A COMPARATIVE STUDY OF INTRATHECAL FENTANYL AS ADJUVANT TO HYPERBARIC BUPIVACAINE FOR POST CESAREAN SECTION ANALGESIA AT MUHIMBILI NATIONAL HOSPIAL

Ulimbakisya Jonathan Kain (MD)

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By

Ulimbakisya Jonathan Kain

A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree of Master of Medicine (Anaesthesiology) of

Muhimbili University of Health and Allied Sciences
October, 2017

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled ‘‘**A *Comparative Study of Intrathecal Fentanyl as Adjuvant to Hyperbaric Bupivacaine for Post Cesarean Section Analgesia at Muhimbili National Hospital.*’’** in (partial) fulfillment of requirements for the degree of Master of Medicine in (Anaesthesiology) of Muhimbili University of Health and Allied Sciences.

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Dr. Edwin .R. Lugazia
Head of Department Anaesthesiology-MUHAS
(Supervisor)

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Date

DECLARATION AND COPYRIGHT

I, **Ulimbakisya Jonathan Kain** declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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DEDICATIONS

I would like to dedicate the results of this study to my lovely wife Beatrice Musira and my children Giana Ulimbakisya and Galvin Ulimbakisya. Thank you!

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LIST OF ABBREVIATIONS

ASA-American Society of Anaesthesiologists

C/S-Cesarean Section

CSF-Cerebral Spinal Fluid

DBP-Diastolic Blood Pressure

GA-General Anaesthesia

HR-Heart Rate

IASP-International Association for the Study of Pain

IVL-Intravenous Line

LA‘s-Local Anaesthetics

LSCS-Lower Segment Cesarean Section

MAP-Mean Arterial Blood pressure

MNH-Muhimbili National Hospital

MOHCDGEC- Ministry of Health, Community Development, Gender, Elderly and Children

MOI-Muhimbili Orthopaedic Institute

MUHAS-Muhimbili University of Health and Allied Sciences

NIBP-Non Invasive Blood Pressure

NPO-Nil per Oral

NSAD's-Non Steroidal Ant inflammatory Drugs

PONV-Post Operative Nausea and Vomiting

POP-Post Operative Pain

SBP-Systolic Blood Pressure

SAB-Subarachnoid Block

SPO_2-Arterial Blood Oxygen Saturation

DEFINITION OF KEY TERMS

Pain- Unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such tissue damage (IASP).

Hypotension -Decrease in systolic blood pressure of more than 20% of baseline value.

Bradycardia - Fall in pulse rate below 60 beats per minute.

Respiratory depression - Respiratory rate less than 10 breaths per minute.

SUMMARY

BACKGROUND

Spinal anaesthesia sometimes referred as subarachnoid block (SAB) is the preferred technique for cesarean section for most women, it is simpler to perform and presence of cerebral spinal fluid gives a more certain end point and hence higher degree of success, It has advantage of rapid onset, less drug use with minimum neonatal depression as well as less incidence of aspiration pneumonitis. It produces fixed duration of anaesthesia and also intraoperative hypotension.

Due to fixed duration of anaesthesia after cesarean section there comes the need of addition post operative analgesics. Supplementation of analgesics after cesarean using spinal anaesthesia has been a challenge and this has been attributed by the fact that individuals have different threshold for pain onset since pain is unpleasant sensation may result in devastating effects to individuals.

Addition of intrathecal opioids to local anaesthetic agents have shown to be beneficial due to the reason that it leads to reduction of the dose of local anesthetic agent to be used resulting to less side effects such as intraoperative hypotension, hemodynamic instability but also provide prolonged early postoperative analgesia with good neonatal outcome. Side effects associated with the use of bupivacaine are dose dependent hence this can be overcome by lowering the dose of local anaesthetic agent and mixing it with additive such as fentanyl.[1]

BROAD OBJECTIVE

To determine the duration of post cesarean section analgesia of intrathecal fentanyl as an adjuvant to hyperbaric bupivacaine in post cesarean section patients at Muhimbili National Hospital.

METHODOLOGY

This study was a single blinded controlled Study which was conducted at Muhimbili National Hospital, Dar-es-Salaam, Tanzania. The study duration was about six months beginning from July 2016.Study population included patients who underwent cesarean section under spinal anaesthesia using hyperbaric bupivacaine coadministered with or without fentanyl.

Preoperatively a thorough history, physical examination and airway assessment was done using a special designed form. Patients were divided into two groups by simple random selection one group was given Intrathecal heavy bupivacaine while the other group was given intrathecal heavy bupivacaine combined with fentanyl. Intraoperatively data recording was done using a special designed form and all intraoperative vitals were monitored and recorded throught the procedure as well as fetal outcome.

Patients were followed up to 24 hours post operative with special designed questionnaire to record duration of post operative analgesia, additional post operative analgesics including their doses and frequency, type and occurrence of associated side effects.

Data was analyzed using SPSS version 11.0 software. Categorical variables were presented as frequency while continuous variables were presented as mean. Chi-square analysis and student t-test was utilized in analysis of categorical and continuous variables respectively. All analysis was two-sided and the level of significance was set at value of $P< 0.05$.A sum total of one million and five hundread thousands, Tanzanian shillings (1,500,000/=Tshs) was used to conduct the study.

INTRODUCTION

The choice of Anaesthetic technique to be used for cesarean section depends on the indication for the surgery, degree of urgency, patient's choice and the clinical judgment of anaesthesiologist. Spinal Anaesthesia is the best anaesthetic technique for lower segment cesarean section as it is simple to perform with rapid onset, complete muscle relaxation, lower incidence of failed block, less drug usage, minimal neonatal depression, reduced incidence of PONV as well as decreased incidence of aspiration pneumonitis.[1]

Spinal anaesthesia is a form of regional anaesthesia, it involves inserting the needle and injecting local anaesthetic agent though the intervertebral space at the level of lumbar 3-4 or at 5-6 into the subarachnoid space to minimize the chances of causing injury to the spinal cord. It has a number of complications which are mainly a result of physiological changes of the block as well as the technique used.

Complications resulting from subarachnoid block may be immediate which includes, intraoperative hypotension and bradycardia which are secondary to sympathetic blockage, nausea and vomiting, high or total spinal as well as pruritus if opioids are used as adjuvants. Delayed complications includes, headache, urinary retention, hematoma, infections, meningitis, epidural abscess, neurological damage to the spinal cord secondary to direct trauma, impaired ventilation if opi**o**ids are coadministered with local anaesthetic agents or during high block.

Since the discovery of opiate receptors in the brain and spinal cord the use of intrathecal opioids has become a common practice as effective method of analgesia. Hydrophilic opioids particularly gives good selective spinal analgesia because it has small volume of distribution and slower clearance from spinal cord however slow spinal cord penetration and prolonged duration in the cerebral spinal fluid results in slow onset, prolonged duration of action and delayed respiratory depression from rostral spread in the cerebral spinal fluid.

Fentanyl is short acting lipophylic opioid which acts on μ receptors, it has rapid onset of action compared to Morphine following intrathecal administration. It inhibits ascending pain pathways hence increasing pain threshold to produce analgesia. Analgesia has been reported to occur within 5-10 minutes following its administration. It is highly protein bound 80-85% and

elimination half life of 2-4 hours. It is metabolized in the liver by enzyme CYP3A4 and its excretion is mainly through urine(75%) also in feces(9%).It does not migrate to the 4th ventricle in sufficient concentration following intrathecal administration as the result augmenting the quality of subarachnoid block without increasing the risk of delayed respiratory depression so this makes it safe alternative than morphine.[2]

It is one of the most widely used agent and commonly added to intrathecal bupivacaine in cesarean delivery by many anaesthesiologists, as it improves quality of anaesthesia without producing significant side effects and improves post-operative analgesia and hemodynamic stability.

Addition of Opioids to local anaesthetics for spinal anaesthesia was first introduced into clinical practice in 1979 with intrathecal morphine as forerunner. Thereafter opioids have gained popularity as it was found to improve the quality of intraoperative analgesia and increasing duration of early postoperative analgesia.

They are commonly added to local anaesthetics for potentiating, reducing their doses and thereby reducing their complications and side effects and offer hemodynamic stability. They also prolong the duration of post-operative analgesia. [2, 3]

For decades lignocaine has been the local anaesthetic of choice for Spinal anaesthesia, unfortunately recent reports of lignocaine neurotoxicity (Caudal equina syndrome) have cast doubts on its use for spinal anaesthesia. Some studies reported incidence of adverse reactions following the use of lignocaine for spinal anaesthesia such as dysaesthesia in buttocks, thigh or lumbar region.

Bupivacaine was introduced by Ecknstam in 1957 and used clinically by Telivno in 1963, hyperbaric bupivacaine is now being used with opioids for almost all surgical cases**.** It belongs to amide group containing local anaesthetics with Pka of 8.1 and 95% protein binding. The primary mechanism of action of local anesthetics is blockade of voltage-gated sodium channels.

Heavy bupivacaine is a common drug used for spinal anaesthesia due to its characteristic of high potency and the dose of 12-15mg is said to be sufficient. During cesarean section traction of peritoneum and handling of intraperitoneal organs occurs resulting into intraoperative visceral

pain, this can be overcome by increasing the dose of hyperbaric bupivacaine but increasing the dose of bupivacaine increase the risk of high block.[3]

LITERATURE REVIEW

Researchers around the world have been trying to demonstrate the duration of post operative analgesia when different opioids are coadministered intrathecally with local anaesthetic agent, different opioids have been used such as morphine and fentanyl.

In 2006 Bano et al tried to demonstrate the effect of intrathecal fentanyl as an adjuvant to hyperbaric bupivacaine in spinal anaesthesia for cesarean section. During this study 12.5mg of 0.5% bupivacaine and 20 micrograms of fentanyl were used. It was found that there was no difference in the onset and maximum height of sensory block with the addition of fentanyl however fentanyl significantly increased the duration of both complete and effective analgesia with fewer side effects of intraoperative nausea and vomiting and bradycardia. Pruritus was the main side effect in the group receiving fentanyl but was of mild intensity hence did not require treatment also there was no effect in neonatal Apgar score.[1]

In 2005 Bogra et al studied the synergistic effect of intrathecal fentanyl and bupivacaine in spinal anaesthesia for cesarean section and it was found that low dose of fentanyl 25mcg used as adjuvant to intrathecal 0.5% hyperbaric bupivacaine provides various advantages which are better intra operative analgesia, good hemodynamic stability, less complications like nausea and vomiting and shivering and prolonged effective analgesia in post operative period. Due to synergistic action with bupivacaine, it helps in reduction of the dose of bupivacaine for spinal anaesthesia hence reduces the incidence of side effects associated with it and assures better quality of anaesthesia without compromising the safety of mother as well as neonate.[2]

In 2014 Gomaa et al did comparison between post-operative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after cesarean section. It was concluded that either intrathecal nalbuphine 0.8mg combined with 10mg bupivacaine or intrathecal fentanyl 25mcg combined with bupivacaine 10mg improves intra-operative analgesia and prolongs early post-operative analgesia in cesarean section. Addition of intrathecal opioids was seen to reduce the dose requirements of local anaesthetic agent hence less incidence of side effects.[3]

In 1999 J.Roussel et al demonstrated the effects of intrathecal fentanyl on duration of bupivacaine spinal blockade for outpatient knee arthroscopy and it was found that fentanyl 25mcg intrathecally did not prolong sensory or motor block when combined with spinal bupivacaine 12mg for outpatient knee arthroscopy patients who receive 25mcg fentanyl had a prolonged post operative analgesia. It was also found that the incidence of side effects which are intraoperative hypotension, Nausea and vomiting was less in the group receiving fentanyl and this was found to be dose dependent.[4]

In 2001 Karamen et al tried to demonstrate the effects of morphine and fentanyl alone or in combination added to intrathecal bupivacaine in spinal anaesthesia for cesarean section. This study utilized 0.2mg of morphine and it was demonstrated that 0.2 mg of intrathecal morphine is as effective as 25mcg fentanyl for intraoperative analgesia and produce better post operative analgesic quality than fentanyl in addition to that it was also seen that the incidence of side effects such as nausea and vomiting, respiratory depression was not significant but the incidence of Pruritus was seen to be higher which necessitated pharmacological intervention when compared to the group which received fentanyl in other studies.[5]

In 2002 N.Biswas et al tried to demonstrate the effect of addition of intrathecal fentanyl to hyperbaric bupivacaine to improve analgesia during intraoperative as well as early post-operative period. During this study 12.5mg of heavy bupivacaine with 25micrograms of fentanyl were used The results concluded that 12.5mcg of fentanyl added with hyperbaric 0.5% bupivacaine 12.5mg for spinal anaesthesia would markedly improve intraoperative anaesthesia and significantly reduced the demand for both intraoperative as well as early postoperative analgesia with good maternal and foetal well being, there was no significant differences between the two groups in terms of Apgar score. In terms of side effects the incidence of Intraoperative hypotension as well as nausea and vomiting was less in the group receiving Fentanyl compared to the group receiving only 0.5% heavy bupivacaine. Pruritus was less which did not necessitate pharmacological intervention.[6]

In 2003 Ogun et al did comparison of intrathecal isobaric bupivacaine-morphine for cesarean delivery, It showed that morphine-ropivacaine combination provides similar sensory block and postoperative analgesia, shorter duration of motor block, less ephedrine requirement similar APGAR scores and umbilical pH values and similar side effects in cesarean section operations

when compared with morphine-bupivacaine which in turn concluded that there was less statististically significance in terms of side effects.[7]

In 2005 Lane et al tried to compare intrathecal fentanyl and diamorphine as adjuvants in spinal anaesthesia for cesarean section, they concluded that Diamorphine 0.25mg gives analgesia equal to fentanyl 15microgram during surgery for LSCS with no significant increase in time to achieve block or increase in systemic side effects. Post operative diamorphine 0.25mg gives analgesia greater than fentanyl 15mcg with no increase in systemic side effects.[8]

In 2009 Salmah et al compared morphine with fentanyl added to Intrathecal 0.5 percent hyperbaric bupivacaine for analgesia after cesarean section. In conclusion, the results of this study showed that the addition of 0.1mg of morphine to 1.8ml 0f 0.5% hyperbaric bupivacaine in spinal anaesthesia provided satisfactory and longer duration of analgesia after cesarean section as compared with the addition of 25mcg fentanyl to 1.8ml of 0.5% hyperbaric bupivacaine.[9]

In 2014 Hillman et al tried to compare the effect of adding Midazolam to fentanyl bupivacaine in cesarean section on the duration and quality of spinal anaesthesia with monitoring of the adverse effects, It was found that Midazolam fentanyl bupivacaine group had prolonged duration of intra and post operative analgesia, duration of motor blockage and reduced post operative analgesic requirements. Also it causes more intraoperative sedation, less intraoperative shivering and less postoperative nausea and vomiting with no effect on the newly born infant. Using 1.8mls hyperbaric bupivacaine 0.5% in cesarean section was associated with cardiovascular stability and less respiratory depression.[10]

In 2014 G.Chavan et al demonstrated the effects of intrathecal fentanyl on subarachnoid block with 0.5% hyperbaric bupivacaine during cesarean section it was found that fentanyl 25mcg mixed as an adjuvant to intrathecal 0.5% hyperbaric bupivacaine offers various advantages which include better surgical analgesia, reduces the intra operative need of analgesic supplement, delays time of post operative rescue analgesia and minimal side effects. Hence it may be recommended that 25mcg fentanyl is safe and promising drug to be added with 0.5%hyperbaric bupivacaine for spinal anaesthesia. In addition to this patients were stable hemodynamically

throughout the procedure which was an advantage in reducing the side effect of nausea and vomiting.[11]

In 2015 Rao et al did evaluation of effective low dose bupivacaine with fentanyl in spinal anaesthesia for LSCS surgeries and it was found that addition of fentanyl 25mcg to 0.5% hyperbaric bupivacaine 6mg and 7mg was effective for spinal anaesthesia in cesarean section surgeries with minimum side effects. Combination of 8mg and 9mg of 0.5% bupivacaine with fentanyl 25mcg were also beneficial in cesarean section surgeries as they provide prolonged duration of early post operative analgesia when compared to 6mg and 7mg but the same combinations were also associated with more side effects and longer duration of motor block which may interfere with early ambulation, Addition of an opioid such as fentanyl did not produce any adverse effects in the mother or the neonate.[12]

STATEMENT OF THE PROBLEM

Comfort after surgery and fear from unrelieved pain remain as the major concerns for patients because poorly managed acute pain can impact negatively on their recovery from surgery discouraging them from early mobilization due to discomfort resulting into increase in morbidity and extend the length of hospital stay.

In our set up pain management post cesarean section is given routinely and not individualized as all patients are given injection Pethidine 100mg immediately after caesarian section and then after every 8hours for 24 hours, then switched to im/oral analgesics mostly NSAID'S particularly Diclofenac, although there is no study done in Tanzania to support this, so patients are not given enough when they need and also has cost implications.

Intrathecal coadministration of hyperbaric bupivacaine with opioids has shown to be effective in prolonging postoperative analgesia with minimal side effects as well as better maternal and neonatal outcomes. Little has been researched on this subject in Tanzania and to the best knowledge of the investigator this will be the first study in this subject.

RATIONALE/JUSTIFICATION

Provision of better intraoperative as well as postoperative analgesia has the potential to not only reduce post operative pain but also to minimizes post operative analgesia requirements and possibly promotes early ambulation and hospital discharge.

This study aims to provide information to practicing anaesthesilogists and guideline developers on the effects of fentanyl as an adjuvant when coadministered with hyperbaric bupivacaine in improving the quality of care of women undergoing caesarean section.

RESEARCH QUESTION

1. What is the duration of post cesarean section analgesia among the patients receiving intrathecal fentanyl with hyperbaric bupivacaine and hyperbaric bupivacaine at MNH?

2. What are the associated side effects within 24 hours among the patients receiving intrathecal fentanyl with hyperbaric bupivacaine at MNH?

OBJECTIVES

Broad Objective

To determine the duration of post cesarean section analgesia of intrathecal fentanyl as an adjuvant to hyperbaric bupivacaine in post cesarean section patients at Muhimbili National Hospital.

Specific Objectives

1. To compare the duration of post cesarean section analgesia among the patients receiving intrathecal fentanyl with hyperbaric bupivacaine and hyperbaric bupivacaine alone.

2. To determine the associated side effects within 24 hours among the patients receiving intrathecal fentanyl with hyperbaric bupivacaine and hyperbaric bupivacaine alone.

HYPOTHESIS

Coadministration of intrathecal fentanyl with hyperbaric bupivacaine in patients undergoing lower segment cesarean section at MNH will provide better intraoperative as well as early postoperative analgesia which in turn reduces the need for rescue and additional postoperative analgesia promoting early patient ambulation and hospital discharge.

METHODOLOGY

Type of Study

Single blinded Controlled Study.

Study Area

This study was conducted at the Muhimbili National Hospital (MNH) in Dar-es- salaam, Tanzania. MNH is a National Referral Hospital, Research center and University Teaching Hospital. It is the largest in the country providing services to residents of Dar –es- Salaam and all other regions in Tanzania. It has 1,500 bed capacities, attending 1,000 to 1,200 outpatient's week, admitting 1,000 to 1,200 inpatients per week.

It has 3000 employees of which 300 are doctors and specialists, 900 registered & enrolled nurses and the rest are supporting operations employees. The hospital has 17 operating rooms and averages of 100000 elective surgeries are done annually. Obstetrics has two operating rooms and one big recovery area which can accommodate three postoperative patients at once with three monitors, the important vital parameters which are monitored include Non invasive blood pressure (NIBP), Pulse rate, Electrocardiogram, Temperature, Urine output and the duration of stay at the recovery room may go up to two hours and averages of 10-20 cesarean sections are done daily.

Study duration

The study was conducted in about six (6) months period.

Study population

The study population included patients undergoing cesarean section under spinal anaesthesia using hyperbaric bupivacaine coadministered with or without fentanyl.

Inclusion Criteria

1. Those who are ASA I and ASA II.

Exclusion Criteria

1. Patients having contraindications to spinal Anaesthesia.

2. Patients with known allergies to these drugs.

Sample Size (N) Calculation

$$N= (Z_{\alpha/2} + Z_{\beta/2})^2 \times \frac{\ln [(1+ \theta)/(1-\theta)]^2}{P_1 + P_2}$$

Where $\theta = \ln (1 - P_1) / \ln (1 - P_2)$

N=Sample size

P_1=Proportion of participants with side effects among control group i.e 36.66%(2)

P_2=Proportion of participants with side effects among test group i.e 16.66%(2)

α=Type I error

β=Type II error

$\theta=\ln(1-0.3666)/\ln(1-0.1666)$

$\theta=2.51$

$$N= (1.96+0.84)^2 \times \frac{[(1+2.51)/(1-2.51)]^2}{(0.3666+0.1666)}$$

N=79 Patients per group

DATA COLLECTION

Selection Method

All Patients who met the inclusion criteria were enrolled into the study. Recruitment was done starting with provision of information regarding the study. All the patients who consented to participate in the study were then randomized into two groups which were group 1 and 2 of which group one are those who were be given only 0.5% of heavy bupivacaine and group 2 are those who were given mixture of preservative free fentanyl and 0.5% heavy bupivacaine. The principal investigator, who was not blinded, prepared a box with folded papers and patients were given a chance to pick one folded paper. The chosen paper indicated into which group the patient was allocated after which they were requested to sign the consent form for participation in the study.

Preoperative anaesthetic assessment

Pre-operative anaesthetic assessment was done which included thorough history and physical examination, Airway assessment by Mallampatti grading then Patients signed the consent form for surgery.

Intraoperative procedures

As the patient enter the operating room, a 16-18 gauge intravenous cannula was inserted and pre-loading with 20mls/kg of 0.9% Normal saline or Lactated Ringers solution was started. The patient was connected to the standard monitors. The baseline non-invasive blood pressure, mean arterial pressure, pulse rate respiratory rate and arterial blood oxygen saturation were recorded.

The principal investigator, who was not blinded in the study, prepared the study drugs. Then patients belonging to group 1 were given 10mg of 0.5% hyperbaric bupivacaine (2mls) and patients group 2 was given 10mg of 0.5% hyperbaric bupivacaine (2ml) with 25 mcg preservative free fentanyl (0.5ml) intrathecally.

Administration of drugs was done after aseptic technique following lumbar puncture performed with 25 gauge quinckle needle in the L3-L4 space in the sitting position. Time was recorded immediately following administration of the drugs in a special designed form attached in the appendices. The cardio–respiratory parameters which are non invasive blood pressure mean

arterial pressure, pulse rate, respiratory rate and arterial blood oxygen saturation continued to be monitored at interval of one (1) minute in the first fifteen (15) minutes then at the interval of five (5) minutes throughout the surgery. Apgar score was recorded at 1 and 5 minutes respectively after delivery of the baby.

Occurrence of side effects was monitored immediately following administration of the drugs at the interval of one (1) minute in the first fifteen (15) minutes and at the interval of fifteen (15) minutes for the remainder of procedure thereafter at the interval of 30 minutes until twenty four hours.

Postoperative procedures

Postoperatively patients were followed in their respective wards to monitor the associated side effects which are Nausea and Vomiting, Pruritus, shivering, and respiratory depression which was recorded in a special designed form attached in the appendices. Post operative pain was assessed by the use of standard 10 centimeter linear visual analog scale. Patients with moderate pain which correspond with the range of 4-6 cm were started on injection pethidine 100 mg eight hourly for 24 hours.

Data Analysis

SPSS version 23.0 software was used for all statistical analyses. Categorical variables were presented as frequency while continuous variables were presented as mean. Chi-square analyses and student t-test was utilized in analysis of categorical and continuous variables respectively. All analyses were two-sided and the level of significance was set at value of $P< 0.05$.

Ethical Consideration

After being given permission to do the study, investigator introduced himself to each individual patient and gave explanation on what the study would be about before asking the patient to participate in the study. Only patients who gave consent were enrolled for the study. All the examinations, tests and investigation methods were procedural, that is, the ones usually done for any patient during preoperative visit. Patients had right to withdrawal from the study.

The investigator was supervised by specialists in the field who was available to guide and assist in case of any problem. The patients' information and results of any test performed were handled confidentially.

The patients in the study were all healthy ASA I and II. Patients were handled the same way they are being handled routinely, without exposing them to any additional risk. All anticipated complications which are Intraoperative hypotension, Nausea and vomiting, Pruritus, Shivering as well as Respiratory depression were handled accordingly, all drugs and equipments were ready.

Ethical Clearance

The proposal was presented to the department of Anesthesiology of Muhimbili University of Health and Allied Sciences. Ethical clearance was thereafter sought from the Research and Publication committee of the Muhimbili University of Health and Allied Sciences and permission to do the study was obtained.

RESULTS

Table 1 displays socio-demographic and clinical characteristics of participants. Between July 2016 to January 2017, we recruited 159 participants. 79 were randomized to group 1 and 80 randomized to group 2. Overall, the mean age was 30.4 (4.6) years. Majority of participants were married (95.5%). With regards to occupation, 83.7% were self employed and the unemployed participants constituted 3.8%. The mean hemoglobin of our cohort was 11.8 g/dL and their mean weight was 71.4 kilograms. Nearly 60% of the participants had blood group O+ and group A- constituted the least (0.6%).

Table 1. Socio-demographic profiles and clinical characteristics of participants at baseline

Characteristic	Overall	Group 1	Group 2	P-value
Age(Years)	30.4 (4.6)	30.2(4.8)	30.5(4.4)	1.0
Marital status				
Single	7 (4.4%)	4(5.1%)	3(3.8%)	0.7
Married	152 (95.6%)	75(94.4%)	77(96.2%)	0.6
Occupation				
Student	5 (3.1%)	2(2.5%)	3(3.7%)	0.7
Unemployed	6 (3.8%)	3(3.8%)	3(3.7%)	1.0
Employed	15 (9.4%)	8(9.4%)	7(8.8%)	0.8
Self employed	133 (83.7%)	66(83.6%)	67(83.8%)	1.0
Weight(Kg)	71.4 (6.6)	71.5(5.9)	71.9(5.3)	1.0
Hemoglobin(g/dL)	11.8 (0.7)	11.8(0.7)	11.8(0.7)	1.0
Blood group				
A+	26 (16.3%)	16(20.3)	10(12.5%)	0.2
A-	1 (0.6%)	0(0%)	1(1.3%)	0.3
B+	37 (23.3%)	17(21.5%)	20(25.0%)	0.6
O+	95 (59.8%)	46(58.2%)	49(61.3%)	0.7

Both groups are similar at baseline as shown in the table above.

Table 2. Duration of Post cesarean section analgesia in minutes by study group.

Group	Observations	Mean	Range	P-value
1(Control)	79	120.6 (23.6)	97-228	<0.001
2(Fentanyl)	80	219.1 (18.0)	142-291	

Complete analgesia lasted longer in group 2(Fentanyl) with the Mean of 219.1 minutes compared to group 1(Control) with the mean of 120.6 minutes, $p<0.001$, as shown in the table above.

Table 3. Comparison of within 24 hours side effects between the two study groups.

Side effects	Group 1(Control)	Group 2(Fentanyl)
Nausea and Vomiting	0	0
Pruritus	0	0
Shivering	0	0
Respiratory depression	0	0
Hypotension	8 (10.1%)	7 (8.8%)
bradycardia	0	0

On comparative analysis of side effects between the two study groups, nausea and vomiting, pruritus, shivering, respiratory depression and bradycardia were not reported by participants in either group. 10.1% and 8.8% of participants in group 1 and group 2 respectively experienced hypotension, however this difference was not statistically different/significant ($p>0.05$).

Table 4. Comparison of Apgar score at 1 and 5 minutes between the two study groups.

APGAR SCORE	Group 1(Control)	Group 2(fentanyl)
<3	0(0%)	0(0%)
4-6	0(0%)	0(0%)
7-10	79(100%)	80(100%)

There is no difference in neonatal Apgar Scores between the two study groups as shown in the table above.

DISCUSSION

The use of general anaesthesia in obstetric patients has been associated with higher mortality rates as compared to regional anaesthesia which has lead to increased use of regional anaesthesia technique. Intrathecal administration of fentanyl is a method to supplement intraoperative anaesthesia as well as for early postoperative analgesia. Following its administration it spreads into cerebral spinal fluid and moves to the opioid receptors and other non specific binding sites in the spinal cord and rostral migration via the cerebral spinal fluid to supraspinal areas. Due to the fact that fentanyl has high affinity for non specific binding sites on the lipid surface only a small proportion of the administered dose migrates to the cervical region.[1]

Intrathecal and epidural administration of Fentanyl at a dose of 12.5 mcg and 50-100 mcg respectively was shown to provide postoperative analgesia for a mean duration of 3-4 hours in a study by Biswas et al and Naulty et al.[6] In consonance to Biswas, this present study found that coadministration of intrathecal Fentanyl (25 mcg) and 0.5% hyperbaric bupivacaine (10mg) provided a mean postoperative analgesia of 3.7 hours. Furthermore, findings of a study by Chavan et al were in unison with this present study as it demonstrated mean postoperative analgesia of 3.5 hours following coadministration of 25mcg of preservative free fentanyl as adjuvant to 15mg of 0.5% hyperbaric bupivacaine. [11] A more recent study by Rao et al which utilized addition of a 25mcg dose of fentanyl to 0.5% hyperbaric bupivacaine 6mg/7mg displayed prolonged duration of analgesia of about 4.3 hours.[12] The variation in duration of postoperative analgesia among studies could be explained by differences in population specifics as well as differences in dosages of fentanyl used.

In this study 8(10.1%) patients belonging to group 1(control) and 7(8.8%) patients belonging to group 2(fentanyl) experienced hypotension episodes of which in both groups it was treated by IV fluids and none of them required pharmacological treatment with vasopressor Ephedrine 3mg which was already prepared in case of a life threatening hypotension. None of the patients from both study groups experienced Nausea and vomiting, pruritus, shivering, bradycardia or respiratory depression. Our findings are similar to those in a study by Bogra et al showed no side effects when fentanyl (25mcg) was coadministered with hyperbaric bupivacaine (7.5 mg).[2] Similarly a study by Biswas et al demonstrated near similar rates of side effects in the 0.5%

hyperbaric bupivacaine arm versus the fentanyl and 0.5% hyperbaric bupivacaine arm.[6] These results affirms the safeness of fentanyl when coadministered with 0.5% hyperbaric bupivacaine.

This study observed no differences in neonatal Apgar scores among the two groups. Such findings are supported by the study done by Biswas et al in 2002 which found that co administration of fentanyl and 0.5% hyperbaric bupivacaine had no effects on the neonatal Apgar scores.[6] Similarly, studies by Bogra et al, Chavan et al, and Rao et al showed no effect in the neonatal Apgar scores.[2, 11, 12] In this present study we chose the dose of fentanyl of 25microgram because it was a dose that was commonly used among published studies that proved to be safe and efficacious.[6, 11, 12]

Study Limitation

This study recruited fairly healthy (ASA I and II) participants and thus our findings might not be generalizable to persons with severe disease (ASA III-VI).

CONCLUSION

In conclusion, the findings of this study show that addition of 25micrograms of preservative free fentanyl to 0.5% hyperbaric bupivacaine for spinal anaesthesia markedly improves both intraoperative as well as early postoperative analgesia. Such effect significantly reduces the demand for rescue and additional postoperative analgesia. Furthermore addition of fentanyl had minimal side effects with good maternal as well as fetal outcome.

RECOMMENDATIONS

The findings of this study calls for addition of fentanyl to 0.5% hyperbaric bupivacaine among women undergoing cesarean section at MNH and in Tanzania at large as it has the potential to improve both maternal and fetal outcomes.

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Appendix

Appendix 1

Pre-anesthetic evaluation form:

A COMPARATIVE STUDY OF INTRATHECAL FENTANYL AS ADJUVANT TO HYPERBARIC BUPIVACAINE FOR POST CAESAREAN SECTION ANALGESIA AT MUHIMBILI NATIONAL HOSPITAL.

Patients Demographics

Hospital ID #…….

Age: …..Years

Weight….. (Kg)

Height… (Cm)

Occupation……

Marital Status…….

Indication for lower segment cesarean section:

General and Physical examination:

Cardiovascular system:

Respiratory system:

Oral cavity:

Airway assessment (Mallampati classification):

Neck:

Spine:

Laboratory investigations Results:

Hb:

MCV:

MCH:

PLT:

Hct:

Blood group:

ASA Grade:

INTRAOPERATIVE REPORTING FORM

IVL secured in _____with 16-18G and 0.9%NS/ RL started.

PRELOADING:

20mls/kg

TIME OF SAB:

GROUP 1-Preservative free bupivacaine 10mg (2mls)

GROUP 2-Preservative free bupivacaine 10mg (2mls) with Preservative free Fentanyl 25mcg (0.5mls).

INTRAOPERATIVE MONITORED VITAL PARAMETERS

		BP(mmhg)	PR(beats/min)	MAP(mmhg)	RR(breaths/min)	SPO_2(%)
Baseline						
	1min					
	2min					
	3min					
	4min					
	5min					
	6min					
	7min					
	8min					
	9min					
	10min					
	11min					
	12min					
	13min					
	14min					

	15min					
	20min					
	25min					
	30min					
	35min					
	40min					
	45min					
	50min					
	55min					
	60min					

NEONATAL OUTCOME.

PARAMETER	
Uterine incision to delivery time(mts)	
APGAR SCORE AT 1min	
APGAR SCORE AT 5min	

Duration of Surgery …….. (Minutes)

POST OPERATIVE REPORTING FORM

PARAMETER	
Time of Subarachnoid block	
Time requiring additional analgesic (in minutes)	
Type of analgesic Given and route	
Dose and frequency of analgesic given	

SIDE EFFECTS

PARAMETER	
Nausea and Vomiting	
Pruritus	
Shivering	
Respiratory depression	
Hypotension	
Bradycardia	

Appendix 2

CONSENT FORM TO PARTICIPATE IN THE RESEARCH

TITTLE: A COMPARATIVE STUDY OF INTRATHECAL FENTANYL

AS ADJUVANT TO HYPERBARIC BUPIVACAINE FOR

POST CESAREAN SECTION ANALGESIA AT MNH

Dear Sir/Madam,

Greetings, My names are Dr. Ulimbakisya Kain, a resident doctor in the Department of anaesthesia at MUHAS. I am conducting a study regarding Intrathecal fentanyl as adjuvant to hyperbaric bupivacaine for post cesarean section analgesia at Muhimbili national hospital.

I am requesting your participation.

PURPOSE OF THE STUDY

To Evaluate Analgesic benefits of Fentanyl Coad ministered with hyperbaric Bupivacaine in Post Cesarean Section patients under Spinal Anaesthesia at Muhimbili National hospital.

HOW TO PARTICIPATE

Patients who will be ready to participate will sign this consent form to approve his/her willingness.

CONFIDENTIALITY

Information obtained from you will be confidential and will be of help in this study and better care for this group of patients in future.

COSTS

You will not be required to pay anything or paid anything for your participation in the study.

VOLUNTARY PARTICIPATION AND RIGHTS TO WITHDRAW

Your participation is voluntary and you have the right to withdraw from participating in our study at any time before the procedure. Whatever your decision may be, it will not affect in any way, your rights to care and treatment.

RISKS We do not expect any risk due to low dose of the study drug.

BENEFITS

You will as well get the benefit of getting appropriate treatment as per need.

We hope that the information from this research will be useful in contributing to improve the quality of care in daily procedures and develop appropriate protocol.

CONTACT PERSONS:

If you have any inquiries about this study, please do not hesitate to contact:

Dr.Ulimbakisya Kain

Principal Investigator

Muhimbili University of Health and Allied Sciences (MUHAS)

Department of Anesthesiology

P.O. Box 65001 Dar Es Salaam.

Tel. +255 715 173625

The Director

Research and Publication Committee

Muhimbili University of Health and Allied Sciences (MUHAS)

P.O. Box 65001 Dar-es-Salaam

Tel: 2150302-6

I will be grateful if you would agree to participate in this study.

I (Initials) _____

Have understood the above information and my questions have been answered by the investigator to my satisfaction. I willingly agree to take part in this research.

Name of the participant: _____

Signature of the participant: _____Date _____

Signature of Investigator _____ Date: _____

Appendix 3

FOMU YA MAKUBALIANO YA KUSHIRIKI KATIKA UTAFITI

Habari! Mimi Dk. Ulimbakisya Kain, ni Daktari katika shahada ya Uzamili katika Chuo Kikuu Cha Afya na Sayansi shirikishi Muhimbili. Nafanya utafiti kuhusu dawa ya Bupivacaine ikichanganywa na fentanyl inayosaidia kupunguza na kucheleweshа kuhisi maumivu kwa wagonjwa , wanaofanyiwa upasuaji wa uzazi katiaka hospitali ya taifa ya Muhimbili.

Ninaomba ushirikiano wako.

Nia ya Utafiti;

Dhumuni nikujua na kuamua ufanisi wa dawa ya Bupivacaine ikichanganywa na fentanyl kwa wagonjwa wa upasuaji wa uzazi hapa katika hospitali ya Taifa ya Muhimbili.

Jinsi ya Kushiriki:

Mgonjwa ambaye yuko tayari kushiriki ataweka sahihi yake, ili kuonyesha utayari. Yatafuata maswali machache ya Utangulizi, kasha vipimo kama uzito, urefu, shinikizo la damu na kiwango cha mapigo ya moyo itapimwa na kuwekwa kumbukumbu.

Usiri:

Taarifa ya matokeo hazitatangazwa kwa yoyote zaidi ya mtafiti. Matokeo ya utafiti kwa ujumla yatasaidia kuboresha huduma ya tiba kwa wagonjwa wajawazito wakati wa upasuaji hapa Hospitali ya Taifa yaMuhimbili.

Gharama:

Hutatakiwa kulipa gharama yoyote kwa kushiriki kwako.

Utayari wakushiriki au kujitoa:

Kushiriki kwako ni hiyari na waweza kujitoa. Lakini haitakunyima haki ya kupata tiba zingine.

Hatari:

Hatutarajii hatari kutokana na dozi ya chini ya utafiti.

Faida:

Kushiriki kwako katika utafiti huu kutakusaidia kujua na kuamua ufanisi wa dawa ya Bupivacaine ikichanganywa na fentanyl kwa wagonjwa wa upasuaji wa uzazi hapa katika hospitali ya Taifa ya Muhimbili.Pia utafaidika kupata matibabu halisia kama itakavyokuwa inahitajika.

Nitakushukuru kwa kushiriki kwako kwenye utafiti huu. Ahsante.

Iwapo utakuwa na swali lolote kuhusu utafiti huu wasiliana na Dkt.Ulimbakisya Kain, Chuo Kikuu Cha Afya na Sayansi za Tiba Muhimbili; Idara yaTiba; S.L.P 65001

Dar-es-salaam. Simu +255 715 17 36 25.

AU

Endapo utakuwa na swali lolote kuhusu haki zako kama mshiriki katika utafiti huu wasiliana na:

Mkurugenzi wa kamati ya utafiti na matoleo chuoni.

Chuo Kikuu Cha Afya na Sayansi za Tiba Muhimbili

S.L.P 65001 Dar-es-Salaam

Tel: 2150302-6

Mimi……nimeelezwa/nimesoma yaliyomo katika fomu hii na nimeelewa maana yake. Nakubali kushiriki katika utafiti huu.

Sahihi……..(Mshiriki) Tarehe……..

Sahihi…….. (Mtafiti) Tarehe……..

Appendix 4:

MUHIMBILI NATIONAL HOSPITAL

Cables: "MUHIMBILI"
Telephones: +255-22-2151367-9

FAX: +255-22-2150534
Web: www.mnh.or.tz

Postal Address:
P.O. Box 65000

DAR ES SALAAM
Tanzania

15/07/2016

In reply please quote:
MNH/TRC/Research/2016/047

Dr. Ulimbakisya J. Kain

RE: PERMISSION TO COLLECT DATA AT MNH: 2016/047

Name of Student	Ulimbakisya J. Kain
Title	Comparative study of intrathecal fentanyl as adjuvant to hyperbaric bupivacaine for post cesarean section analgesia at Muhimbili National Hospital
Institution	MUHAS
Supervisor	Dr. Edwin Lugazia
Period	15th July 2016 – 15thJanuary 2017

You have been permitted to collect data in respect to the undertaking of the above mentioned study.

Please ensure that you abide to the ethical principles and other conditions of your approval.

Sincerely,

Dr. Faraja Chiwanga
Ag. Head of Teaching, Research and Consultancy Coordination Unit

Cc: HOD – Anaesthesiology
Obstetrics and Gynaecology