups A and C was statistically significant (P-value=0.0001.) Seven patients (11.3%) in Group B had chest tightness. There was a statistical significant difference in the incidence of chest tightness in Group B as compared to Groups A and C (P-value = 0.001.)
Anatomical plane in which discomfort was first noticed is shown in Table VII. No patient felt any form of discomfort when skin and muscle were being manipulated. Eleven patients (17.7%) had discomfort when peritoneum was being manipulated in Group B, none in other two groups. This difference between Group B as compared to Group C and A was highly significant (P-value = 0.0001). Thirteen patients (21.0%) had discomfort when intestine was being manipulated in Group B, none in the other two groups. The difference in Group B as compared to Group A and C was statistically significant (P-value = 0.0001).

Using frequency of intra-operative pain (minimum of VAS score of 40mm) and discomfort following intestinal and peritoneal manipulation, the intra operative symptoms of inadequate block were assessed and shown in Table VIII. A total of 29 patients (46.8%) in Group B had one of these intra-operative pain and discomfort but none was observed in Group A and Group C, the difference was highly statistically significant (P-value=0.0001). This signified that 29 patients (46.8%) in Group B significantly had inadequate anaesthesia whereas no patient (0.0%) in Groups A and C had inadequate anaesthesia.

Figure 1 shows the trend in pulse rate over time. The difference in base line pulse rate among the three groups was not statistically significant (P-value = 0.42). The differences in mean pulse rates at 3min, 6min, 9min, 12min and 15min did not achieve any statistical significance at each of these time interval (P-values= 0.71, 0.65, 0.32, 0.15 and 0.97 respectively.) Also difference in the mean pulse rate at 18min, 23min, 28min, 33min, and 38min showed statistical insignificance (P-values = 0.11, 0.27, 0.39, 0.26 and 0.78 respectively.) However the difference in the mean pulse rate among the three groups at 43min, 48min, and 53min was statistically significant (P-values = 0.01, 0.07 and 0.012 respectively.)
The trend in systolic blood pressure over time is shown in figure 2. Intra-operative trend in systolic blood pressure showed a fall in systolic blood pressure at 3min, 6min, 9min, 12min and 15min. The difference in base line mean systolic blood pressure did not achieve any statistical significance (P-value = 0.085.)

The difference in mean systolic blood pressure at 3min, 6min, 9min, 12min and 15min among the three groups were statistically insignificant (P-values = 0.32, 0.58, 0.45, 0.25 and 0.069; respectively.) The mean value of systolic blood pressure at 18min, 23min, 28min and 33min did not achieve any statistical significant difference (P-values = 0.24, 0.31, 0.98 and 0.37 respectively.) The difference in the mean systolic blood pressure at 38min, 43min, 48min and 53min was statistically significant (P-values = 0.041, 0.001, 0.001 and 0.015 respectively.) Trends in diastolic blood pressure and mean arterial blood pressure over time are illustrated in figure 3 and 4 and they were similar to the trend observed with systolic blood pressure.

Table IX shows incidence of intraoperative complications. None of the patients in Group A and C had any complaint of pain, chest tightness, vomiting, retching or nausea. Five patients (8.1%), 7 patients (11.1%), and 3 patients (4.8%) in Group B reported pain, chest tightness and vomiting respectively. The difference in the incidence of pain or chest tightness was statistically significant (P-value=0.011 or 0.001 respectively.) Three patients (4.8%) had episodes of nausea and another three (4.8%) had retching in Group B. The difference in the incidence of vomiting, nausea or retching among the three groups was not statiscally significant (P-value=0.108, 0.108 or 0.108 respectively.) No patients in Group A and Group C had bradycardia whereas one patient (1.6%) in Group B had bradycardia. This signifies that there was no statistically significant difference among the three groups (P-value = 1.000.) Fifteen (24.2%), 13 (20.9%) and 15 (24.5%) patients respectively in Groups A, B and C had hypotension. The difference in the incidence of
hypotension among the three groups was not statistically significant (P-value = 0.886.) Shivering occurred in 3 patients (4.8%) in Group B but was not observed in Group A or C which was not statistically significant (P-value = 0.108.) Itching was significantly higher in Group A (P-value= 0.035.) Four patients (6.5%) in Group A had itching, none was observed in Group B and C. Paraesthesia occurred in one patient (1.6%) in Group A none was observed in Group B or C. The difference was not significant when compared Group A with Group B and C (P-value = 1.000.)

Figure 5 shows changes in VAS scores over time post-operatively. Median VAS score at 30min in Group B was significant compared with median VAS scores of Groups A and C (P-value = 0.02.) The difference in the median VAS scores at 1, 2, 3, 4 and 5 hours was statistically significant (P-values= 0.036, 0.001, 0.033, 0.04 and 0.024 respectively.) However the difference in the median VAS scores among the three groups at the 6th and 7th hour did not achieve any statistical significance (P-values= 0.78 and 0.21 respectively.) The difference was not significant at 8, 9 and 12 hours (P-value=0.49, 1.00 and 0.72 respectively) but was significant at the 11th hour (P-value=0.034.) This was significant because the same dosing regime of analgesic was given to all the patients, resulting in more patients in placebo group to have mild to moderate pain in most of the hours but more marked at 11th hour.

Figure 6 shows duration of pain free period in minutes. This was taken as the period between injection of spinal solution and the time the patient requested for first rescue analgesic or the time the patient had VAS score equal or greater than 40mm. Mean and standard deviation time for Group A with regard to first analgesic request was 304 ±67.91 min, Group B was 146.59 ± 36.62 min and Group C was 238.39 ± 61.28 min. Inter group comparison of duration of pain relief was done using Mann-Whitney test of significance. The difference in the duration of pain relief was highly significant when
comparing duration of pain relief in Groups B and C (P-value = 0.001). The difference in the duration of pain free period between patients in Group A and Group C showed statistical significance (P-value = 0.001). Also there was a statistically significant difference in duration of pain free period between Group A and Group B (P-value = 0.001). This signified that the longest duration of pain relief was observed in Group A as compared to Group C and Group B. However Group C had significant longer duration of pain free period than Group B.

Table X shows incidence of post-operative complications. Apart from headache and vomiting, there were no other complications within 12 hours postoperatively among the study population. One patient (1.6%) complained of headache post operatively in Group A but no such complaint was reported in Group B and Group C. The difference in the incidence of the headache amongst the three groups was statistically insignificant (P-value = 1.000.) The incidence of vomiting occurred in 2 patients (3.2%) in Group A as compared to 3 patients (4.8%) in Group B and 10 patients (16.1%) in Group C. The incidence of post-operative vomiting was significant statistically (P-value=0.016.)

Table XI shows the degree of patient’s satisfaction for each group. Every patient was satisfied in Group A and C but 17 patients (27.4%) in Group B were not satisfied with the quality of analgesia produced. This difference was highly significant statistically (P-value = 0.0001.) Forty six patients (73.8%) and 45 (72.1%) in Groups A and C respectively were excellently satisfied with the analgesia as compared to 21 (33.9%) in Group B. The difference was highly significant (P-value = 0.0001.)

Table XII shows degree of surgeon’s satisfaction for each group. No surgeon in Group A reported dissatisfaction but 18 patients (29%) in Group B and 1 patient (1.6%) in Group C had their surgeons reporting dissatisfaction. The difference was significant (P-value = 0.0001.)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 62) Mean ± SD</th>
<th>Group B (n = 62) Mean ± SD</th>
<th>Group C (n = 62) Mean ± SD</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.58 ± 1.37</td>
<td>28.79 ± 1.34</td>
<td>28.55 ± 1.23</td>
<td>0.54</td>
</tr>
<tr>
<td>Height (metres)</td>
<td>1.65± 0.01</td>
<td>1.64±0.01</td>
<td>1.65± 0.01</td>
<td>0.17</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.34 ± 1.25</td>
<td>67.32 ± 1.48</td>
<td>68.84 ± 1.71</td>
<td>0.56</td>
</tr>
<tr>
<td>Sex distribution [n(%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (37.1%)</td>
<td>25 (40.3%)</td>
<td>22 (35.5%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Female</td>
<td>39 (62.9%)</td>
<td>37 (59.7%)</td>
<td>40 (64.5%)</td>
<td></td>
</tr>
<tr>
<td>ASA Status [n(%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>56 (91.5%)</td>
<td>57 (91.9%)</td>
<td>55 (88.3%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6 (8.5%)</td>
<td>5 (8.1%)</td>
<td>7 (11.7%)</td>
<td>0.83</td>
</tr>
<tr>
<td>Interspace</td>
<td>Group A (n = 62) No (%)</td>
<td>Group B (n = 62) No (%)</td>
<td>Group C (n = 62) No (%)</td>
<td>P. value</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>L2L3</td>
<td>2 (3.2)</td>
<td>6 (9.7)</td>
<td>3 (4.8)</td>
<td>0.391</td>
</tr>
<tr>
<td>L3L4</td>
<td>60 (96.8)</td>
<td>56 (90.3)</td>
<td>59 (95.2)</td>
<td>0.391</td>
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</table>
Table III: SENSORY LEVEL ATTAINED AFTER SPINAL BLOCK

<table>
<thead>
<tr>
<th>Time</th>
<th>Group A (n = 62)</th>
<th>Group B (n = 62)</th>
<th>Group C (n = 62)</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>Median (range)</td>
<td>Median (range)</td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>T9(T7 – T11)</td>
<td>T10(T8 – T11)</td>
<td>T10(T8 – T10)</td>
<td>0.470</td>
</tr>
<tr>
<td>2 mins</td>
<td>T5(T4 – T8)</td>
<td>T7(T6 – T9)</td>
<td>T8(T5 – T10)</td>
<td>0.065</td>
</tr>
<tr>
<td>3 mins</td>
<td>T4(T2 – T6)</td>
<td>T6(T5 – T8)</td>
<td>T6(T4 – T7)</td>
<td>0.059</td>
</tr>
<tr>
<td>4 mins</td>
<td>T4(T2 – T6)</td>
<td>T6(T4 – T6)</td>
<td>T4(T2 – T6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Dermatome</td>
<td>Group A (n = 62) No (%)</td>
<td>Group B (n = 62) No (%)</td>
<td>Group C (n = 62) No (%)</td>
<td>P. value</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>T2</td>
<td>15 (24.2)</td>
<td>0 (0.0)</td>
<td>8 (12.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>T4</td>
<td>36 (58.1)</td>
<td>12 (19.7)</td>
<td>35 (56.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>T6</td>
<td>11 (17.7)</td>
<td>50 (80.3)</td>
<td>19 (30.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Classification of Pain (VAS Score)</td>
<td>Group A (n = 62) No (%)</td>
<td>Group B (n = 62) No (%)</td>
<td>Group C (n = 62) No (%)</td>
<td>P. value</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>No Pain (0)</td>
<td>62 (100.0)</td>
<td>55 (88.7)</td>
<td>62 (100.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild Pain (1 – 39)</td>
<td>0 (0.0)</td>
<td>2 (3.2)</td>
<td>0 (0.0)</td>
<td>0.330</td>
</tr>
<tr>
<td>Moderate (40 – 69)</td>
<td>0 (0.0)</td>
<td>4 (6.5)</td>
<td>0 (0.0)</td>
<td>0.035</td>
</tr>
<tr>
<td>Severe Pain (70 and above)</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Table VI: DISCOMFORT FOLLOWING INTESTINAL MANIPULATION

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 62) No (%)</th>
<th>Group B (n = 62) No (%)</th>
<th>Group C (n = 62) No (%)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Retching</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Dragging sensation</td>
<td>0 (0.0)</td>
<td>8 (12.9)</td>
<td>0 (0.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Chest Tightness</td>
<td>0 (0.0)</td>
<td>7 (11.3)</td>
<td>0 (0.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Parameter</td>
<td>Group A (n = 62) No (%)</td>
<td>Group B (n = 62) No (%)</td>
<td>Group C (n = 62) No (%)</td>
<td>P. value</td>
</tr>
<tr>
<td>-------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>-------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Skin</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Muscle</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>0 (0.0)</td>
<td>11 (17.7)</td>
<td>0 (0.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Intestine</td>
<td>0 (0.0)</td>
<td>13 (21.0)</td>
<td>0 (0.0)</td>
<td>0.0001</td>
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</table>
### Table VIII: INTRAOPERATIVE SYMPTOMS OF INADEQUATE BLOCK

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n = 62) No (%)</th>
<th>Group B (n = 62) No (%)</th>
<th>Group C (n = 62) No (%)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0 (0.0)</td>
<td>5 (8.1)</td>
<td>0 (0.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>0 (0.0)</td>
<td>7 (11.3)</td>
<td>0 (0.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dragging sensation</td>
<td>0 (0.0)</td>
<td>8 (12.9)</td>
<td>0 (0.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Retching</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Incomplete Block</td>
<td>0 (0.0)</td>
<td>29 (46.8)</td>
<td>0 (0.0)</td>
<td>0.0001</td>
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</table>
### Table IX: INTRA-OPERATIVE COMPLICATIONS

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group A (n = 62) No (%)</th>
<th>Group B (n = 62) No (%)</th>
<th>Group C (n = 62) No (%)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>0 (0.0)</td>
<td>5 (8.1)</td>
<td>0 (0.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>0 (0.0)</td>
<td>7 (11.3)</td>
<td>0 (0.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Retching</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypotension</td>
<td>15 (24.2)</td>
<td>13 (20.9)</td>
<td>15 (24.2)</td>
<td>0.886</td>
</tr>
<tr>
<td>Shivering</td>
<td>0 (0.0)</td>
<td>3 (4.8)</td>
<td>0 (0.0)</td>
<td>0.108</td>
</tr>
<tr>
<td>Itching</td>
<td>4 (6.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.035</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Complication</td>
<td>Group A (n = 62) No (%)</td>
<td>Group B (n = 62) No (%)</td>
<td>Group C (n = 62) No (%)</td>
<td>P. value</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (3.2)</td>
<td>3 (4.8)</td>
<td>10 (16.1)</td>
<td>0.016</td>
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</table>
Table XI: DEGREE OF PATIENT’S SATISFACTION FOR EACH GROUP

<table>
<thead>
<tr>
<th>Satisfaction</th>
<th>Group A (n = 62) No (%)</th>
<th>Group B (n = 62) No (%)</th>
<th>Group C (n = 62) No (%)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not satisfied</td>
<td>0 (0.0)</td>
<td>17 (27.4)</td>
<td>0 (0.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Satisfied</td>
<td>5 (8.2)</td>
<td>8 (12.9)</td>
<td>7 (11.5)</td>
<td>0.676</td>
</tr>
<tr>
<td>Very satisfied</td>
<td>11 (18.0)</td>
<td>16 (25.8)</td>
<td>10 (16.4)</td>
<td>0.351</td>
</tr>
<tr>
<td>Excellent</td>
<td>46 (73.8)</td>
<td>21 (33.9)</td>
<td>45 (72.1)</td>
<td>0.0001</td>
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</tbody>
</table>
Table XII: DEGREE OF SURGEON'S SATISFACTION FOR EACH GROUP

<table>
<thead>
<tr>
<th>Satisfaction</th>
<th>Group A (n = 62)</th>
<th>Group B (n = 62)</th>
<th>Group C (n = 62)</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td></td>
</tr>
<tr>
<td>Not satisfied</td>
<td>0 (0.0)</td>
<td>18 (29.0)</td>
<td>1 (1.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Satisfied</td>
<td>4 (6.6)</td>
<td>11 (17.7)</td>
<td>5 (8.2)</td>
<td>0.090</td>
</tr>
<tr>
<td>Very satisfied</td>
<td>12 (19.7)</td>
<td>13 (21.0)</td>
<td>11 (17.7)</td>
<td>0.902</td>
</tr>
<tr>
<td>Excellent</td>
<td>46 (73.8)</td>
<td>20 (32.3)</td>
<td>45 (72.6)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
0 = Baseline

**Figure I:** Trend in Pulse Rate (beats/min) over Time
Figure 2: Trend in Systolic Blood Pressure (mmHg) over Time
**Figure 3:** Trend in Diastolic Blood Pressure (mmHg) over Time.

0 = Baseline
Figure 4: Trend in Mean Arterial Blood Pressure over Time
Figure 5: Trend in post-operative median VAS score over Time
Fig. 6: Time of First Analgesic Requirements (minutes)
CHAPTER FIVE
DISCUSSION

The results showed that intrathecal tramadol and intrathecal fentanyl were effective in mitigating visceral pain and discomfort during bupivacaine subarachnoid block for appendicectomy.

The study showed that the addition of intrathecal fentanyl and intrathecal tramadol to hyperbaric bupivacaine for spinal anaesthesia in patients who underwent appendicectomy significantly improved the quality of intraoperative analgesia without increasing the side effects such as respiratory depression, nausea, vomiting, hypotension, bradycardia or shivering.

This study further demonstrated that most patients and surgeons were very satisfied with intrathecal tramadol and fentanyl in mitigating visceral pain and discomfort during bupivacaine subarachnoid block for appendicectomy. These visceral pain and discomfort result from peritoneal and intestinal manipulation during appendicectomy. Peritoneum and intestine have innervations as high as T₄, therefore any level of sensory block below T₄ may result in visceral pain and discomfort. In some cases, a maximum height of sensory block (T₄) for appendicectomy may not be attained if intrathecal 0.5% hyperbaric bupivacaine is used alone; hence the need to add intrathecal opioid to bupivacaine for management of visceral pain and discomfort that are manifested during appendicectomy.

In this study, a placebo group was used as comparison, but there exists the options of using either a contemporary standard drug and/or placebo as a comparator. Thomas et al. in the United Kingdom argued that it was unethical to protect a group when all patients were actually exposed to the same high risk procedures. The fact that 3mls of 0.5% hyperbaric bupivacaine is being used, without addition of opioid, in this
environment justified its use as placebo in this study. Selvaraju et al in South Africa\textsuperscript{37} and Akpa et al\textsuperscript{38} in Nigeria both administered 3mls of 0.5% hyperbaric bupivacaine to all the patients they studied. In this study, 3mls of 0.5% heavy bupivacaine was chosen because, for more than three years in our centre, 2.5-3mls of 0.5% heavy bupivacaine is given intrathecally to non-obstetric population (2.2-2.5mls for obstetric population) without intrathecal opioid, but to our knowledge, there is paucity of result concerning the use of subarachnoid block for appendicectomy. Hence, the need to use 3mls of 0.5% heavy bupivacaine plus 0.5ml of normal saline as control, compared with intrathecal fentanyl and tramadol. This thus provides local study of the drugs.

Experimental studies have shown that addition of opioids to local anaesthetic agent intrathecally was able to relieve visceral pain and discomfort.\textsuperscript{51,52} Apart from the works of Parthasarathy et al\textsuperscript{10}, Susmita et al\textsuperscript{11}, Alhashemi et al\textsuperscript{41} and Frikha et al,\textsuperscript{42,44} many researches have not been carried out on intrathecal administration of tramadol especially for procedures such as appendicectomy.

The dose regime used in this study was based on the study carried out by Belzarena\textsuperscript{29} which demonstrated that intrathecal fentanyl 0.5 – 0.75 µg/kg provided excellent surgical anaesthesia. Mean intrathecal fentanyl doses used by Techanivate et al\textsuperscript{2} in their study were 0.18 and 0.33 µg/Kg. In this present study fixed dose (25µg) of fentanyl was used. Based on the average weight of patients in the fentanyl Group, the average intrathecal dose of fentanyl used in this study was 0.36µg/Kg. This dose was more than the dose used by Techanivate et al\textsuperscript{2} but less than the dose used by Belzarena.\textsuperscript{29} Twenty five milligram of intrathecal tramadol was considered adequate for the study based on the work carried out by Alhashemi\textsuperscript{41} where 25mg of intrathecal tramadol was proven to be safe during spinal anaesthesia. Although Frickha et al\textsuperscript{44} used 50mg tramadol, Parthasarathy\textsuperscript{10} used 10mg and Susmita\textsuperscript{11} used 20mg of tramadol in their
studies but 25µg of fentanyl is equipotent with 25mg of tramadol according to report by Duthie.\textsuperscript{53} He also reported that tramadol has the same analgesic potency as pethidine, one fifth (1/5) that of nalbuphine, one-tenth (1/10) that of morphine and one-thousandth (1/1000) that of fentanyl.

One of the advantages of using intrathecal fentanyl is its rapid onset.\textsuperscript{52} This study demonstrated that intrathecal fentanyl and intrathecal tramadol had faster onset and higher level of block than placebo. This was in agreement with the study conducted by Singh et al\textsuperscript{54} where fentanyl mean onset time was found to be $2.72 \pm 1.51\text{min}$. Although in the same study sufentanil mean onset time was shorter $1.88 \pm 0.92\text{min}$. In another study, Cherng et al\textsuperscript{55} concluded that epidural injection of the mixture of 100µg fentanyl and 2% lidocaine solution accelerated the onset of sensory block. Bogra et al\textsuperscript{34} also found that onset time of sensory block to T\textsubscript{6} was faster with the group that received intrathecal fentanyl during spinal anaesthesia for Caesarean section. This was in agreement with the work of Motiani et al\textsuperscript{52} who demonstrated that intrathecal fentanyl 25µg as adjuvant led to an earlier onset compared with placebo.

The result of the present study differed from the observations of Techanivate et al\textsuperscript{2} and Singh et al\textsuperscript{12} who, in different studies, demonstrated that intrathecal fentanyl did not enhance onset of sensory block during bupivacaine subarachnoid block. The onset time to T\textsubscript{4} sensory block in this present study did not agree with that of Techanivate et al\textsuperscript{2} probably because a high volume dose (4mls) of 0.5% bupivacaine was used as against 3mls in this study. This high volume was enough to cause a rapid onset in the three groups studied by them. It was documented by Bogra et al\textsuperscript{34} and Randalls et al\textsuperscript{57} in separate trials that the onset of sensory block to T\textsubscript{4} was faster with increasing bupivacaine doses.
Pain and discomfort are major problems during subarachnoid block for appendicectomy.\textsuperscript{2} In this present study, all patients who had intrathecal fentanyl and intrathecal tramadol had complete sensory block (no patient had any form of pain or discomfort) whereas only thirty-three patients (53.2\%) in placebo group had complete sensory block \{29 patients (46.8\%) patients had pain or discomfort\} which was significant when comparing placebo with fentanyl groups or tramadol (P-value = 0.0001). This agrees with Techanivate et al\textsuperscript{2} that demonstrated complete sensory block in the patients that received either 20µg or 10µg of fentanyl as compared with the placebo group which had complete sensory block in only 65\% of patients. This is also in agreement with Bogra et al\textsuperscript{34} who demonstrated that fentanyl was required to abolish visceral pain experienced by pregnant women during Caesarean section. The need to add intrathecal opioid to bupivacaine whenever peritoneum and intestine will be manipulated was supported by numerous researchers\textsuperscript{2,12,54} in different studies. Other studies have demonstrated the need to add opioids to local anaesthetic in order to improve intra-operative analgesia.\textsuperscript{30,31,32,36,52} Intrathecal tramadol is capable of mitigating visceral pain and discomfort as observed by Parthasarathy et al,\textsuperscript{10} Alhashemi et al\textsuperscript{41} and Susmita et al\textsuperscript{11}. Their finding is supported by the finding in this study.

In this study, time to first analgesic request was significantly prolonged in fentanyl group compared with placebo group (304.73 versus 146.59 minutes P-value = 0.0001). This result corroborates the findings of Techanivate et al,\textsuperscript{2} in which time to first request for postoperative analgesic was significantly prolonged when comparing fentanyl group with placebo group (11.0 hours versus 4.7 hours respectively, P-value < 0.05). The time to first request for analgesic in the fentanyl group was much longer when comparing studies of Techanivate et al with this present study. This was probably due to a high volume of heavy bupivacaine administered. It has been reported that increasing doses of
bupivacaine leads to increased duration of action.\textsuperscript{34,56} The trial conducted by Belzarena\textsuperscript{30} also supported the result of this study. The patients in the fentanyl group who received 25µg fentanyl had longer postoperative analgesia (305min) compared with placebo group (197min) and this was statistically significant amongst the obstetric population studied.

John et al\textsuperscript{57} achieved prolonged sensory and motor block when 25µg of fentanyl with 12mg of bupivacaine was administered to a particular group of patients. They found that time to first analgesic requirement was 617min in fentanyl group compared with 418min in placebo group; this was in support of the study of Mutiani et al\textsuperscript{52} that reported a prolonged duration of sensory block with 25µg fentanyl. This was also in agreement with results obtained by other researchers for varying types of procedures, including Caesarean section, lower limb surgery and labour analgesia.\textsuperscript{19,28,58,59} The average duration of analgesia produced by lipophilic opioid (fentanyl and sufentanil) is between 2 and 5 hours whereas that of hydrophilic opioid (morphine) is between 12 and 24 hours.\textsuperscript{60,61} The longer duration observed by John et al might be due to involvement of analgesia for somatic pain as opposed visceral pain.

Intrathecal tramadol, according to this study, prolonged postoperative analgesia with time for analgesic request of 238.39min compared with placebo group with mean time for analgesic request of 146.59min. This difference was highly statistically significant (P-value = 0.001.) This is similar to the work of Partharasathy and co-workers\textsuperscript{10} who demonstrated that intrathecal tramadol prolonged post-operative analgesia. The time for first analgesic request was statistically significantly prolonged in tramadol group (310 minutes) while it was 131 minutes in the control group. They concluded that a single dose of intrathecal tramadol is a useful tool to overcome postoperative pain, especially in the initial stages and lesser necessity for advanced
monitoring equipment. Also, the result from Susmita et al\textsuperscript{11} study showed that the duration of analgesia provided by intrathecal administration of 20mg tramadol with 15mg of 0.5% hyperbaric bupivacaine significantly prolonged postoperative analgesia after major gynaecological surgeries. In contrast to the above studies, Alhashemi et al\textsuperscript{41} demonstrated that there were no differences between the study groups with regard to postoperative morphine requirement. They then concluded that intrathecal tramadol was not different from saline in its effect on postoperative morphine requirement after TURP. Alhashemi et al\textsuperscript{41} postoperative analgesic study failed to achieve any significance, because intramuscular morphine 5mg was given to all the study groups every 3 hours. Five milligram of morphine intramuscularly was enough to alleviate pain and alter pain score produced from VAS scores.

Side-effects are mediated by opioid receptors.\textsuperscript{62,63} Segmental analgesia after intrathecal opioids administration should confer a lower side-effect profile compared with systemic opioids administration. A recent prospective survey of 6000 patients reported a low incidence of side effects and good patients’ satisfaction after single administration of low dose intrathecal opioids.\textsuperscript{36} The side effects of intrathecal opioids are sedation, sweating, delayed gastric emptying, urinary retention, pruritus, nausea and vomiting and respiratory depression.\textsuperscript{64} Previous studies have suggested that side-effects are dose-related.\textsuperscript{29} High dose intrathecal opioids administered in error may result in an acute apnoeic episode requiring naloxone and supportive ventilation.

This clinical trial also compares the trends of haemodynamic changes following induction of spinal anaesthesia using bupivacaine with or without opioids. The findings in this study support the hypotension episodes recorded from the study carried out by reseachers which showed no significant difference in the episode of hypotension between fentanyl group and control group.\textsuperscript{2,19,57} Alhashemi et al\textsuperscript{41} and Frikha et al\textsuperscript{44} found that
intrathecal tramadol did not affect blood pressure which was in agreement with the findings of Parthasarathy et al\textsuperscript{10} and this present study. This signified that intrathecal opioid did not significantly cause hypotension, the episodes of hypotension in these different studies was probably due to the effect of different doses of bupivacaine.

In this present study, no patient had bradycardia in fentanyl and tramadol groups. One patient (1.6\%) had bradycardia in placebo group. One patient in group 20 had bradycardia, no one had bradycardia in groups 10 and 0 in Techanivate et al\textsuperscript{2} study. There was no significant difference in the incidence of bradycardia amongst the study population of John et al.\textsuperscript{57}Bogra et al\textsuperscript{34} reported that bradycardia resulted from the blockade of sympathetic cardio-accelerator fibres and decreased venous return to the heart. In their study, bradycardia occurrence was overall 7\%, with no significant intergroup variation. This supported the findings of Parthasarathy,\textsuperscript{10} Alhashemi\textsuperscript{41} and Susmita.\textsuperscript{11}

Shivering occurrence did not achieve any significant difference when comparing patients in tramadol group with fentanyl and control groups. No patient in fentanyl group and tramadol group had shivering but three (4.8\%) patients in control had shivering according to this study. This was not in accordance with Techanivate et al\textsuperscript{2} who observed shivering in fourteen patients (70\%) in placebo group and nine (45\%) and eight (40\%) in the groups with 10µg fentanyl and 20µg of fentanyl respectively. The difference was significant (P-value = 0.05). This might be due to the sympatholytic effect of high dose of intrathecal bupivacaine used in their study (4ml) of 0.5\% as against 3ml of 0.5\% that was used in this present study. Biswas et al,\textsuperscript{19}Bogra et al\textsuperscript{34} found no significant difference in the episodes of shivering. However, Wheelahan\textsuperscript{65} reported that adding epidural fentanyl to epidural lidocaine decreases the shivering threshold compared with epidural lidocaine
alone. Petel et al.\(^6\) demonstrated that intrathecal fentanyl was significantly better than intravenous fentanyl and placebo in the prevention of intra-operative shivering.

In this study, itching occurrence was 6.5% in the fentanyl group with significant intergroup variation. In the similar study conducted by John et al.\(^5\) nine patients (33.3%) out of 27 with intrathecal fentanyl had itching intra-operatively and finding from these studies also corroborated finding of Hunt et al.\(^6\) Techanivate et al.\(^2\) did not record any itching episode amongst their study population. Unlike John et al.\(^5\), Techanivate\(^2\) and this present studies recorded lower incidence of itching probably because higher doses of hyperbaric bupivacaine were administered when compared with the dose administered by John et al.\(^5\). It has been documented that local anaesthetic agent and dextrose independently decrease the incidence of pruritus when added to intrathecal fentanyl solution.\(^68,69\) This might be attributed to low dose of intrathecal fentanyl used (10µg and 20µg) in the two groups treated with fentanyl. Biswas,\(^1\) Bogra et al.\(^3\) and Dahlgren et al.\(^7\) reported no significant difference in the incidence of pruritus among the study population. Parthasarathy\(^10\) and Susmita et al.\(^11\) recorded no itching in the group treated with tramadol in their studies which was in agreement with this present study. Frickha et al.\(^4\) finding was not in support of Parthasarathy\(^10\), Susmita\(^11\) and this present study by reporting more episodes of itching in the tramadol group. The high incidence of itching reported by Frickha\(^4\) might be associated with high dose of opioids (50mg of tramadol plus 10µg of fentanyl) administered to each of the patients in one of the groups in the obstetric population studied.

High anaesthetic level of block also results in respiratory compromise,\(^7\) which can be managed by conversion to general anaesthesia.\(^7\) Reuben et al.\(^2\) reported that none of the patients who received intrathecal fentanyl up to 50µg experienced respiratory depression, even in elderly patients who had cardiac and pulmonary diseases. Also in the
study carried out by Techanivate,\textsuperscript{2} none of the patients experienced respiratory rate < 12 cycles per minute and SPO\textsubscript{2} < 92\% during the operation. This was in support of this study, no patient had respiratory depression and SPO\textsubscript{2} never dropped below 95\%.

One patient (1.6\%) in this study had post-dural puncture headache. This was observed in the fentanyl group. This complication is usually associated with the use of large bore needles for spinal anaesthesia, generally the larger the bore of the needle the bigger the opening left in the meninges.\textsuperscript{73,74} This allows cerebrospinal fluid to escape, lowering CSF pressure. Because of the increased incidence of post-dural puncture headache with large bore needle\textsuperscript{38,75} 25G Quincke needles were used. In a series of spinal anaesthetics using 16 guage needles, headache constituted the most common complication, as high as 18\% of the patients, developed post-dural puncture headache.\textsuperscript{38}

Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla, possibly through delta receptors. This, combined with opioid receptors on gastro-intestinal tract, promotes nausea and vomiting. There is little evidence suggesting that one opioid is consistently more emetogenic than the other.\textsuperscript{38}

Post operative vomiting was highest in the tramadol group in this study. Ten (16.1\%) patients had vomiting in tramadol group versus 3 (4.8\%) and 2 (3.2\%) in the placebo and fentanyl groups respectively. This was significantly high compared with the work of Parthasarathy,\textsuperscript{10} where only (4\%) of the patients vomited post-operatively among 25 patients administered with intrathecal tramadol. Since incidence of vomiting is dose dependent, the difference between Parthasarathy’s study and this study in terms of post-operative vomiting might be due to low dose (10mg) of intrathecal tramadol administered to each of the patients in the tramadol group by Parthasarathy and colleagues.\textsuperscript{10} Frikha et al\textsuperscript{42} recorded more frequency in vomiting. This might be due to
high dose (50mg) of intrathecal tramadol injected into subarachnoid space of each of the pregnant women scheduled for Caesarean section.
CONCLUSION

This study shows that intrathecal tramadol 25mg is equipotent with 25µg of intrathecal fentanyl in mitigating intra-operative pain and discomfort following peritoneal and intestinal manipulation during bupivacaine subarachnoid block for appendicectomy.

The intrathecal opioids both produce comparable haemodynamic changes and post-operative analgesia with minimal peri-operative side effects.
STUDY LIMITATION

Ideally, an opioid like pethidine should have been used as rescue analgesic but because of its non availability during the period of study, pentazocine was substituted.
RELEVANCE OF STUDY

Effective subarachnoid block enables the anesthesiologist to employ simple, safe and cheap anaesthesia for every patient scheduled for appendicectomy. This common surgical emergency in Nigeria deserves some anaesthetic attention.

According to this study, use of preservative-free tramadol or fentanyl in addition to bupivacaine spinal block will result in adequate sensory block for almost all patients scheduled for appendicectomy. This study showed that intrathecal tramadol (25mg) is equipotent intra-operatively with intrathecal fentanyl (25µg) in mitigating pain and discomfort following intestinal manipulation during appendicectomy. Since tramadol is cheap and available, Nigerian anaesthetists can now utilize its benefits of intrathecal administration in the management of appendicectomy and avoid patient’s pain and discomfort that follow intestinal and peritoneal manipulation.
RECOMMENDATIONS

1. Effort should be made by anesthesiologist to make sure that at least a minimum height of sensory block at T6 is reached before appendicectomy is commenced. This usually occurs about 4 minutes after induction of spinal anaesthesia.

2. In situations where fentanyl is unavailable, intrathecal tramadol at a dose of 25mg can be used. It is safe, cheap, effective and readily available.
REFERENCES


APPENDIX I
ETHICAL CLEARANCE

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DIRECTOR OF ADMINISTRATION:
S. O. IDUBOR
(IRS: MPH, Health Admin, & Planning, Tennessee, APHA)

ETHICS AND RESEARCH COMMITTEE

CLEARANCE CERTIFICATE

PROTOCOL NUMBER: ADM/E.22 A/VOL. VII/416

PROJECT TITLE: INTRATHecal TRAMADOL VERSUS FentanyL FOR VISCERAL PAIN
CONTROL DURING BUPIVACAINe SUB-ARACHNOID BLOCK FOR
APPENDICECTOMY

PRINCIPAL INVESTIGATOR(S): DR. AFOLAYAN JIDE M

DEPARTMENT/INSTITUTION: ANAESTHESIOLOGY, UNIVERSITY OF BENIN
TEACHING HOSPITAL, BENIN CITY.

DATE CONSIDERED: 21ST JULY 2010

DECISION OF THE COMMITTEE: APPROVED

REMARK:

CHAIRMAN: PROF. I. EVBUEMWN SIGNATURE & DATE: 21/7/2010

Supervisors: DR. F.E. AMADASUN; DR. (MRS) P.N. EDOMWONYI

DECLARATION BY INVESTIGATOR(S)

PROTOCOL NUMBER (Please quote in all enquiries)

To be completed in four and three copies returned to the Secretary, Ethics and Research Committee,
medical Services and training division, University of Benin teaching hospital, Benin City.

I/We fully understand the conditions under which I am/we are authorized to conduct the above-
mentioned research and I/We undertake to resubmit the protocol to the Ethics and Research
Committee.

Signature: [Signature] Date: 4th August, 2010

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APPENDIX II

PROFORMA ON INTRATHECAL TRAMADOL VERSUS INTRATHECAL FENTANYL FOR VISCERAL PAIN CONTROL DURING BUPIVACAINE SUB-ARACHNOID BLOCK FOR APPENDICECTOMY

1. Serial Number_________________________  2) Group Number
3. Hospital Number________________________  4) Height/Age____________
5. Weight_______________________________  6) Sex____________________
7. ASA status____________________________
8. Baseline Pulse Rate____________________  Blood Pressure___________
   Respiratory rate_______________________  SPO2____________________
9. Position during lumbar puncture___________
10. Volume of N/saline for preloading________
11. Inter current medical ailment___________
12. Needle size and type____________________
13. Lumbar interspace used________________
14. Dose of bupivacaine____________________
15. Type of spinal solution used:  A, B, or C
16. Time of injection of spinal solution______
17. Baseline PR........BP ........ SPO2........ RR.......... Level of maximum block........
18. PR, RR, BP, SPO2

<table>
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19. Onset of Sensory Block

<table>
<thead>
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20. VAS SCORE following skin incision

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<th>9min</th>
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</table>

21. Time of skin incision____________________

22. Supplementary analgesic agent: Type___________ Time___ Dose__

23. Supplementary anti emetic agent: Type___________ Time___ Dose__

24. Other supplementary agents: Type___________ Time___ Dose___

25. Rescue general anaesthesia: Time_______________ Type________

Why____________________________

26. Intraoperative complications

Hypotension          Paraesthesia          Inadequate block
Shivering          Bradycardia          Others__________
Respiratory distress Itching
Metallic taste          High spinal

27. Discomfort following visceral manipulations

Vomiting              Pain              Others__________
Relching            Chest tightness
Nausea              Dragging sensation

28. Anatomical level in which discomfort is first noticed.

Skin       Muscle       Peritoneum        Intestine

29. Time surgery ended______________

30. VAS score at the end of surgery ____________
31. Duration of surgery in minutes_____________

32. Postoperative VAS score.

<table>
<thead>
<tr>
<th>Time</th>
<th>30mins</th>
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<th>3hr</th>
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</table>

33. Postoperative complications
   - Headache
   - Backache
   - Vomiting
   - Difficulty in voiding
   - Others________

34. Time of first analgesic requirement postoperatively____________

35. Duration of pain free________________________

36. Degree of patient’s satisfaction
   - Not satisfied
   - Satisfied
   - Very satisfied
   - Excellent

37. Degree of surgeon’s satisfaction:
   - Not satisfied
   - Satisfied
   - Very satisfied
   - Excellent
VISUAL ANALOGUE SCALE

0mm — 100mm

0 = No Pain
1-39mm = Mild Pain
40-69mm = Moderate pain
70mm and above = Severe pain
100mm = Worst pain