Analgesic effectiveness of intrathecal tramadol added to Bupivacaine compared with Bupivacaine alone for spinal anesthesia For Mothers Delivered by Cesarean Section at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia.

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Advisor: Mulualem Sitot (Bsc, Msc. In Anesthesia, Lecturer)

Thesis Submitted to School of Medicine, Department of Anesthesia for Partial Fulfillment of the Requirements of Masters of science in Anesthesia.

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Addis Ababa, Ethiopia

Addis Ababa University
College Of Health Science
School Of Medicine, Department Of Anesthesia

Observational Prospective Cohort Study on Analgesic Effect Of Intrathecal Tramadol As An Adjuvant With Bupivacaine For Spinal Anesthesia In Comparison With Spinal Anesthesia With Bupivacaine alone For Mother Delivered By Cesarean Section at Empress Zewditu Memorial Hospital, From January 1 to March 30, 2018.

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Declaration

I declare that this thesis is my original work in partial fulfillment of the requirements for the degree of Msc in Anesthesia. I understand that plagiarism will not be tolerated and all directly quoted material has been appropriately referenced.

Name: _____

Signature: _____

Submission to the Department of Anesthesia, Addis Ababa University.

Date of Submission: _____

This thesis work has been submitted for examination with my/our approval as Advisors on the Msc in Anesthesia course.

Name	Signature
_____	_____

Abstract

Background: Spinal Anesthesia has become more widely practiced anesthetic technique. It is simple to institute, rapid in its effect and produces excellent operating conditions. Postoperative pain after cesarean section is common and more intense compared to post vaginal delivery pain. Therefore, intrathecal adjuvants play an important role in maternal analgesia in the postoperative time. It has been shown in clinical studies that using tramadol intrathecal can provide longer duration of analgesia, without the common side effects of opioids.

Objective: To compare analgesic effectiveness of intrathecal tramadol as an adjuvant with bupivacaine in comparison with bupivacaine alone for mother delivered by cesarean section at Empress Zewditu Memorial Hospital from January 1 to March 30, 2018.

Methods: Hospital based observational prospective cohort study was employed for 62 laboring mothers who fulfilled inclusion and deliver by cesarean section under spinal anesthesia selected with systematic random sampling from schedule list. Data was collected immediately after SA administration at 5, 10, 15, 20, 30, 40 minutes. Starting from the immediate postoperative time, an assessment was done at 1, 2, 3, 4, 5, 6 and 12 hours for numerical rating scale (NRS). Based on normality assumption, analysis was done by independent t test, Mann –Whitney U test, $\chi 2$ or Fisher's exact test as appropriate. P-value <0.05 was consider as statistically significant.

Result: Hemodynamic change was comparable and there was no adverse effect between the groups. The median pain scores were lower in exposed (BT) group at the 2^{nd}, 3^{rd}, 4^{th} and 5^{th} hours postoperatively and there was statistical significant difference at 2^{nd}, 3^{rd}, 4^{th} and 5^{th} hours postoperatively between exposed (BT) and non-exposed (BA) groups ($p<0.001$). The duration of anesthesia was effectively prolonged in group BT (245.33 ± 22.854 minutes) compared to group BA (135.00 ± 21.735 minute) ($p<0.001$).

Conclusion and Recommendation: This study showed that intrathecal tramadol (20 mg) can safely be used along with bupivacaine in subarachnoid blockade to prolong the duration of analgesia.

We recommend the use of intrathecal tramadol additive for effective post-operative analgesia for cesarean section.

Acknowledgment

First of all I wish to acknowledge my debts to my advisor Mr. Mulualem Sitot for his continuous help and guidance, and I wish to thank him for his suggestions, comments and valuable advice to develop this research.

There are no words to express my feeling towards those who enlightened my way throughout the period of conducting this thesis.

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Lists of Acronyms

ASA: American Association of Anesthesiologist

BS: Bupivacaine Alone

BT: Bupivacaine with tramadol

CD: Cesarean Delivery

C/S: Cesarean Section

GA: General Anesthesia

HA: Alternative Hypothesis

HO: Null Hypothesis

IQR: Interquartile Range

IRH: Institutional Review Board

MAP: Mean Arterial Pressure

NRS: Numerical Rating Scale

SA: Spinal Anesthesia

SD: Standard Deviation

TAP: Transverse Abdominal Plane

VAS: VisualAnalogueScore

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Chapter One: Introduction

1.1 Background

Cesarean delivery (CD) can be the best way to insure the safety of the mother and the baby especially, if the baby is in distress in the later stage of pregnancy(1). The choice of anaesthesia for caesarean section depends on the reason for the operation, degree of urgency, the desires of the patient and the judgment of anesthesiologist. General anaesthesia for the CD is associated with relatively greater maternal risk than regional anaesthesia (2). Spinal Anaesthesia (SA) has therefore become more widely practiced anaesthetic technique in CD. It is simple to institute, rapid in its effect and produces excellent operating conditions. It also avoids fetal as well as maternal risks of GA, requires minimum postoperative anaesthesia care and provides adequate postoperative analgesia(3).

Bupivacaine is the most commonly used drug worldwide for spinal anaesthesia in CD. Its effect lasts longer than other local anaesthetics with minimal side effects and it is also affordable. Spinal anaesthesia with local anaesthetic agents, especially bupivacaine, has side effects such as hypotension, respiratory depression, vomiting and shivering in a dose dependent fashion(4). Hypotension is one of the commonest side effects and can affect both the mother and the fetus or the neonate. Its side effects are dose dependent, therefore different approaches have been attempted in order to avoid spinal-induced complication including the use of small dose of bupivacaine or lowering local anesthetic and mixing it with additives like neuraxial opoids, tramadol(5).

The provision of effective anesthesia during the procedure and post-operative analgesia is still evolving and getting fine-tuned in the specialty of anesthesia. One of the primary aims of anesthesia is to provide analgesia during the surgical procedure(5).

Spinal anesthesia with 0.5% hyperbaric bupivacaine is routinely administered nowadays for cesarean section and major gynecological surgery. To increase the duration of analgesia produced by local anesthesia, a number of adjuvants have been added through the central neuraxial route. Intrathecal opioid administration has been demonstrated to provide effective postoperative analgesia after a variety of surgical procedures, at the cost of increased risk of respiratory depression. Tramadol, in contrast to a centrally acting opioid analgesic, has minimal respiratory depressant effect, because it has 6000 fold less affinity for μ receptors compared to morphine. It also inhibits serotonin and norepinephrine reuptake in the spinal cord and has no

reported neural toxicity. Therefore, tramadol has the potential to provide effective postoperative analgesia, with no risk of respiratory depression after central neuraxial administration. However, pruritus, nausea, vomiting, urinary retention, activation of herpes labials and risk of unpredictable respiratory depression have directed the clinicians to use a lower dose of tramadol that can be used intrathecally to produce effective and prolonged analgesia without such complications(6).

The analgesic effect of the centrally acting opioid, tramadol, is well-known. It has been shown in clinical studies that using tramadol epidural can provide longer duration of analgesia, without the common side effects of opioids(7).

Cesarean section is among the most commonly performed surgeries in women and central neuroxial anesthesia is the technique of choice for this procedure. Although numerous side effects related to obstetric anesthesia had been described, subarachnoid anesthesia has a clear tendency to be used more often than epidural and combined spinal-epidural technique(8)

It is safe, easy to perform, effective, low failure rate, no systemic local anesthetic toxicity, inexpensive, prevents aspiration pneumonia, and has a high rate of maternal satisfaction(9).

It also produces a deep anesthesia, inhibits the stress response to surgery, and blunts the autonomic and somatic responses to pain, and facilitate breathing, coughing, sighing and early ambulation and finally, efferent sympathetic blockade results in increased blood flow to the blocked area resulting in better wound healing. It also reduces the risk of deep vein thrombosis and thrombo- embolism(10).

The study will be undertaken to evaluate the duration of analgesia and/or pain free period produced by intrathecal tramadol added to bupivacaine in obstetric patients undergoing major cesarean section.

1.2 Statement of the Problem

Cesarean section is among the most commonly performed surgeries in women and central neuroxial anesthesia is the technique of choice for this procedure. Although numerous side effects related to obstetric anesthesia had been described, subarachnoid anesthesia has a clear tendency to be used more often than epidural and combined spinal-epidural technique. It is safe, easy to perform, effective, low failure rate, no systemic local anesthetic toxicity, inexpensive, prevents aspiration pneumonia, and has a high rate of maternal satisfaction(10).

The main limitations of spinal anesthesia (SA) are its short duration of action and do not provide prolonged postoperative analgesia when it is performed only with local anesthetics. Adding adjuvants drugs to intrathecal local anesthetics improves quality and duration of spinal blockade, and prolongs postoperative analgesia. Reducing the dose of local anesthetics used in SA can decrease some of the side effects such as maternal hypotension, high spinal block, prolonged motor block. By inducing better analgesia after cesarean section with intrathecal additives, the recently given birth mother is better able to take care of her newborn, which immediately improves mother-baby relationship(11).

Postoperative pain after cesarean section is common and more intense compared to post vaginal delivery pain. When this kind of pain is not prevented nor treated properly, it can evolve to chronic pain which means a serious health problem. Therefore, intrathecal adjuvants play an important role not only in maternal analgesia, but in the future of the newborn. There are several adjuvant drugs used to enhance spinal anesthesia; morphine is the most frequently used and also many other opioid agonists such fentanyl, sufentanyl, hydromorphone, diamorphine, and meperidine have been well studied (12).

Tramadol is a centrally acting analgesic agent with a terminal elimination half-life of 5.5 hours and provides clinical analgesia for 10 hours after epidural administration. Tramadol stimulates the μM- receptors and to a lesser extent the δ and κ receptors. It also activates spinal inhibition of pain by decreasing the reuptake norepinephrine and serotonin. Although tramadol is one-fifth as potent as morphine as an analgesic, it causes less respiratory depression and pruritus. It was suggested by other studies that tramadol may have local anesthetic effects on peripheral nerves(13). The effective dose range of intrathecal tramadol for postoperative analgesia is confusing until date.

Therefore, our study will be performed to demonstrate that intrathecal administration of 20 mg of tramadol when used with 0.5% bupivacaine prolonged the postoperative analgesia in the patients without producing related side effects like hypotension, nausea, vomiting, pruritus and respiratory depression.

1.3 Significance of the Study

Across the world, subarachnoid anaesthesia is the most used anaesthetic procedure for Cesarean delivery. Compared to general and epidural anaesthesia, its main disadvantage is a short duration action and most important, the lack of prolonged postoperative analgesia. Provision of post cesarean delivery analgesia is of great consequence since it accelerates early ambulation, decreases maternal morbidity, improves parturient outcome, decrease cost, and most important augment the quality of the mother-infant relationship from the moment of birth.

Opoid like fentanyl and morphine are widely used as intrathecal adjuvant with bupivacaine to prolong postoperative analgesia, but these drugs are not easily available in most of hospitals, especially rural area00 where majority of our population are served. Tramadol in contrast to a centrally acting opioid analgesic has minimal respiratory depressant effect(14), because it has 6000-fold less affinity for μ receptors compared to morphine and it also inhibits serotonin and norepinephrine reuptake in the spinal cord and has no reported neural toxicity(15).

The cost of tramadol is relatively low, easily available that makes routine use is reasonable in all hospital in Ethiopia. Such studies in resource limited area can improve pain management and patient comfort. Therefore, conducting such a research to find alternatives for pain management in the postoperative period is expected to decrease the side effects of opioids and other drugs.

There is also an inter individual variability for pain perception, assessment, recognition and endurance that are affected by social, cultural, cognitive, genetic factors(16).

As I know in Ethiopia there is no published data for the same title in the same population. The adaptation of intrathecal tramadol with bupivacaine may become a good alternative analgesic technique spinal anesthesia for cesarean section. This study will also provide necessary information used for future research and studies.

Chapter Two: Literature Review

The provision of effective anesthesia during the procedure and post-operative analgesia is still evolving and getting fine-tuned in the specialty of anesthesia. One of the primary aims of anesthesia is to provide analgesia during the surgical procedure. Anesthesiologists/anesthetists are the leaders in the development of acute post-operative pain services and application of evidence based practice to acute post-operative pain and creation of innovative approaches to acute pain management(17).

A Randomized double blinded placebo study done in India by Chakra borty S. JC et.al. in 2008 to evaluate the duration of analgesia and/or pain free period produced by intrathecal tramadol added to bupivacaine in 50 patients undergoing major gynecological surgery under spinal anesthesia found that statistically significant reduction of VAS score and the duration of analgesia was 380 ± 11.82 min and 210 ± 10.12 minute in patients receiving 15 mg of 0.5% hyperbaric bupivacaine and 20 mg tramadol , as compared to patients receiving 15 mg of 0.5% hyperbaric bupivacaine alone respectively. This study concluded that the duration of analgesia provided by intrathecal administration of 20 mg tramadol with 15 mg of 0.5% hyperbaric bupivacaine was significantly longer than that provided by intrathecal bupivacaine alone(17).

A randomized placebo controlled study done in 2015 by Rakshith BP et.al. in India on effectiveness of addition of intrathecal tramadol with hyperbaric bupivacaine in prevention of shivering in parturient undergoing cesarean section under spinal anesthesia showed that the analgesic effect of the block last for a mean duration of 232 min and SD of 97.6 min in tramadol group and mean 176 min and SD of 42.3 min in normal saline group and concluded that the incidence of anesthesia induced shivering significantly reduced while prolonging both sensory and motor components of the subarachnoid block(18).

A comparative study in 2016 by Geetanjali S. et.al. in India conducted to evaluate safety and efficacy of the intrathecal tramadol and to determine the postoperative analgesia. Sixty ASA I and II patients were randomly assigned to two groups. Group B (n=30) received 3ml of 0.5% heavy bupivacaine with 0.5ml of normal saline and group BT (n=30) received 3ml of heavy bupivacaine with 0.5ml(25mg) of preservative free tramadol by intrathecal route at L3-L4 intervertebral space. In group BT patients the VAS score was significantly lower as compared to group B patients. The mean duration of analgesia was 393.33±123.21 minutes in group BT, where as in group B it was 167.47±12.46 minutes, which was found to be statistically significant.

Conclude that 25mg tramadol with hyperbaric bupivacaine intrathecally provides a better postoperative analgesia in lower abdominal surgeries(19).

A randomized control study done in 2016 by Masamaddi G.S. et.al. In India on Hemodynamic and Sedative Effects of Intrathecal Tramadol with Bupivacaine and Bupivacaine Alone in Patients Undergoing Elective Lower Abdominal Surgery found that tramadol 25 mg in combination with bupivacaine 0.5% heavy can be safely administered intrathecally for better post-operative analgesia in lower abdominal surgical procedures without producing hemodynamic instability and minimal sedation. Both the groups were comparable with respect to age, sex, height, and weight distribution, ASA grade and duration of the surgery(20).

A randomized, double-blind study done in USA by Journal of Anesthesiology Clinical Pharmacology in 2016 on intrathecal ropivacaine with or without tramadol for lower limb orthopedic surgeries the time of sensory block onset was 9.2 ± 4.9 min and 8.6 ± 5.3 min (P = 0.714) in group R and group RT, respectively. The motor block onset was also comparable in both the groups (P = 0.112). The duration of sensory block was 147.2 ± 37.4 min in group R and 160.4 ± 40.9 min in group RT (P = 0.252). The median maximum block height achieved in both the groups was T6 and the time to achieve the maximum block was also comparable statistically (P = 0.301).It concluded that the addition of intrathecal tramadol 25 mg to the isobaric ropivacaine does not alter the block characteristics produced by intrathecal ropivacaine alone(21).

Randomized controlled trial study done in Pakistan by Zahid F. et.al.in 2017 on intrathecal tramadol as an adjuvant in subarachnoid block to prolong the duration of analgesia showed that the duration of anesthesia was effectively prolonged in group TB which was 181.56 ± 12.42 mins as compared to group SB which was 120.93 ± 15.54 mins. VAS score was significantly lower in group TB. This study showed that intrathecal tramadol (25mg) can safely be used along with bupivacaine in subarachnoid blockade to prolong the duration of analgesia and improve the quality of anesthesia as well(22).

A randomized clinical study in India by Dandona S. et.al.in 2017 on the comparison of intrathecal tramadol and fentanyl as adjuvant in abdominal and lower limb surgeries; Hemodynamic parameters, such as pulse, systolic blood pressure, diastolic blood pressure and oxygen saturation were comparable in both the groups. Visual analog scores were significantly

lower in the group b (fentanyl bupivacaine) patients as compared to the group a (tramadol bupivacaine) patients. The group a patients had got significantly higher sedation scores as compared to Group b patients. Fentanyl seems to be a better alternative to tramadol as an adjuvant to spinal bupivacaine in surgical procedures as it provides prolonged duration of the sensory block, longer duration of postoperative analgesia and lesser number of doses of rescue analgesia is required(23).

Study done by Tandon, et al. in 2017 on comparative Clinical Study of Intrathecal Hyperbaric Bupivacaine 0.5% with 25 mg Pethidine Versus 25 mg Tramadol for Infraumbilical Surgeries found that the mean duration of postoperative analgesia in the Pethidine and the Tramadol groups was 316.10±8.27min and 405.60±10.25min respectively (P <0.001). Hemodynamic changes along with incidence and severity of side effects for both Pethidine and Tramadol are similar when used intrathecally as adjuvant to Bupivacaine(24).

Hypothesis Test

HO1: There was no statically significant different in hemodynamic status between tramadol bupivacaine group and bupivacaine alone group.

HA1: There was statically significant difference in hemodynamic status between tramadol bupivacaine group and bupivacaine alone group.

HO2: There was no statically significant difference in duration analgesic effect of the tramadol bupivacaine group and bupivacaine alone group.

HA2: There was statically significant different in duration analgesic effect of the tramadol bupivacaine group and bupivacaine alone group.

HO3: There was no statically significant different in severity of postoperative pain in the two groups.

HA3: There was statically significant different in severity of postoperative pain in the two groups.

Conceptual Farm Work

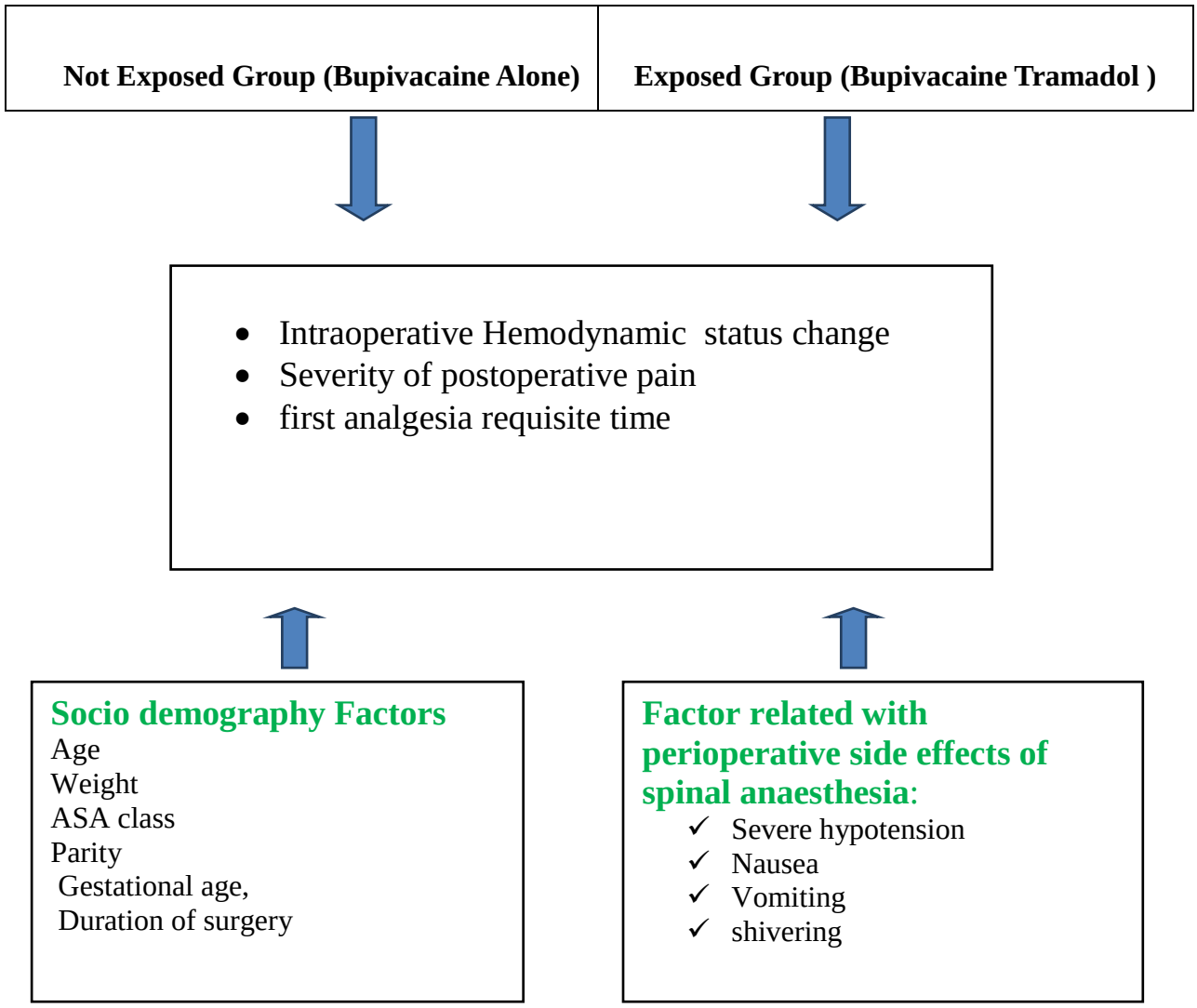

Figure 1: schematic presentation of conceptual frame work

Chapter Three: Objectives

3.1 General objective

To assess the Analgesic Effectiveness of Intrathecal Tramadol added With Bupivacaine and Bupivacaine alone For Spinal Anesthesia for Mothers undergoing cesarean Section at Empress Zewditu Memorial Hospital, from January 1 to March 30, 2018, Addis Ababa, Ethiopia.

3.2 Specific objectives

- To compare the intraoperative hemodynamic status in BT group and BA group
- To Assess the severity of post operative pain in the BT group and BA group
- To compare BT and BA groups for the time to first analgesic request

Chapter Four: Method and Materials

4.1 Study Area and period

The study was conducted at Empress Zewditu Memorial hospital which is located in capital city of Ethiopia, Addis Ababa. The Hospital is operated by the ministry of health; it has a total of 128 beds out of these 46 beds is for obstetrics, gynecologic & postnatal ward. The study was conducted from January 1 to March 30, 2018.

4.2 Study Design

Observational prospective cohort study design was employed.

4.3 Source Population

All pregnant mothers who were delivered by cesarean section at the Empress Zewditu Memorial hospital.

4.4 Study population

Pregnant mothers who underwent cesarean section under spinal anesthesia at Empress Zewditu Memorial hospital that fulfilled the inclusion criteria during the study period

4.5 Eligibility Criteria

4.5.1 Inclusion Criteria

Mothers that underwent cesarean section under spinal anaesthesia with 0.5% Bupivacaine alone or 0.5 % bupivacaine combined with 20 mg tramadol and those who were American society of Anesthesiologist (ASA) class I and II.

4.5.2 Exclusion Criteria

All mothers who delivered by cesarean section under spinal anaesthesia with added adjuvant other than tramadol, Transverses abdominal plexus (TAP) block, Those receiving spinal anaesthesia with lidocaine, Those Who required systemic analgesia intraoperatively and Failed spinal anesthesia.

4.6 Study Variables

4.6.1 Dependent Variable:

- Intraoperative hemodynamic status
- Severity of postoperative pain which was measured by NRS (0-10) and
- First analgesia requisite time.

4.6.2 Independent variables

Socio-demographic variables: age, weight, height, Parity, gestational age, ASA category, time from intrathecal injection to delivery of the child, duration of surgery and intraoperative IV fluid given.

Factor related with perioperative side effects of spinal anaesthesia: Nausea/vomiting, severe hypotension, shivering, pruritis, maternal respiratory depression and bradycardia.

4.7 Sample Size Calculation and Sampling Techniques

4.7.1 Sample Size determination

Sample size was determined based on previous study on 2015 in Indian; on effectiveness of addition of intrathecal tramadol with hyperbaric bupivacaine in prevention of shivering in parturient undergoing cesarean section under spinal anesthesia showed that the analgesic effect of the block last for a mean duration of 232 min and SD of 97.6 min in tramadol group and mean 176 min and SD of 42.3 min in normal saline group (18). By assuming equal sample size for two groups, the sample size was determined by the formula as,

$$n_1 = n_2 = \frac{(z_{\alpha/2} + z_{\beta})^2 (\sigma_1^2 + \sigma_2^2)}{\Delta^2}$$

Where, $n1=n2= \frac{(1.96 +0.84)^2 \ (97.6^2+42.3^2)}{(232-176)^2}$

$= 28$

N_1= number of c/s under spinal anesthesia with bupivacaine alone group

N_2 = number of C/s under Spinal anesthesia with tramadol bupivacaine group

Z= 95% confidence interval =1.96

$1-\beta$ = the power function at 80%= 0.84

Ten percent of additional sample was included by assuming loss to follow up from the study and the total sample was become 31 for each group.

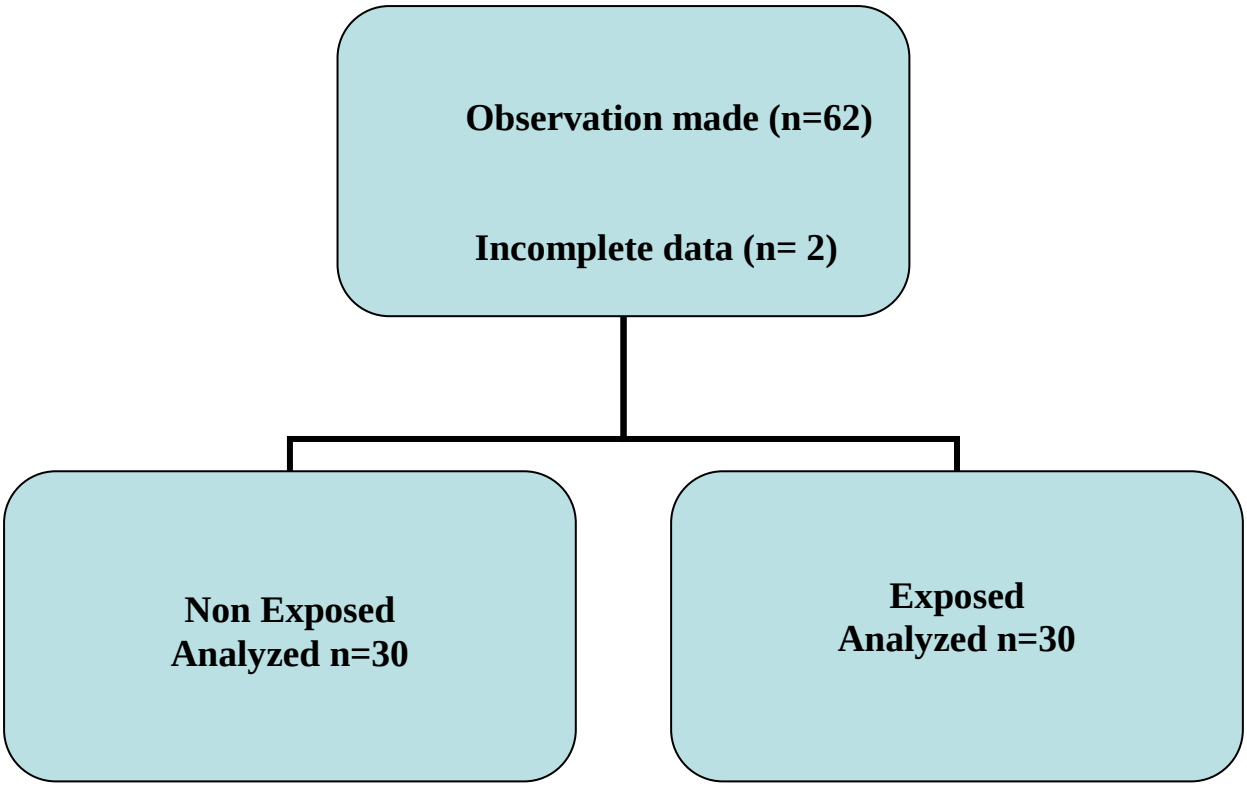

Figure 2: schematic presentation patient enrollment in the study.

4.7.2 Sampling Technique

Systematic random sampling technique was used to select study participants daily operation schedule list. Depending upon average values of the previous surgery per 3 months on the log book, 132 elective cesarean sections were operated. The sampling interval; K was determined using the formula: K=N/n; where, n = total sample size, N = population per 3 months. 62 participants were recruited. Therefore, the sampling interval was 2 and the first study participant (random start) was selected using lottery method from the first day operation schedule list after which data collector recruit 1 patient for every 2 consecutive patients cesarean section under spinal anesthesia, after grouping based on whether they received spinal bupivacaine alone or bupivacaine with tramadol till the required sample size was reached.

4.8 Data Collection Methods

Questioner was prepared in English which includes socio demographic data, physical characteristics of the patient, preoperative vital signs, parity, gestational age, ASA classification. The data collection was under taken by two Anesthetists after getting training and the principal investigator supervise the completeness of the data daily. During each procedure the During each

procedure two intravenous line opened,10mg metoclopramide IV, preloaded, basic monitoring was applied, spinal anesthesia 12.5mg bupivacaine alone or 12.5mg bupivacaine with 20mg tramadol was given in sitting position. Intraoperative hemodynamic data was collected immediately after SA administration at 5, 10, 15, 20, 30 and 40 minutes.

Starting from the immediate postoperative time, presence and scale of pain, time for the first analgesic request as well as analgesics need was assessed by the other trained data collector. These assessments were done at 1 hrs, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr and 12 hr for numerical rating scale (NRS). The categories of patients were identified by the data collector. The NRS was determined by the patient marking their pain intensity on a line which 0 – 10 numbers (with 0 = no pain to 10= the worst possible pain, was explained to all the patients.)

4.9 Data Quality Control Issue

To ensure the quality of data, pretest of the data collection tool was done on patients by taking 10 respondents (5 BT group and 5 BA group) who undergone cesarean section under spinal anaesthesia and were not included in the main study. Data was checked for completeness, accuracy and clarity on the day of collection by the principal investigator. Data clean up and cross checking was done before analysis. Training was given for data collectors and supervises for two days on how to approach study subject and on how to use data collection tool. Supervision was done by principal investigator.

4.10 Data Analyzing and processing

Data was checked manually for completeness and then coded and entered into EPI info version 7; then transferred to SPSS version 20 computer program for analysis. A Shapiro Wilk test was used to test for distributions of data while homogeneity of variance was assessed using Levene's test for equality of variance. The data was normally distributed homogenous with except for postoperative pain severity.

Numeric data were described in terms of mean ± SD for symmetric and median (Interquartile range) for asymmetric numeric data. Comparison of numerical variables between study groups were done using independent t- test and Manny Whitney test based for symmetric and asymmetric data respectively. Frequency and percentage were used to describe categorical variable and statistical difference between groups were tested using Chi-square. A p value <0.05 with power of 80% considered statistically significant.

4.11 Dissemination plan:

The research paper will be prepared in four copies and will be disseminated to college of health science, school of medicine/department of anesthesia, Empress Zewditu Memorial hospital and Addis Ababa University student research office.

4.12 Ethical Consideration

Ethical clearance was obtained from the university ethical clearance committee before the start of the study. Then after official letter for permission was requested from collage of public health and medicine and it was given to Empress Zewditu Memorial hospital clinical director office for permission for conducting the study. Moreover, the objective of the study was explained to both hospital administration and obstetric patients included in the study. Verbal consent from the respondents was asked before study and their confidentiality was kept.

4.13 Operational Definition

Caesarean section: Is delivery of the fetus along with placenta and Membrane under anesthesia through the incision of Abdominal and intact uterine wall after the fetus reached viability.

Spinal anesthesia: It is a type of regional anesthesia in which local anesthetic Agents is administered in subarachnoid space.

Severe Hypotension: Defined as a Systolic blood pressure of below 90 mmHg or lower than 30% of starting systolic blood pressure or MAP less than 60 mmHg (5).

Bradycardia: Defined as a heart rate less than 50 beats/minutes (25).

Respiratory depression: Defined as a respiratory rate less than 10 breaths per minute or oxygen saturation less than 90% will be consider (5).

NRS: Numerical Rating Scale which is a method of pain assessment determined by the patient making a mark of their pain intensity on a line which has 0 – 10 numeric number. 0=No pain and 10=Worst possible pain (26).

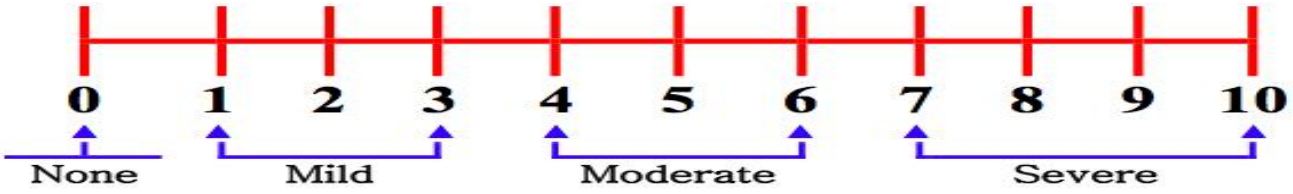

Figure 3: Adopted from the National Initiative on Pain Control (NICP ^{TM})

Time for first analgesia request: a time in minutes from the end of surgery to a first time analgesia were given. (27).

Pruritis: Defined as any scratch or itching complained by the patient and its intensity was assessed as mild (itching was only a minor concern), moderate (itching was a primary concern) or severe (unbearable patient requires treatment).

ASA I: a healthy patient with no organic/physiological/psychiatric problems.

ASA II: controlled medical conditions with mild systemic effect and no limitation of functional ability.

ASA III: medical condition with severe systemic effect, limitation in functional capacity.

ASA IV: poorly controlled medical conditions associated with significant impairment in functional ability that is potential threat to life.

ASA V: critical condition, little chance of survival without surgical procedure.

ASA VI: brain dead patient undergoing organ donation.

Chapter Five: Result

5.1 Demographic and Perioperative Characteristics

A total of 60 patients (30 pregnant mothers in each group) were finally involved for analysis of the study based on whether they received spinal anesthesia using bupivacaine added with tramadol or bupivacaine alone for cesarean delivery.

There was no statistical significance difference between two groups in demographic data and perioperative characteristics such as age, BMI, ASA status, gestational age, time from intrathecal injection to delivery of child, total IV fluid given and duration of surgery (see table 1).

Table 1: Demographic data and Perioperative Characteristics of study participants (mean and SD are analyzed by independent t test; median and IQR: Ch- square) at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia from January to March, 2018.

Variables		Group BA(*n* = 30)	Group BT (*n* = 30)	*P* value
Age in year (Mean ±SD)		28.17 ± 5.072	26.67 ± 4.544	0.233
BMI in kg/m^2 (Mean ±SD)		24.40 ± 2.493	24.63 ± 2.399	0.709
ASA status in n (%):	I	21 (70)	27 (90)	0.052
	II	9 (30)	3 (10)	
Parity in n (%)	< P 3	22 (73.3)	23 (76.7)	0.820
	≥ P 3	8 (26.7)	7 (23.3)	
Gestational age (Mean ±SD)		39.47 ± 1.279	39.10 ± 1.062	0.232
Time from intrathecal injection to delivery of child (Mean ±SD)		12.43 ±1.305	12.40 ± 1.380	0.924
Total IV fluid given intraoperative (in ml) (Mean ±SD)		2023 ± 400	1893 ± 0357	0.342
Duration of surgery (Mean ±SD)		36.40 ± 2.608	36.37 ± 2.606	0.961

NB. BT=Bupivacaine with Tramadol added, BA= bupivacaine alone, SD= Standard deviation, ASA= American society of anesthesiologist, BMI= Body Mass Index, P= Para, n: Independent T test and X^2 test was used, p-value < 0.05 considered statistically significant.

5.2. Intraoperative hemodynamic status between groups

There was no statistical significant difference in the base line HR and MAP as well as intraoperative mean heart rate and MAP at 5, 10, 15, 20, 30 and 40 minutes between the exposed and non exposed groups (Table 2).

Table 2: Mean intraoperative heart rate and mean blood pressure of participants at various time intervals analyzed by independent t test at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia from January to March, 2018.

Vital signs	BA group (n=30)	BT group(n=30)	P-value
Base line vital sign			
HR (Mean± SD)	85.07 ± 8.967	88.53 ± 9.179	0.144
MAP(Mean± SD)	88.03± 5.156	90.07± 7.343	0.220
Vital sign at 5 minute			
HR (Mean± SD)	87.60 ± 10.146	89.37 ± 9.261	0.484
MAP (Mean± SD)	74.43± 5.244	77.50± 6.972	0.059
Vital sign at 10 minute			
HR (Mean± SD)	88.93 ± 9.938	88.83 ± 9.443	0.968
MAP (Mean± SD)	68.50± 6.463	70.90± 6.305	0.151
Vital sign at 15 min			
HR (Mean± SD)	89.57 ± 10.119	90.20 ± 8.798	0.797
MAP (Mean± SD)	66.03± 8.130	68.80± 6.754	0.157
Vital sign at 20 minute			
HR (Mean± SD)	90.60 ± 9.551	90.00 ± 8.329	0.796
MAP (Mean± SD)	66.33± 7.967	69.43± 7.422	0.124
Vital sign at 30 minute			
HR (Mean± SD)	90.80 ± 8.771	89.87 ± 8.472	0.677
MAP(Mean± SD)	69.67± 5.797	72.27± 7.488	0.138
Vital sign at 40 minute			
HR (Mean± SD)	89.93 ± 8.098	89.90 ± 7.950	0.987
MAP(Mean± SD)	71.20 ± 5.429	73.13± 5.698	0.184

NB. BT=Bupivacaine with Tramadol added, BA= bupivacaine alone, SD= Standard deviation, HR= Heart rate, MAP= mean arterial blood pressure, Independent T test was used, p-value < 0.05 considered statistically significant.

The SaO2 and RR are comparable in the non exposed (BA) and Exposed (BT) group at base line, at 5, 10, 15, 20, 30 and 40 minutes (table 3).

Table 3: mean intraoperative oxygen saturation and Respiratory rate of the study participants analyzed by independent t test at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia from January to March, 2018.

Variables	Group BA(n = 30)	Group BT (n = 30)	P value
Baseline SaO2 and Respiratory Rate (Mean± SD)			
SaO2	97.63 ± 0.490	97.50 ± 0.630	0.364
RR	16.90± 0.845	17.03± 0.928	0.563
SaO2 and Respiratory Rate at 5 minute (Mean± SD)			
SaO2	97.67 ± 0.802	97.70 ± 0.702	0.865
RR	16.40 ± 1.276	16.97 ± 0.964	0.057
SaO2 and Respiratory Rate at 10 minute (Mean± SD			
SaO2	97.77 ± 0.971	97.97 ± 0.718	0.368
RR	16.37 ± 1.691	16.67 ± 1.026	0.410
SaO2 and Respiratory Rate at 15 minute (Mean± SD			
SaO2	98.07 ± 0.907	98.27 ± 0.640	0.328
RR	16.20 ± 1.789	16.50 ± 0.900	0.415
SaO2 and Respiratory Rate at 20 minute (Mean± SD			
SaO2	98.33 ± 0.959	98.33 ± 0.661	1.000
RR	16.03 ± 1.497	16.10 ± 0.845	0.832
SaO2 and Respiratory Rate at 30 minute (Mean± SD			
SaO2	98.43 ± 0.728	98.43 ± 0.568	1.000
RR	15.97 ± 1.273	16.03 ± 0.669	0.800
SaO2 and Respiratory Rate at 40 minute (Mean± SD			
SaO2	98.47 ± 0.730	98.40 ± 0.498	0.681
RR	15.47 ± 2.886	16.07 ± 0.691	0.273

NB. BT=Bupivacaine with Tramadol added, BA= bupivacaine alone, SD= Standard deviation, RR= Respiratory rate, SaO2= Oxygen saturation, Independent T test was used, p-value < 0.05 considered statistically significant.

5.3. Comparison of Postoperative pain severity by NRS Scale

The Mann Whitney U test showed that the median pain score was comparable in the 1st, 6th and 12th postoperative hours between the exposed and non-exposed groups. But the median pain

scores were lower in exposed (BT) group at the 2nd, 3rd , 4th and 5th hours postoperatively and there was statistical significant difference at 2nd, 3rd, 4th and 5th hours postoperatively between exposed (BT) and non-exposed (BA) groups (p<0.001) (table 4).

Table 4: Comparison of postoperative pain severity using NRS between BA & BT group analyzed by Mann Whitney U test at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia from January to March, 2018.

NRS score in (Median and IQR)	Group BA(n =30)	Group BT (n = 30)	P value
NRS score at 1 hr	0 (0)	0 (0)	1.00
NRS score at 2 hrs	2 (1-3)	0 (0)	<0.001
NRS score at 3 hrs	7 (6-8)	0 (0)	<0.001
NRS score at 4 hrs	4(3-5)	2 (1-3)	<0.001
NRS score at 5 hrs	2 (2-3)	7 (6-7)	<0.001
NRS score at 6 hrs	2(2-3)	2 (1-3)	0.093
NRS score at 12 hrs	1(1-2)	1 (1-2)	0.576

NB. BT=Bupivacaine with Tramadol added, BA= bupivacaine alone, NRS= Numeric Rating Scale, IQR= Interquartile Range, p-value < 0.05 considered statistically significant.

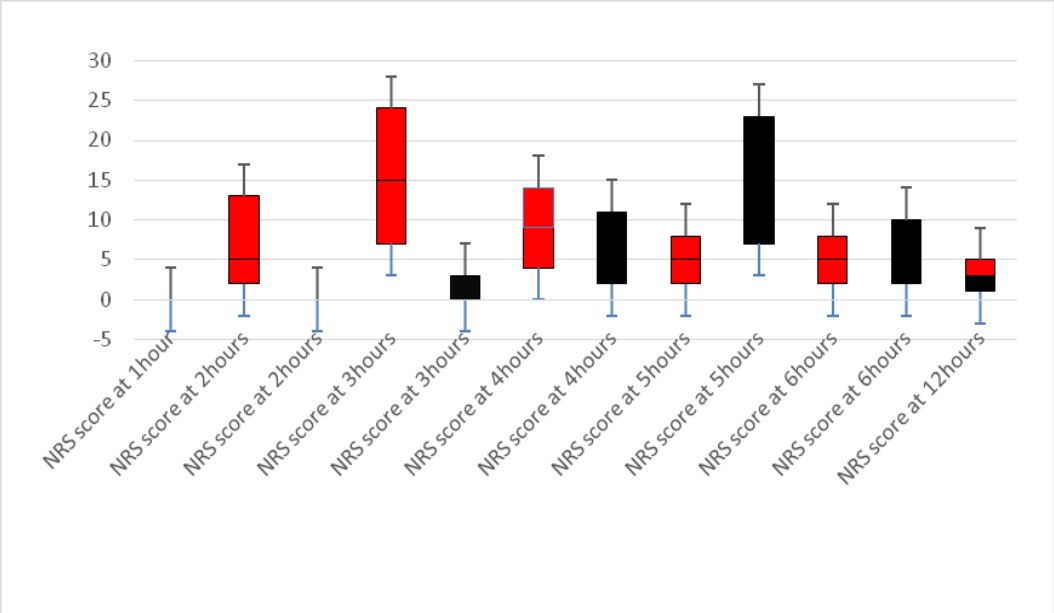

Figure 4: Box plot that shows postoperative Numeric Rating scale pain scores in media and IQR of BT (**Black**) and BA (**Red**) at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia from January to March, 2018.

5.4. Comparison of time to first analgesia request

The independent t- test showed that time to first analgesia request was significantly longer in bupivacaine tramadol group with mean and standard deviation of 245.33 ± 22.854 minute in exposed compared to non exposed group (135.00 ± 21.735 minute) with p value of (p <0.001) (see Table 5).

Table 5: Comparison of time to first analgesia request in minute between two groups analyzed by independent t test at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia from January to March, 2018.

Variable	BA (n=30)	BT (n=30)	P value
Time to first analgesia request in minute (Mean± SD)	135.00 ± 21.735	245.33 ± 22.854	<0.001

NB. BT=Bupivacaine with Tramadol added, BA= bupivacaine alone, SD= Standard Deviation, p-value < 0.05 considered statistically significant.

5.5 Incidence of intraoperative complication between exposed and non exposed groups

Three (10%) patients in exposed group and five (16.7%) in non exposed group developed severe hypotension in the intraoperative period and patients were treated with IV fluid but none of them needed vaso-active drugs (p=0.352). The incidence of nausea and vomiting was 30% and 13.3% in BT and 13.3% and 6.7% in BA group respectively, but there was no statistical significant difference between the groups. Seventeen patients (56.7%) were developed shivering in bupivacaine alone group, which was statistically significant with P value <0.001. There was no statistical significant difference between the groups in terms of Pruritis, respiratory depression, fetal bradycardia and Apgar score (table 6).

Table 6: Incidence of intraoperative complication between the groups analyzed by Chi-square test at Empress Zewditu Memorial Hospital, Addis Ababa, Ethiopia from January to March, 2018 (in number and percertage).

Incidence of intraoperative Complication in n (%)	Group BT(n = 30)	Group BA (n = 30)	P value
Severe Hypotension	5 (16.7%)	3 (10%)	0.352
Nausea	4 (13.3%)	9 (30%)	0.105
Vomiting	2 (6.7%)	4 (13.3%)	0.238
Shivering	17 (56.7%)	0%	<0.001
Pruritis	0%	2 (6.7%)	0.246
Respiratory depression	1 (3.3%)	0%	0.500
Fetal bradycardia	1 (3.3%)	0%	0.500
APGAR score (mean± SD): at 1 minute	7.93 ± 0.691	8.13 ± 0.776	0.296
at 5 minutes	9.53 ± 0.629	9.57 ± 0.568	0.830

NB. BT=Bupivacaine with Tramadol added, BA= bupivacaine alone, SD= Standard Deviation, n= number of patient, Chi-square test was used, p-value < 0.05 considered statistically significant.

Chapter six: Discussion

Opioids have been the cornerstone of analgesia ever since their discovery. Intravenous, Intrathecal or Epidural routes have all been used for pain relief in surgical patients. Opioids have also been used along with local anesthetics to enhance the efficacy. Many studies have shown morphine, fentanyl and sufentanyl to be the most commonly used agents with satisfactory results (28). Tramadol is a centrally acting partial opioid analgesic agent with terminal half-life of 5.5 hours and Serotonin reuptake inhibition and norepinephrine reuptake inhibition also contributes to its analgesic properties (29). Some studies show that tramadol may have local anesthetic effect on peripheral nerves as well (30).

Numeric rating scale which is regularly favored in clinical setting due to their simple administration relatively consistent result and its correlation with that of VAS score (31). NRS and VAS equally effective and interchangeably used for assessment of postoperative pain (32). Another study assess the compatibility of the NRS to the VAS and they found strong correlation (r=0.94 .95%CI+.93+.95CI) (33).

In our study the intraoperative vital signs (MAP & HR) were comparable in both groups. The current study demonstrated MAP, HR, SaO2 and RR were comparable in tramadol added group compared to bupivacaine alone group immediately at 5, 10, 15, 20, 30 and 40 minute.

Our result was line with study done by Geetanjali S et.al that showed there was no significant difference between groups in the pattern of decrease in systolic or diastolic BP, RR, heart rate, and SPO2 with p value of > 0.05(19).

This study result also in line with the study done by Masamaddi et.al. on hemodynamic and Sedative Effects of Intrathecal Tramadol with Bupivacaine and Bupivacaine Alone in Patients Undergoing Elective Lower Abdominal Surgery found there was no hemodynamic instability in Tramadol with Bupivacaine and Bupivacaine Alone groups (20).

Our study demonstrates that the median NRS pain score was comparable in the 1^{st}, 6^{th} and 12^{th} postoperative hour between the exposed and non-exposed groups. But the median pain scores were lower in exposed (BT) group at the 2^{nd}, 3^{rd} , 4^{th} and 5^{th} hours postoperatively and there was statistical significant difference at 2^{nd}, 3^{rd}, 4^{th} and 5^{th} hours postoperatively between exposed (BT) and non-exposed (BA) groups ($p<0.001$).

This was comparable with study done in Pakistan by Zahid F. et.al.in 2017 on intrathecal tramadol as an adjuvant in subarachnoid block to prolong the duration of analgesia showed that the VAS score was significantly lower in group TB (22).

The result of our study is also comparable with study done in India by Chakra borty S. JC et.al. in 2008 on Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries found that a higher VAS score (≥ 4) was observed in non exposed group , whereas exposed group patients showed significantly lower VAS score (< 4) for more than six hours after the intrathecal injection(17).

In contrast to our study randomized clinical study in India by Dandona S. et.al.in 2017 on the comparison of intrathecal tramadol and fentanyl as adjuvant in abdominal and lower limb surgeries; showed that that higher VAS score in tramadol group when compared to fentanyl group(23).

The possible reason may be the higher pharmacological potency profile of fentanyl.

Our study showed a distinct advantage of adding tramadol to intrathecal bupivacaine as it effectively prolonged the duration of analgesia, there was statistical significant difference between the groups in terms of to time to first analgesia request with mean and standard deviation of 135.00 ± 21.735minute (in Bupivacaine alone) and 245.33 ± 22.854 minute (in bupivacaine with tramadol) (p= < 0.001).

Our study was comparable with a randomized double blinded placebo study done in India by Chakra borty S. JC et.al. in 2008 in 50 patients undergoing major gynecological surgery under spinal anesthesia found statistically significant prolongation in duration of analgesia which was 380 ± 11.82 min and 210 ± 10.12 minute in patients receiving 15 mg of 0.5% hyperbaric bupivacaine and 20 mg tramadol , as compared to patients receiving 15 mg of 0.5% hyperbaric bupivacaine alone respectively(17).

Our study was also comparable with a study done by Rakshith BP et.al. which showed that the analgesic effect of the block last for a mean duration of 232 minute and SD of 97.6 minute in tramadol group and mean 176 minute and SD of 42.3 minute in bupivacaine normal saline group (18).

Our study was also in line with study done by Zahid F. et.al. in 2017 on intrathecal tramadol as an adjuvant in subarachnoid block showed that the duration of anesthesia was effectively

prolonged in group BT which was 181.56 ± 12.42 minutes as compared to group SB which was 120.93 ± 15.54 minute (22)

This current study was in line with a comparative study conducted by Geetanjali S. et.al. in India that found statistically significant difference in the mean duration of analgesia which was 393.33±123.21 minutes in group BT and 167.47±12.46 minutes in group Bupivacaine alone (19).

Our finding showed the incidence of nausea and vomiting in the intraoperative period was 30% and 13.3% in BT and 13.3% and 6.7% in BA group. Although the proportion was higher in BT group compared with BA group, there was no statistical significant difference between the groups in the incidence of nausea and vomiting with p value >0.05.

In contrarily to our study, randomized placebo controlled study done in 2015 by Rakshith BP et.al. in India found that the increased incidence of nausea and vomiting between the tramadol with bupivacaine group and bupivacaine alone group with p value of < 0.001(18).

The possible explanation of this contradiction is in our study area the routinely use of aspiration prophylaxis metoclopramide for all mothers delivered by cesarean section.

Our finding showed none of patients developed intraoperative shivering in bupivacaine tramadol group compared with the proportion of patients who developed intraoperative shivering in bupivacaine alone group which was 57.5% (p<0.001)

Our finding is comparable with a randomized placebo controlled study done in 2015 by Rakshith BP et.al. in India found that the incidence of anesthesia induced shivering was 66% in bupivacaine saline group compared with 16% in tramadol with bupivacaine group with p value <0.001 (18).

The likely explanation for low incidence of intraoperative shivering in bupivacaine tramadol group may be due to anti shivering action intrathecal administered tramadol.

6.1 Limitation of the Study

Limitation our study were lack of standard pain management protocol in the study area. Use of secondary data for preoperative and intraoperative variables and most studies we used for comparison were randomized control trial were among limitation of this project

6.2 **Strength of the Study**

Study participant were homogenous between the bupivacaine alone and bupivacaine with tramadol group.

Chapter Seven: Conclusion and Recommendation

7.1 Conclusion

The result of our study demonstrates that intrathecal tramadol (20mg) can safely be used along with bupivacaine in subarachnoid blockade to prolong the duration of analgesia.

7.2 Recommendation

We recommend the addition of tramadol with bupivacaine in spinal anesthesia for cesarean section for prolongation of post-operative analgesia.

We also recommend that randomized control trial study will be conducted.

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Annex I: Questionnaire

Addis Ababa University, College of Health Sciences Department of Anesthesia

Analgesic Effect Of Intrathecal Tramadol As An Adjuvant With Bupivacaine For Spinal Anesthesia In Comparison With Spinal Anesthesia With Bupivacaine alone For Mother Delivered By Cesarean Section, Empress Zewditu Memorial Hospital.

This questionnaire is to assess the Analgesic Effect Of Intrathecal Tramadol As An Adjuvant With Bupivacaine For Spinal Anesthesia In Comparison With Spinal Anesthesia With Bupivacaine alone For Mother Delivered By Cesarean Section, Empress Zewditu Memorial hospital. The main concern of this study is to fill the information gap on the hemodynamic change, analgesic effect of intrathecal tramadol as an adjuvant with bupivacaine, severity of postoperative pain and first analgesic requisite time. So you are kindly requested to participate on this study and provide appropriate response to questions. Your participation is voluntary. Only anonymous data will be analyzed and I strictly keep confidentiality of participants. Therefore I kindly request you to respond for the following questions based on your willingness. If you feel or face any problem regarding your participation, you can contact the principal investigators by 0912686917.

Thank you for your participation!

የ ማጠይቅ ፈቃድ

ጤፍ ይስጥልኝ !

እኔ _____ እባላለሁ ፡ በአዲስ አበባ ዩኒቨርሲቲ አንስቴዝያ ትምህርት ክፍል የምርምር ቡድን ወስጥ እየሰራሁ እገኛለሁ ፡ ከሜረግለዎት የሞለጃ ቀዶጥገና በኋላ ስለሚሰሞዎት የሆድ ቁስለት ህመሜና በአጠቃላይ ስላለውአገልግሎት የተወሰኑ ጥያቄዎችን ልጠይቅዎት እፈልጋለሁ ፡ የዚህ ማጠይቅ ዋና ዓላማ በግሜሽ (ከወገብ በታች) በሚሰጥ ሞደንዘዣየሚወልዱ እናቶችን ጠቤነትና የህሞሁኑ ታን (ማጠንን) በተሞለከተ ለማጥናት ሲሆን እርስዎ ከጥናቱ የሚገኙት ጥቅምም ሆነ ጉዳት የለሞ ፡ ነገር ግን ከዚህ በኋላ በኦፕራሲዮን ለሚወልዱ እናቶች ትክክለኛወን ሞድሃኒት በመሚጥ የእናቶችን ህመምለመቀነስ ይጠቅሜል፡ ፡

ለመሳተፍ ፈቃደኛ ነዎት? ለመሳተፍ ፈቃደኛ ከሆኑ የሞጥለትን ጥያቄዎች እጠይቅዎታለሁ ፡ ፡

ለማንኛውምለሚነሱት ጥያቄ ካለዎት ተሞራሚወን በሞጥለውአድራሻ ማ ጋገር ይቻላል፡ ፡ +251912686917.

Part I: Demographic data and anesthetic base line characteristics.

Serial no.	Variables	
101	Age	_____ years
102	Weight in Kg	_____ kg
103	Height	1 meter & _____ cm
104	Gestational age	_____ weeks
105	ASA status (E if emergency)	A. A. I B. II
106	Parity	_____
107	Duration of surgery	_____ minute
108	Type of local Anesthetic used	A. 0.5 % bupivacaine of _____mg B. 0.5% Bupivacaine _____mg with 20mg Tramadol
109	Time from intrathecal injection to delivery of child	_____ minute

Part II: Questions related to baseline and intraoperative hemodynamic status

S. no.	Vital Sign	Time	Baseline	5min.	10min.	15min.	20min.	30min.	40min.
201	Heart rate								
	BP(mmHg): SBP/DBP								
	(MAP)								
	Respiratory rate								
	SaO_2								

Part III: Incidence of perioperative complication

Serial no.	**Complications**	Answer
301	Hypotension	**A.** Yes B. No
	Nausea	A. Yes B. No
	Vomiting	A. Yes B. No
	Shivering	A. Yes B. No
	Pruritis	A. Yes B. No
	Respiratory depression	A. Yes B. No
	Fetal bradycardia	A. Yes B. No
	Total IV fluid given i intraoperatively	_____**milliliter**
302	APGAR score at 1 minute	
303	APGAR score at 5 minutes	

Part IV: Questions on postoperative pain severity measured by numerical rating scale (NRS)

S.no	NRS score at	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	12 hr
401								

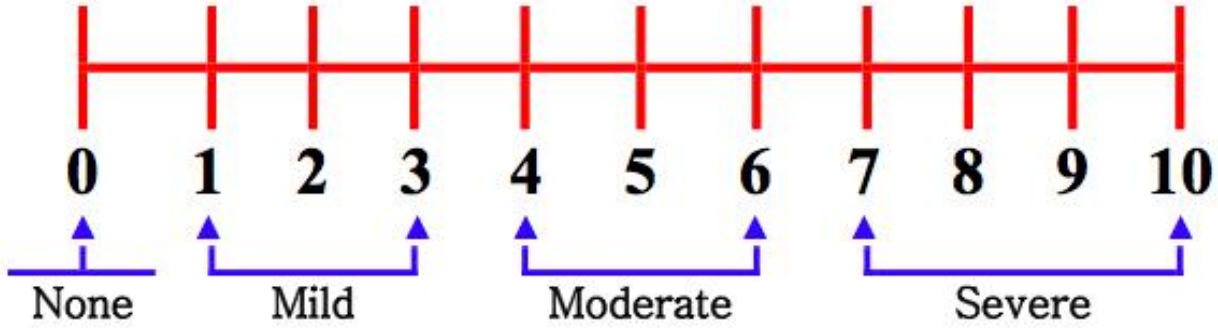
402. Time to first analgesic request time after patient arrived in the recovery or ward

A. Arrived at _____ pm/am (time per 12 hr)
B. Analgesic request time _____ pm/am (time per 12 hr)
C. Duration till first analgesia request _____ minutes

Annex II: Pain Assessment Tool

English version

The numeric rating Scale (NRS)



This scale will be taken 7 times within the first 12 hours and patients will be asked to rate their pain and will be recorded at 1hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr and 12 hrs postoperatively

After training on this tool patients will be asked to rate their pain based on the following:

A. What number would you give your pain on this 0 to 10 scale?
B. When the explanation on the scale will not be clear to the patient, further explanation of the assessment scale will be done.

0= No pain

1-3= mild pain

4-6= Moderate pain

7-10=Severe pain