ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCE
SCHOOL OF MEDICINE
DEPARTMENT OF ANESTHESIA

COMPARING THE EFFECTIVENESS OF DEXAMETHASONE, FENTANYL AND MORPHINE AS AN ADJUVANTS TO INTRATHECAL BUPIVACAINE FOR POSTOPERATIVE PAIN IN ELECTIVE LOWER LIMB ORTHOPEDICS SURGERY AT ADDIS ABABA PUBLIC HOSPITALS 2022/2023. PROSPECTIVE COHORT STUDY

INVESTIGATOR: ALI DIMMA (MSC STUDENT)

A RESEARCH THESIS SUBMITTED TO SCHOOL OF MEDICINE; DEPARTMENT OF ANESTHESIA AS PARTIAL FULFILLMENT OF THE REQUIREMENT IN MASTER OF SCIENCE DEGREE IN ANESTHESIA.

JUNE 2023
ADDIS ABABA, ETHIOPIA

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Full tittle of research project	Comparing the effectiveness of dexamethasone, fentanyl and morphine as adjuvants to intrathecal bupivacaine for postoperative pain in elective lower limb orthopaedics surgery at Addis Ababa public hospital 2022/2023. prospective cohort study
Duration of project	December 1, 2022 to February 28, 2023
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Source of funding	Addis Ababa university
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Declaration

I, the undersigned Msc student declare that this thesis is my original work in partial fulfillment of the requirement for the masters of science degree in anesthesia. I understand that plagiarism will not be tolerated and all directly quoted materials had been appropriately referenced.

Name ……signature…….

Approval of the primary Advisor
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Signature……. Date …….

Date of submission: ……

This thesis work has been submitted for examination with my/our approval as advisors on the masters of science degree in anesthesia.

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LISTS OF ABBREVIATIONS

AaBET	Addis Ababa burn emergency and trauma hospital
AAU	Addis Ababa University
ALERT	All Africa Leprosy and Rehabilitation Training Center
ASA	American Society of Anesthesiologist
BD	Bupivacaine with dexamethasone
BF	Bupivacaine with fentanyl
BM	Bupivacaine with morphine
C/S	Cesarean Section
HR	Heart Rate
IASP	International Association for the study of pain
IM	Intramuscular
IV	Intravenous
LA	local anesthetics
HR	Heart rate
MAP	Mean Arterial Blood Pressure
Mg	Milligram
µg	microgram
NRS	Numeric Rating Scale
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
PACU	Post Anesthesia Care Unit
PNB	Peripheral Nerve block
PCA	Patient Controlled Analgesia
RCT	Randomized control trials
SA	Spinal anesthesia
SD	Standard Deviation
SPO2	Arterial Blood Saturation
SPSS	Statistical Package for the Social Science
TASH	Tikur Anbesa Specialized Hospital
USA	United States of America

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ABSTRACT

Background: *Postoperative pain management during lower limb surgery remained a serious issue despite advances in surgical approach, anesthetic modality, and pain therapy. Spinal anesthesia is the most commonly used anesthetic technique for pain control during orthopedic surgery. The main drawback of spinal anesthesia with bupivacaine is that it only provides analgesia for a brief period of time. Opioids like fentanyl and morphine are commonly used as adjuvants with local anesthetics, while steroids like dexamethasone have lately been studied as an intrathecal adjuvant to lessen disadvantages of spinal anesthesia.*

Objectives: *The main aim of this study was to compare analgesic effectiveness intrathecal morphine versus intrathecal dexamethasone, and intrathecal fentanyl as adjuvant to heavy bupivacaine for management of post orthopedic surgery pain in Addis Ababa hospitals from Dec 1, 2022 to Feb 28, 2023.*

Methodology: *A hospital based multicenter prospective cohort study was employed on 87 patients who undergone elective lower limb orthopedics surgery under SA fulfilling the inclusion criteria. Those who had received bupivacaine with dexamethasone were grouped as (BD-group), those who received bupivacaine with fentanyl were grouped as (BF- group) and those who received bupivacaine with morphine were grouped as (BM- group). The participants in the study were selected by systematic random sampling technique. Data was collected by preoperative chart review, intraoperative observation and postoperative patient interview. The data was entered into SPSS version 20 and analysis of variable was undertaken by using one-way ANOVA, Kruskal-Wallis H- rank test, and χ^2 test.*

Result: *The median numerical rating scale score was significantly lower in BD group during early 8 hours after surgery compared to BF group and BM group. The average duration for the first analgesic request was substantially shorter in the BF group compared to the BD and BM groups.; (367.9±65.64), (702.1±72.09), and (667.07±75.3) minutes respectively ($p < 0.001$). The total tramadol consumption was significantly lower in BD group 50(45-80) compared to BF group 75(55-100) and BM group 70(55-80) with ($p<0.05$).*

Conclusion and Recommendation: *Use of dexamethasone and Morphine as adjuvant with intrathecal bupivacaine are effective analgesic techniques for lower limb orthopedic surgery for prolonging analgesic period, reducing postoperative pain score and analgesic consumption. We recommend the use of intrathecal dexamethasone with heavy bupivacaine as an alternative to morphine for managing postoperative pain during lower limb surgery in resource limited area.*

Key Words: Intrathecal Adjuvants, dexamethasone, opioids, post-orthopedic pain.

CHAPTER ONE: INTRODUCTION

1.1 Background Information

International pain association defined Pain as an unpleasant sensory and emotional experience that is associated with or described in terms of actual or potential tissue damage(1). Postoperative pain is defined as nociceptive pain that the patient's experiences due to surgery that occurred in the recovery room, ICU, or in ward. Pain is the primary discomfort that the patient express anxiety even more than surgery itself, and vital sign to provide information for practitioners during patient management by taking into account its length, affected body part, patient type, intensity, and pathology(2).

Patients undergoing orthopedic surgery typically have musculoskeletal dysfunctions such as unstable fractures, deformities, joint disorders, diseased or necrotic tissues, traumas, or tumors, which complicate the pain management protocol throughout treatment(3).

Globally, around 28.3 million orthopedic surgical procedures were conducted, with Sub-Saharan Africa having the highest number due to trauma, and orthopedic surgical procedures are predicted to increase 4.9% per year(4). The most common surgical treatments include, amputation, joint replacement, arthroplasty, meniscectomy, Open Reduction with Internal Fixation(ORIF), and Closed Reduction with Internal Fixation(CRIF) in fracture(5).

Despite advances in orthopedic procedures and pain management strategies, orthopedic surgery remains one of the most painful treatments discussed in surgical specialties, and insufficient post-operative pain management remains a substantial burden on the health care system(6,7). In the first 24 hour after lower extremity orthopedics operation, 68.7% of patients experienced moderate to severe postoperative pain; more than half of patients experienced it after spinal anesthesia(7).

Inadequately managed postoperative pain leads to a variety of complications following the procedure, including an increased risk of thromboembolic events, respiratory impairment, anxiety, sleep disturbance, a longer hospital stay, and chronic pain after surgery, all of which place a burden on the patient, health care providers (who must provide critical follow-up), and the community (8).

Currently, there are a number of methods available for treating postoperative pain following orthopedic surgery. Examples of these include narcotics (oral and intravenously), peripheral nerve blocks, local infiltration, spinal (LA alone or combined with adjuvant) and epidural analgesia, non-steroidal anti-inflammatory medications, anticonvulsants, multimodal analgesia, patient controlled analgesia(PCA), and paracetamol(3).

Regional anesthesia is the most preferred anesthetic technique for many orthopedic procedures in recent decades. It involves the injection of a local anesthetic solution to peripheral nerves or subarachnoid space that supply sensory and motor neuron to operative structures(9). For short procedures, spinal anesthesia (SA) is the most widely utilized regional anesthetic block because it delivers great anesthesia, minimum cognitive impairment, and good postoperative analgesia (10).

Spinal anaesthesia is achieved by injecting small amounts of local anesthetic (LA) into subarachnoid space. The injection is usually performed in either sitting or lateral position in lumbar spine below the level where spinal cord ends (L2). It is a simple procedure and has the potential to provide excellent operational conditions for surgery below the umbilicus. In spinal anesthesia, bupivacaine has a long duration action that provides analgesia for 130-230 minutes(11)

Bupivacaine is LA that relieves pain by blocking nerve conduction. It is used for suppression of perioperative and postoperative pain and appropriate for procedures lasting 2hours. However, most orthopedic procedures last longer than two hours and require extra anesthesia intraoperatively and immediate analgesia postoperatively (12). So additives as additional technique are desired to prolong analgesic duration to cover both intraoperative and postoperative pain(13). As a result, various additives were commonly investigated with low dose bupivacaine in daily surgical and post-surgical pain suppression and to improve sensory and to extend local anesthetic duration(14).

Opioids are the most commonly utilized additives with local anesthetic, and their use in neuraxial blocks has evolved over the last 50 years(15). Opioid binds on opioid receptors to act in the central and peripheral nerve system to block neurotransmitters that facilitate pain

transmission. Opioids enhance the antinociception of local anesthetics via G protein coupled receptor mechanisms by hyperpolarizing afferent sensory neurons.

The use of preservative-free morphine with bupivacaine has widely practiced in neuraxial blocks across all age groups. Intrathecal Morphine in 0.1-0.2mg range has demonstrated good analgesic efficacy in obstetric and orthopedic subsets(13). Morphine is relatively hydrophilic and remains in CSF for a longer time and occupies the rostral receptor site for longer duration. However, its use in neuraxial blocks causes respiratory depression (both early and late), nausea, vomiting, pruritus, and urinary retention. Additionally intrathecal fentanyl with dose range of 10-25 µg has also been shown to extend the analgesic duration and fasten sensory block with a better adverse effect profile than morphine(13,14).

Dexamethasone is a glucocorticosteroid that works by reducing ectopic neuronal discharge, inhibiting K^+ channel mediated discharge of nociceptive C-fibers, and reduce the release of inflammatory mediators(16). It reduces the onset time and increase the duration of analgesia when administered alongside a local anesthetic during regional anaesthesia. This may be a result of reduced regional blood flow and inflammation, thus slowing local anesthetic absorption(16). Many clinical study uses intrathecal dexamethasone at doses ranging from 4 to 8 mg to standard doses of hyperbaric bupivacaine 0.5% in orthopedic surgeries(13).

1.2 Statement of the problem

Postoperative pain is type of acute nociceptive pain that occurs due to skin incision, extensive bony and soft tissue extraction and manipulation, and inflammatory mediator release after a surgical procedure. Unrelieved pain after surgery can interfere with sleep and physical functioning, negatively impacting patient wellbeing on multiple levels(17). Inadequate pain management is critical problem in surgical patients which results in negative outcomes on cardiovascular and respiratory system as well as poor wound healing, a prolonged hospital stay and increased health care cost(18).

Evidence from a prospective Germany cohort study of 50,523 patients from 179 surgical groups showed that pain score on immediate postoperative day were highest after orthopedics procedure. From 40 procedures with highest pain score; 22 were orthopedics procedures on extremity and only 15.5% of patients from 3,462 orthopedics cases receives regional anesthesia for pain treatment(6)

In Africa, controlling postoperative pain remains a serious challenge, as up to 95.2% of patients experience it and most of clinical setting in the content have shortage of opiates for controlling moderate to severe pain(19). Study conducted in Tanzania on 281 patients who undergone elective lower limb surgery showed that; 70% of patients had moderate to severe postoperative pain and 31.7% of patients had numeric rating score (NRS) of higher than 7 during immediate 24 hour after surgery and pain was mainly managed by systemic opioids(20).

According to survey study conducted in saint Paulos health and Millennium medical college (SPHMMC) about 49.5% of orthopedics surgical patients develop moderate and sever pain immediately after surgery and the remaining 47.7% of patients develop mild pain at that time and 54.7% of patients developed it after operated under SA. Majority of the patients were managed by tramadol with diclofenac (47.9%), diclofenac alone (29.4%)(21).

According to a study conducted at Jimma university specialized hospital, approximately 88.2% of surgical patients experience moderate to severe pain 6 hour after surgery; 58.4% of patients were inadequately treated during this time; and approximately 57% of patients require more analgesic prescriptions at this time. Despite higher severity of pain by NRS score at 6, 12, and 24 hours

(6.5±1.63, 5.7±1.6, and 4.9±1.6cm, respectively), postoperative pain was mostly treated with tramadol (92.9%) and diclofenac (7.1(22).

Despite years of progress in pain management, tramadol and NSAID continue to be the mainstay of postoperative pain therapy in many Ethiopian clinical setting(7,22). Because most opioids have severe side effects such as nausea, vomiting, pruritus, constipation, and drowsiness, their usage is limited(23), and NSAIDs alone are insufficient for controlling postoperative pain(21).

Due to limited analgesic duration and greater pain score in postoperative period if bupivacaine was administered alone, anesthetists in our clinical setting prefer to combine additives such as dexamethasone, fentanyl and morphine with it(24,25). There is a scarcity of resources such as opioids, epidural kits, and peripheral block equipment, which aids in the management of severe and extreme pain.

Despite increased emphasis on pain management programs and the establishment of new pain management standards, many patients continue to experience severe pain following surgery, and researchers are working to develop better analgesics therapy to lengthen pain free period and reduce complications. To find a better adjuvant to improve the patients` postoperative pain management, Single shoot spinal block technique combining bupivacaine with multiple adjuvants is often used.

1.3 Justification of the study

One of the main concepts of postoperative pain management is that the patient`s need and expectations for safe and efficient pain control after surgery. Effective pain control can lessen psychological and physical stress after surgery; ultimately decrease postoperative complication and increasing the body's ability to recover. However, there is no one medication or method that can provide the best pain relief while maintaining normal physiologic function without imposing additional risk to surgical patient. There are a few studies done in our country to evaluate the analgesic approach of postoperative pain treatment despite postoperative pain was not appropriately controlled even by opioid and non-opioids in clinical setup(22).

Many studies have been performed to compare quality of intraoperative anesthesia and adjuvant adjusted reduction in spinal anesthesia complication by using different additives with LA in orthopedics surgery. Despite the presence of racial, cultural, genetic and socio demographic difference in the perception of pain; most of these studies have been conducted in developed world and western population(26,27). And there was no study conducted on comparing analgesic duration of dexamethasone and morphine as adjuvant with bupivacaine for postoperative pain control in orthopedics surgery.

The World Health Organization (WHO) analgesic ladder recommend regional and peripheral nerve block as part of a multimodal analgesia in the perioperative and postoperative period to reduce opioid costs and side effects(28). Even though epidural and peripheral nerve block has effective results in postoperative pain control; the cost and inaccessibility of epidural kit and scarcity of equipment for peripheral nerve block made us to find alternative therapy for pain control in a resource limited area.

In our country as far as our knowledge and searching ability, there is no related published evidence on the same topic in the same area. Therefore, the results benefit our patients, anesthetists and others as a source of information for further research and a major contribution to the literature. Furthermore, the findings of this study will be useful for program planners and policymakers in developing the improved pain management protocols that cover immediate postoperative pain and selection of appropriate adjuvant with bupivacaine to promote patient satisfaction with anaesthesia and surgery and to decrease health care cost in resource limited area.

CHAPTER TWO: LITERATURE REVIEW

Many surgeons and anesthesiologists continue to struggle with postoperative pain management, particularly in low- and middle-income countries(22). The incidence of moderate and severe pain varies around the world, ranging from 14% to 55% in Western countries(29), 95.2% in Africa(19) and 88.2% in our country(22) with the highest incidence on first day of surgery.

Despite all research efforts to improve acute postoperative pain management; still up to 30% of operated patients shows pain scores higher than 7 on a visual analog scale (VAS) of 0-10(29). A study conducted by Ansbert S.et al found that the prevalence of postoperative pain after elective orthopedic surgery was 61%, 73%, 67% and 58% at 4, 24, 36 and 48 hours respectively(30).

A number of studies have been addressed analgesia for lower limb orthopedic surgery including epidural, spinal nerve block, peripheral nerve block, multimodal analgesics, local anesthetics infiltration and opioid based management(13,14). Various adjuvants were used with local anesthetics during spinal anesthesia for intraoperative analgesia as well as to extend analgesic effects of LA for postoperative period(13).

2.1 Intrathecal dexamethasone with bupivacaine

Dexamethasone administration to surgical patients decreases pain severity by slowing LA absorption, due to reducing systemic blood flow and inflammation at surgical site(16).

A Study done in Iran on 2011 by Aliakbar N *et.al* effects of adding (8mg) dexamethasone on 15mg of heavy spinal bupivacaine showed that; there is significant improvement on duration of onset sensory block and prolonged the duration of analgesia (401.92±72.44 minutes) versus (202±43.67 minute) in the case and control group respectively with ($P<0.05$) and the first analgesic prescription in case group was significantly delayed(12).

The study of randomized control trail in India on 2017 by Subrata D et al on Evaluation of efficacy of dexamethasone (8mg) as an adjuvant to bupivacaine(15mg) for spinal anesthesia in abdominal surgery showed that pain free time-period was longer in case compared to control; 388.65 ± 56.43 and 198.45 ±49.23minute respectively(31).

A recent study in India on 2019 conducted by Sharma A et al on assessment of efficacy of 8mg dexamethasone as an adjuvant to 15mg bupivacaine for spinal anesthesia showed that pain free time-period for case group was 214.25 minutes as compared to control group that was 225.54 minute which is less time in case groups compared with most study but they does not compare the time at which the patient require first analgesia and NRS score between groups (32).

The study done in Egypt on 2020 by Ashraf S *et.al* on comparative study between intrathecal 8mg dexamethasone and 5µg dexmedetomidine on 12.5mg heavy bupivacaine for cesarean section showed that; time to first rescue analgesia for dexamethasone group was significantly longer than dexmedetomidine 196.69 ± 5.4 versus 174.26 ± 12.1 respectively for p value < 0.05(33).

The study done in Egypt on 2021 by Ahmed Abd EL-Hamed Hassan *et al* on comparison of 4mg intrathecal dexamethasone versus 10 µg dexmedetomidine with 10mg heavy bupivacaine for lower limb orthopedics surgery showed that; prolonged duration of analgesia for dexamethasone group (319±21.06min) than control (199.75±18.22) and the first analgesic request time for dexamethasone group was delayed than control group with $p<0.05$(34).

The randomized control study done in India on 2021 by Kaur N et.al on comparing the effect of 4mg dexamethasone versus 25µg fentanyl as adjuvants to 12.5mg heavy spinal bupivacaine for orthopedic surgery showed that; duration of analgesia was longer in BD group (311.43±13.59) than BF group (197.86±12.14). Time to require first analgesia was delayed in dexamethasone groups compared with fentanyl and control group. No patient requires analgesic for first four hours after surgery compared to 30 patient and 11 patients requires analgesia at that time for fentanyl and control groups. 20%, 11%, and 8% of patients develop pruritus, nausea/vomiting and shivering respectively in fentanyl groups(10).

A more recent prospective comparative randomized double blinded study in Egypt on 2022 by Mohammed E *et.al* using 4mg dexamethasone with 15mg heavy bupivacaine for spinal anesthesia during lower extremity surgery showed that; VAS scores had no difference between groups during early 8^{th} hour of postoperative period for dexamethasone and control group. However, VAS at 10, 12, and 24-hour was significant between dexamethasone and control

group. Mean onset time of sensory blockade was early on dexamethasone group than control(35).

The study done in Iran on 2022 by Mohammad S et.al on comparison of intrathecal 4mg dexamethasone and 12.5mg bupivacaine alone for cesarean section; mean VAS score was less for dexamethasone compared to control (5.4±1.0, 9.6±1) and first analgesic request time was (345.83±0.4, 251.52±1.8) longer in dexamethasone groups than control groups(36).

2.2 Intrathecal Fentanyl with bupivacaine

Fentanyl appears to be one of the most commonly used neuraxial opioids, and it is approved for use in a variety of countries(37). Because of its relatively high lipid solubility, it has more restricted segmental activity and a faster onset of action than other opioids. Intrathecal fentanyl was used with doses ranging from 10 to 25µg provide 2-4 hours of analgesia(38).

The study done in Turkey on 2010 by Ayten S, Kemal S and Zeynep E on comparative study of intrathecal 25µg fentanyl versus 0.2mg morphine with heavy bupivacaine showed; the first analgesic request time in fentanyl group was shorter compared to morphine groups and almost equally less person require analgesia for first 4 hours after surgery in both groups. The intrathecal morphine provide a long duration of postoperative analgesia; however the duration gets longer when it was combined with plain bupivacaine instead of heavy(39).

The RCT study done in Iran on 2012 by Khezri M et.al on comparison of 25µg fentanyl and 15mg bupivacaine lower limb surgery showed that; Time for first analgesic request was more delayed in case group compared to control group; 699.375 ± 79.80minute and 343.76 ± 76.32minute respectively; for p value <0.05. Onset of sensory and motor block was significantly faster in fentanyl group and more patient develop hypotension and bradycardia in fentanyl group and reduces total consumption of analgesia in 12hr period (40).

The study of RCT in Iran on 2014 by Hassani V et.al at comparing 15mg bupivacaine with sufentanyl versus 15mg bupivacaine with 25µg fentanyl in spinal anesthesia for patients undergoing lower extremity surgery showed that, VAS score was 5.4 ± 1.8 for fentanyl and 6.9 ± 2.7 for control group. First opioid request hour was 4.2 ± 2 and 3.8 ± 1.1 for fentanyl and control groups respectively and dose of opioid was 1.1 ± 0.3 and 2 ± 0.6mg for fentanyl and control groups respectively(41).

The prospective randomized double blinded study on comparing intrathecal bupivacaine combined with fentanyl and sufentanil in abdominal and lower limb surgeries in India on 2015 showed that, the duration of analgesia was longer for fentanyl group compared to control, 216.70 ± 27.48 min, and 119 ± 14.65 min respectively(42).

The result of the study of randomized clinical trial in Iran on 2018 by Rahimzadeh P et.al, Comparative addition of 25µg fentanyl to 12.5mg heavy intrathecal bupivacaine in orthopedic procedure in lower limbs showed; that first analgesia request time (min) 296.33 ± 44.83 for fentanyl and 221.83 ± 22.26 bupivacaine alone and NRS six hours after surgery 6.16 ± 1.44 for fentanyl group and 6.30 ± 1.17 for bupivacaine alone group(43).

The prospective cohort study done in Ethiopia on 2022 by Ebrie A et al on hemodynamic and analgesic effects of injecting 10mg bupivacaine with 25µg fentanyl versus 8mg bupivacaine with 25µg fentanyl in obstetrics patient during cesarean section showed that; the intraoperative hypotension is significantly reduced if low dose of bupivacaine has used for spinal block and no patients develop nausea and vomiting intraoperatively from 30 patients who take low dose bupivacaine with fentanyl and 2 patients develop shivering intraoperatively and first analgesic request time was 294.6±99.5min(25).

2.3 Intrathecal morphine with bupivacaine

The study done in Malaysia on 2009 by Salmah G and Choy YC on comparing the effect of intrathecal morphine (0.1 mg) versus intrathecal fentanyl (25 µg) for analgesia after cesarean section showed that; the time to first PCA morphine dose was at (297.4 ± 112.0) minutes in morphine group and (197.7 ± 60.0) minutes in fentanyl group with ($p<0.05$). Over 24hour study period, there were significantly lower VAS pain scores at 6, 12, 18 and 24 hours in morphine group compared to fentanyl Group ($p<0.05$)(44).

The randomized control trial in Japan on 2010 by Masaaki M et.al on efficacy of 0.2mg intrathecal morphine with 15mg bupivacaine versus 15mg alone for lower extremity bone fracture surgery showed that; the mean VAS score for morphine groups was significantly lower at 4 hour after surgery, at mean pain score (1.6 ± 2.2 mm) for the morphine group and a mean pain score 6.6 ± 3.8 mm for the control group ($p<0.001$). In addition the time until the first use of

supplemental analgesics was 13 ± 9.8 hour in morphine group and 3.7 ± 1.8 hour in control group with ($p<0.001$)(45).

The RCT study done in Turkey on 2011 by Karaman S et al the effectiveness of adding 0.2mg morphine and 25µg fentanyl to 10mg bupivacaine during spinal anesthesia showed that; first analgesic request time in morphine group (20.5±6.7) hour and in fentanyl group (4.2±3.9) hour and 55% of patients in fentanyl groups develop postoperative pruritus compared to 35%of patients in morphine group develop postoperative pruritus and more patient develop nausea in morphine group at postoperative period. However there was no significance between groups in developing nausea/vomiting and pruritus during intraoperatively(46).

The randomized control trial study in China on 2016 by Qi X et.al on comparison of intrathecal 0.1mg morphine and 10mg bupivacaine alone for cesarean section showed that; time to first analgesia request was prolonged in morphine (16.78±5.90) versus 3.53±1.68hr for control group. Total volume of analgesics required for 24hr was 18.75±4.70 and 56.92±14.02 for case and control groups(47).

The randomized control study done in Turkey on 2016 by Refika Kiliçkaya et al on the Effects of adding intrathecal 25µg fentanyl versus intrathecal 0.1mg morphine to 12.5mg heavy bupivacaine for spinal anesthesia in elective total knee replacement surgery; there was significant difference between groups on intraoperative hypotension and postoperative nausea and vomiting. The first analgesic request time was shorter in fentanyl group (2.6 ± 0.6) versus 5.9 ± 1.3 for morphine and almost all patients 24 (96%) requires analgesia at 6hours after injection of bupivacaine with fentanyl groups and more than half patients (14 (56%) requires additional analgesia at 6hour period after injection of bupivacaine with morphine. However there is no significant difference in additional analgesia request between groups at 12hours(48).

The RCT study done in south Korea on 2022 by Y Choi et al showed that injecting 0.4mg morphine with 5mg bupivacaine for postoperative analgesia during liver surgery; the postoperative pruritus was more common on those patients who take bupivacaine with morphine 9 (30%) patients from 30 total patients who take drugs for treatment of pain(49).

2.4 Conceptual frame work

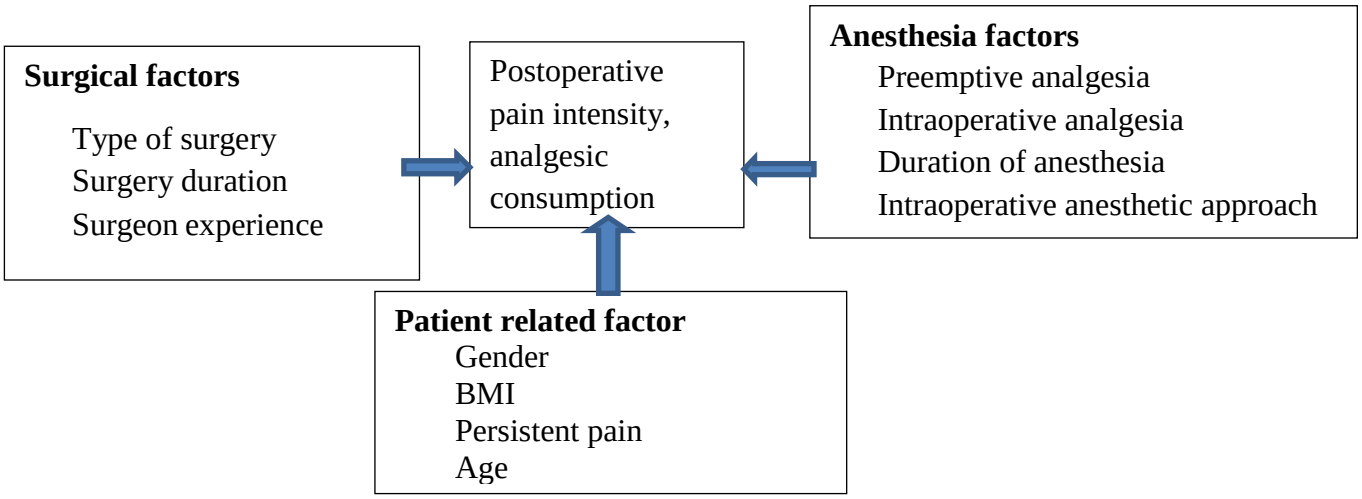

Figure 1 conceptual framework adapted from different pieces of literatures (7,50)

Research hypothesis

Pain intensity scale and time to first analgesic request is different in patient who receives bupivacaine with morphine and dexamethasone intrathecally compared to those who receive fentanyl for postoperative pain management for lower extremity orthopedics surgery.

HO: There is no statistically significant difference in NRS, time to first analgesic request and total analgesic consumption between groups

HA: There is statistically significant difference in NRS, time to first analgesic request and total analgesic consumption between groups.

CHAPTER THREE: OBJECTIVES

3.1 General objective

To compare the analgesic effectiveness of dexamethasone, fentanyl, and morphine as adjuvants to spinal bupivacaine for postoperative pain management in elective lower limb orthopedic surgery at public hospital in Addis Ababa between December 1, 2022, and February 28, 2023.

3.2 Specific objective

To compare pain score by NRS among groups

To compare time to first analgesic request among groups

To compare total analgesic consumption among groups over 24 hours

CHAPTER FOUR: METHODOLOGY

4.1 Study area

This study was carried out in Tikur Anbesa specialized hospital (TASH), ALERT, and AaBET Hospitals, all of which are public hospitals in Addis Ababa, Ethiopia`s capital. It is the country`s largest city with an area of 540km^2 and 11 subcities. The city has 13 government hospitals; the above hospitals were selected purposively for their case load in trauma and orthopedics surgery(50). AaBET hospital was established in 1968 by Emperor Haile Selassie, and currently it serves as medical school by affiliating with SPHMMC since 2007 and it have 200 beds for burn, emergency and trauma patients and 2 beds for elective orthopedics surgery. ALERT and TASH hospitals were operated under federal government. ALERT hospital was opened in 1922 and it contains 240 beds and 3 operation table for orthopedics procedures. TASH was established in 1961 and it has 800 beds and 4 operation table for orthopedics surgery. It is a tertiary care teaching hospital affiliated with Addis Ababa University. These hospitals have seven operation table for elective orthopedics surgery and average number of lower limb orthopedics surgery done at each hospital is six to eight per day and from those average of three to four patients undergo elective lower limb surgery. Review of anesthesia and orthopedics log books the above hospitals showed that; there were a total of 222 patients underwent lower limb orthopedics surgery under spinal anesthesia from September 1, 2022 – November 1, 2022. Anesthetists use opioids and dexamethasone for extending LA duration.

4.2 Study design and period

A multicenter a hospital based prospective cohort study was employed between December 1, 2022, and February 28, 2023.

4.3 Population

4.3.1 Source population

All patients who underwent lower limb orthopedics surgery under spinal anesthesia at TASH, AaBET and ALERT hospitals

4.3.2 Study population

All ASA I and ASA II adult patients who underwent elective lower limb orthopedics surgery under spinal anesthesia that fulfills eligible criteria during study period.

4.4 Eligibility Criteria

4.4.1 Inclusion criteria

ASA I and II physical status, adult patients and elective orthopedics procedures under spinal anaesthesia were included.

4.4.2 Exclusion criteria

Patients who take peripheral block in Operation table, recovery room, and in ward.
Failed spinal, combined spinal with general anesthesia,
Other doses of intrathecal morphine, dexamethasone and fentanyl for adjuvants during SA
Patients who have phantom pain, polytrauma and patient refusal for follow up.

4.5 Study variable

4.5.1 Dependent variables

- Pain severity (measured by: NRS score),
- Time to first analgesic request in minutes
- Total postoperative Analgesic consumption in 24 hours in mg

4.5.2 Independent variables

- Socio demographic characteristics: age, sex and BMI
- Duration of surgery
- ASA physical status
- Exposure status (dexamethasone or morphine or fentanyl)

4.6 Operational definition

Postoperative pain: defined presence of pain during postoperative period which is occurred at an immediate postoperative time after surgical procedures.
Numerical pain rating scale (NRS): is the most appropriate approach of pain assessment in which patients are asked to point to the number between 0 and 10 that best describes their pain severity at various time intervals throughout a 24-hour period (5).

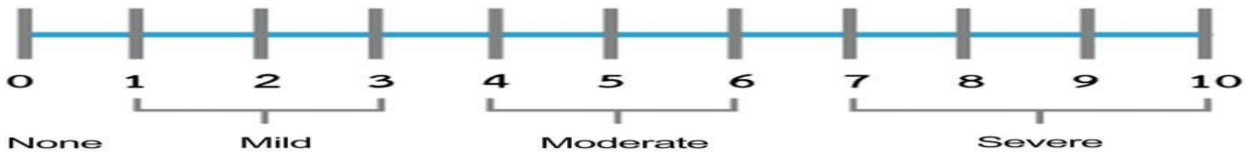

Figure 2 Numeric Rating Scale of pain intensity sore adapted from literature (6)

Time to first analgesic request: is the time at which the patient request first rescue analgesia for pain after spinal anesthesia.

Adjuvants: are drugs; when co-administered with local anesthetic agents; it improve the speed of onset sensory block, prolong duration of analgesia and it counteract side effects of LA(13).

Total post-operative analgesia consumption: Cumulative analgesic drug dosages given in mg within the first 24 hours following spinal anesthesia.

Duration of analgesia: is defined as the time in hour during which the patient does not report any pain following sensory block during spinal anesthetic injection.

Duration of motor block: the duration between the ends of Bromage 3 and free feet movement after intrathecal injection.

Motor block was assessed by the modified Bromage scale

0: No motor loss, 1: Inability to flex the hip, 2: Inability to flex the knee and 3: Inability to flex the ankle(25).

4.7 Sample size and sampling technique

4.7.1 Sample size determination

Our primary goal was to compare pain intensity by numeric rating scale (NRS) score among groups at 24 hours, time to first analgesic request, and total analgesic use following surgery. According to results from recent study in Asia and Egypt, the mean pain score after surgery was 1.31±1.3 when morphine has administered with heavy bupivacaine(48), and mean of total analgesic dosage, when fentanyl has administered with heavy bupivacaine was 2.23±0.43(51) and mean time for first analgesic request when dexamethasone has administered with heavy intrathecal bupivacaine was 2.97±0.32hr(34), with $\alpha = 0.05$, power of study (1-β) of 90%. Using comparison of mean formula;

$$n = (z\,\alpha/2 + z\,\beta)^2\,(\sigma 1^2 + \sigma 2^2)/(\mu 2 - \mu 1)^2$$

$N1 = (1.3^2+0.43^2)\ (1.96+1.28)^2 / (2.23-1.31)^2=24$

$N2= (1.3^2+0.32^2)\ (1.96+1.28)^2 / (2.97-1.31)^2=7$

$N3= (0.43^2+0.32^2)\ (1.96+1.28)^2 / (2.97-2.23)^2=6.$

Using largest sample size for all group and added a 20% contingency, this study involved total of 87 patients, since there are three study groups.

4.7.2 Sampling procedure

Participants in the study were chosen by through systematic random sampling. According to the reviewed data, the average number of elective lower limb orthopedics surgeries performed under spinal anesthetic with dexamethasone, fentanyl, and morphine additives for the last three study months within study hospitals; 54 in ALERT, 36 in AaBET and 45 in TASH was (N=135), with total of 87 patients recruited with a probability of around 65%. Using the consecutive patients scheduled for elective lower limb surgery as a sampling frame, data was collected from 2 participants for every 3 patients who underwent lower limb orthopedics surgery, and the sampling interval of K=N/n 135/87 = 1.5.

The adjuvants were prepared and coded by the data collector anesthetist; selected patients from the daily schedule drew the adjuvant from alternatives by lottery method. Anesthetists in selected hospitals employ 20mg bupivacaine alone or 15-17.5mg bupivacaine with morphine, or fentanyl, or dexamethasone. Each patient receives 15mg bupivacaine and 1ml of additives. Group BF (fentanyl group) participants who takes 15mg bupivacaine with 25µg fentanyl, Group BM (morphine group): participants who takes15mg bupivacaine with 0.2mg morphine, and BD (dexamethasone group): patients who takes 15mg bupivacaine with dexamethasone(4mg).

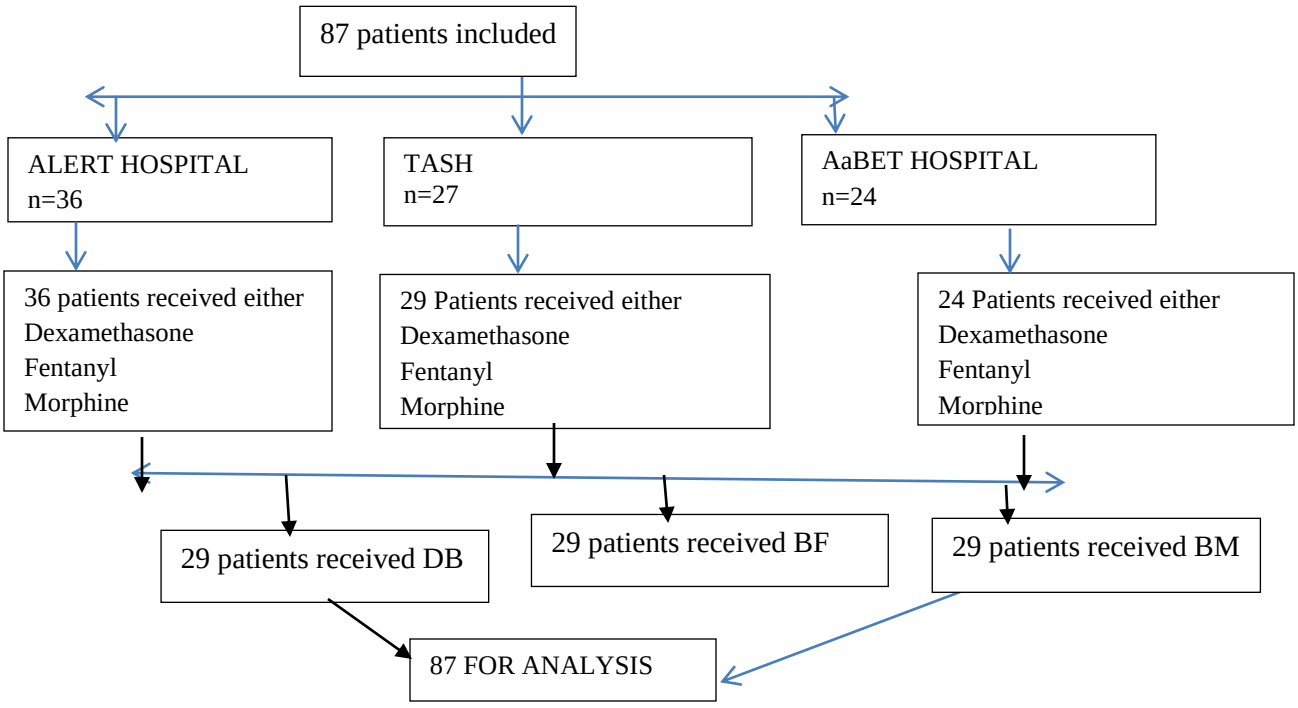

Figure 3 Proportional allocation and enrollment chart for patients.

4.8 Data collection technique and patients

The data was collected using a pretested questionnaire written in English that included an Amharic and English consent form, demographic data, initial vital signs, and other variables. Three BSc anesthetists and two MSc anesthetists were assigned as data collectors. After reassuring the patient about the procedure, verbal and written agreement was obtained from each study patient; those who met the inclusion criteria and agreed to participate in the study were thoroughly evaluated by history-taking and chart review before anesthesia, intraoperative observation and postoperative patient interview. The patient was instructed how to rate their pain severity postoperatively on an eleven-point NRS scale ranging from 0 to 10 by the data collector on the morning of surgery

All drugs were prepared prior to spinal needle insertion, and normal monitoring was used. Demographic information such as gender, age, BMI, and baseline vital sign hemodynamic variable were collected. After cleaning the location with antiseptic solution, the responsible anesthetist administered spinal anesthetic in the sitting position, containing bupivacaine with dexamethasone, fentanyl, or morphine for additions. The patient was then instructed to lie down

in a supine position immediately following the administration of SA. The data collector measures the heart rate and mean arterial pressure (MAP) every 5 minutes, 10 minutes, 15 minutes, 30 minutes, and 1 hour, and then every 30 minutes for the next 4 hours. The outcome on a piece of paper labeled with the patient's file number. Following spinal anesthesia, intravenous fluid co-loading was administered throughout the intraoperative time.

The beginning of sensory block was determined and documented by pinching with a toothed pick up. The modified Bromage scale (26) was used to assess and score lower extremity motor blockage.

Time of onset of motor blockade, the time elapsed from the commencement of spinal anesthesia from Bromage grade 0 to grade III, and duration of motor blockade, the time elapsed from the start of the motor block to complete return of muscular strength.

Postoperative pain was measured using a numeric rating scale at 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours.

When the patient's NRS was greater than 3, responsible staff administered the first rescue analgesics, which determined the time from the onset of sensory block to the first painkiller request. Any complications related to spinal anesthesia were handled by competent personnel.

4.9 Data quality control

To ensure the data's reliability and validity, data collectors and supervisors received training and brief orientations on the objectives of evaluation tools. Furthermore, a pretest of the data collection tool (questionnaire) was performed at TASH two weeks before the commencement of actual data collection, which is not included in the main study. On the day of data collection, the primary investigator reviewed the data for completeness, accuracy, and clarity. Regular supervision and follow-up were maintained. Incomplete data was not entered into the SPSS database. Data cleaning and cross-checking for missing data, as well as organizing documents sequentially and storing them in a safe and secure place was completed.

4.10 Data analysis and interpretation

Data was checked manually for completeness and was cleaned and entered into SPSS version 20 for analysis. The data was test for normality using histogram and Shapiro Wilk normality test and homogeneity of variance by Levene’s test for normally distribution. Data was normally

distributed and homogenous with exception of postoperative pain score and analgesic consumption. Data was statistically described in terms of mean ±SD for one way analysis of variance (ANOVA) test result, median (IQR) for Kruskal Wallis test result and frequency (%) for chi square test result. Comparison of normally distributed numerical variables between study groups was done by using one way (ANOVA) with post hoc analysis for multiple tests and non-normally distributed data was done by using Kruskal-Walli's test. The comparison of categorical variable was done by using chi square test and p value <0.05 was considered as statistically significant.

4.11 Ethical Consideration

Before beginning a study, ethical approval was acquired from the anesthesia department ethical clearance committee. Official support letters were sent to hospitals, and permission for data collection was obtained from a competent authority who prepared IRB letters for approval in each research hospital. The study's goals and significance were described to the patients verbally and in writing, and each participant provided informed permission. Confidentiality was maintained throughout the investigation by omitting identifiers and identifying patients using codes. The patients' participation in the study was entirely voluntary; those who refused to engage in the study or who desired to withdraw at any time were not restricted.

4.12 Dissemination plan

The research will be presented to the full anesthesia department team. It will also be presented at the annual research conference of the Ethiopian Anesthetist Association (EAA). The study will be submitted to reputable publications for publication.

CHAPTER FIVE: RESULTS

5.1 Demographic and preoperative Characteristics

During the study period, a total of 87 patients (29 lower limb orthopedic patients in each group) were included for final analysis based on whether they received spinal anesthesia with bupivacaine and dexamethasone, or bupivacaine and fentanyl or bupivacaine and morphine at the beginning of surgery for postoperative analgesia. There was no statistically significant difference among the groups with respect to Sociodemographic patient characteristic; like age, sex, BMI, ASA status and preoperative diagnosis.

Table 1 Sociodemographic characteristics of the patients who underwent lower limb orthopedics surgery at study hospital in study period (n1=n2=n3=29).

	Spinal anesthesia adjuvants			**P value**
	BD	BF	BM	
Age(years)*	36.6 ±14.4	34.5±12.5	32.2±10.14	0.408
BMI (kg/m^2) *	21.9±1.6	21.9±1.8	21.9±1.3	0.967
SEX(M/F)	18/11	16/13	23/6	0.137
ASA status: ASA I	20(69%)	23(79.3%)	20(69%)	0.596
ASA II	9(31%)	6(20.7%)	9(31%)	
Diagnosis				
Upper leg bone	9(31%)	11(37.9%)	15(51.7%)	
The knee	7(24.1%)	4(13.8%)	8(27.6%)	0.126
Lower leg bones	10(34.5%)	8(27.6)	6(20.7%)	
Foot bone	3(10.3%)	6(20.7%)	0	
Surgeon's experience				
Resident	7(24.1%)	7(24.1%)	8(27.6%)	0.941
Senior	22(75.9%)	22(75.9%)	21(72.4%)	

NB: Value are presented as: Mean±SD, Number (%), BD= bupivacaine with dexamethasone, BF= bupivacaine with fentanyl and BM= bupivacaine with morphine, BMI = body mass index, one way ANOVA (*) and chi-square test used, $p<0.05$ was considered as significant.

5.2 Comparison of perioperative heart rate and mean arterial blood pressure at different time interval

A one-way ANOVA test was run to determine if there were difference in mean heart rate and mean arterial blood pressure at different time interval between groups. The result showed that there was no significant difference in perioperative heart rate and mean arterial blood pressure at all-time interval as shown in table 2 and table 3 respectively.

Table 2 perioperative heart rate at different time intervals between groups at study hospital in study period (n1=n2=n3=29).

Spinal anesthesia adjuvant	**HR @ 5min**	**HR@ 10min**	**HR @ 15min**	**HR @ 30min**	**HR @ 60min**	**HR@ 90min**	**HR @ 120min**
BD	78.03±7.4	79.1±7.9	73.7±5.8	75.1±4.6	82.8±7.3	73.9±4.6	75.1±5.5
BF	78.4±7.5	79.6±6.4	73.76±5.1	74.5±5.6	82.1±7.7	73.5±5.1	73.8±4.2
BM	81.1±6.7	79.4±7.2	74.3±4.6	75.3±6	84.2±6.7	73.6±6	74.2±5
P value	0.208	0.968	0.879	0.858	0.544	0.947	0.586

NB: Value presented as Mean±SD: One way ANOVA test, and $p<0.05$ taken as statistically significant

Table 3 Perioperative mean arterial pressure at different time interval between groups at study hospital in study period (n1=n2=n3=29).

Spinal anesthesia adjuvant	**MAP@5**	**MAP@10**	**MAP@15**	**MAP@30**	**MAP@60**	**MAP@90**	**MAP@120**
BD	86.0±5.3	85.07±5.7	83.5±6.5	83.9±5.3	74.59±4.7	82.6±6	81.3±5.5
BF	84.86±5.7	85.5±6.7	83.1±5.2	81.48±6.5	74.8±5.7	80.8±6.2	82.8±7.7
BM	88.1±5.4	85.8±6.2	86.6±5.8	84.8±5.9	73.7±4.8	83.1±5.4	84.38±6.5
P value	0.081	0.905	0.051	0.096	0.684	0.287	0.225

NB: Value presented as Mean±SD: One way ANOVA test, and $p<0.05$ taken as statistically significant

5.3 Comparison of postoperative pain NRS score among groups

The Kruskal Wallis test was used to compare the median postoperative pain score between groups. The result was comparable at 2hour and 24hour. In the next 4 and 6 hours of postoperative period; the median pain score was significantly higher in the BF group compared with BD and BM group 1(0-2) vs 0(0-0) vs 0(0-0) cm at 4hr and 5(3-6) vs 1(0-1) vs 2(1-2) cm at 6hr respectively. At 8 postoperative hours; median pain score was significantly higher in BM group compared to BD and BF group; 4(3-5) vs 2(1-3) vs 2(2-5) cm respectively with p-value <0.05. The median pain score was significantly lower in BF group compared to BD and BM group, 2(1-4) vs 5(3-5) vs 4(2-5) cm at 12 hours respectively, (p<0.05). There was no median NRS score difference between the three groups in 24hour after surgery with *p* value >0.05 as shown in figure [4].

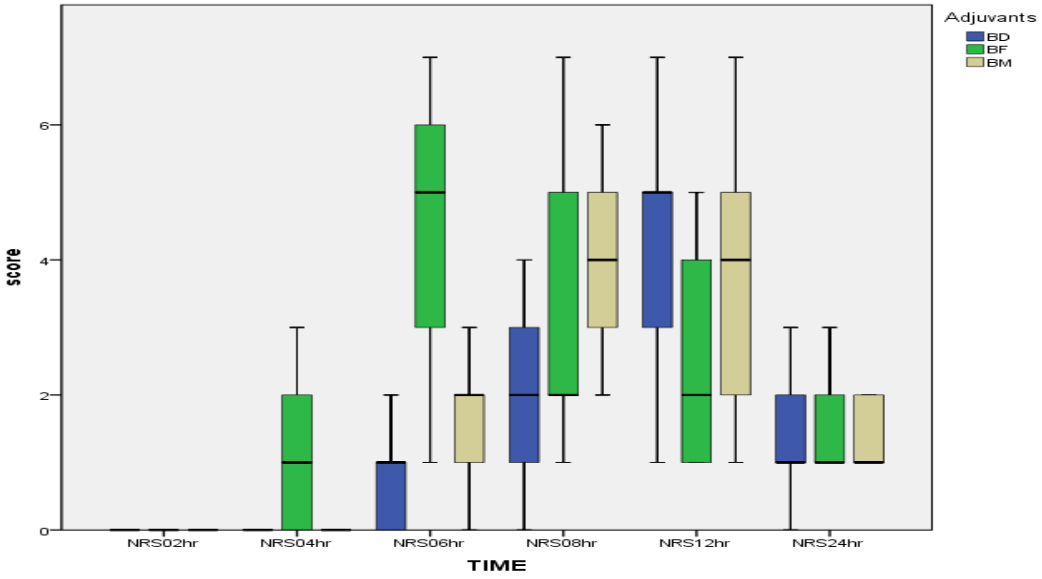

Figure 4 Whisker and Box plot showing median and interquartile range of postoperative pain using NRS score of patients who underwent elective orthopedics surgery under SA.

5.4 Comparison of first rescue analgesic request time and postoperative analgesic consumption between groups

A one-way ANOVA test and Kruskal Wallis test were run to compare the mean and median time taken for first analgesic request time and postoperative analgesic consumption respectively between group. The result showed that; the time from first intrathecal injection to initial rescue analgesics was significantly different among groups with p value=0.001. Patients in group BF

had request the first analgesics at earlier time compared to BD and BM group, 367.93±65.64 vs 702.1±72.09 vs 667.07±75.3 minute respectively as shown in [Fig 5]

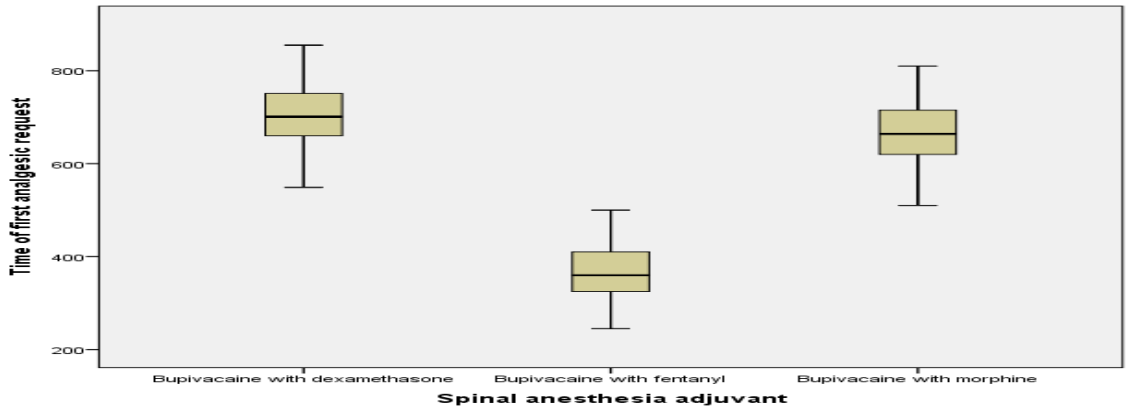

Figure 5 comparison of meantime for postoperative first analgesic request among groups of patients in study hospital.

The total tramadol consumed for postoperative pain was significantly lower in BD group compared with BF and BM groups with p <0.05.

Table 4 Postoperative analgesic request time and total analgesic consumption at study hospital in study period.

Variables	spinal anesthetic adjuvants			Post hoc test		
	BD	BF	BM	P^1	P^2	P^3
First analgesic request time(M)*	702.1±72.09	367.93±65.64	667.07±75.3	0.152	0.001	0.001
Total tramadol consumption¥	50(45-80)	75(55-100)	70(55-80)	0.122	0.001	0.032

NB: Value presented as: Median (Q1-Q3) ¥, and mean ±SD: One way (ANOVA)* with post hoc multiple tests and Kruskal Wallis test was used; P^1, BD vs BM; P^2, BD vs BF; P^3, BM vs BF; P<0.05 taken as significant.

5.5 Comparisons of Characteristics of spinal anesthesia among groups

The time taken for onset of sensory block was significantly delayed in BM group compared to BD and BF group with P < 0.05. However, there was no statistically significance difference in onset of sensory block between group BD and group BF with *p*=0.594.

The time required for onset of motor block was significantly delayed in BM group compared with BD and BF group. However, there was no statistically significance difference in minutes for onset of motor block in BD and BF group with p value 0.575.

The time taken for completion of motor block was significantly delayed in BM group compared with BD and BF group with ($p < 0.05$). However, there was no statistically significant difference in minutes for completion of motor block between group BD and group BF with p value 0.635. The duration of motor block was significantly prolonged in BM group compared with BD and BF group, ($p < 0.05$). The duration of analgesia was significantly shorter in the BF group (3.48±0.2 hour) compared with duration in BD group (5.72±0.52hour) and in BF group (5.74±0.43hour) with $P < 0.05$ as shown in table 5 below. However, there was no significant difference in analgesic duration between BD and BM group with p value 0.988. Quality of analgesia was good during intraoperative period; thus no one require analgesics during intraoperative period.

Table 5 Characteristic of spinal anesthesia and duration of analgesia between group at study hospital in study period (n1=n2=n3=29).

Characteristics	**BD**	**BF**	**BM**	**P value**
Onset of sensory block(min)	1.22±0.32	1.38±0.3	4.25± 0.99	0.001
Onset of motor block(min)	1.8±0.39	2.06±0.48	7.2±1.6	0.001
Complete motor block(min)	2.74±0.35	3.2±0.5	14.7±3.26	0.001
Duration of motor block(hour)	3.52±0.2	2.5±0.3	4.08±0.4	0.001
Duration of analgesia (hour)	5.72±0.52	3.48±0.2	5.74±0.43	0.001
Duration of surgery(minute)	122.1±42.3	113.1 ±27.4	123.2±17.1	0.381

NB: Values are presented as Mean±SD: One Way ANOVA test; and $p<0.05$ taken as significant

5.6 Comparison of the incidence of perioperative complication among groups

In terms of perioperative complication, 2(6.9%) patients in BD group, 3(10.3%) patients in BF group and 6(20.7%) patients in BM group were developed nausea (p value =0.258) which shows there was no significant difference between groups. 2(6.9%) patients in BM group were developed vomiting and none of the patients were developed vomiting in BD and BF group. 8(27.5%) patients in BD group and 7(24.1%) patients in each BF and BM groups were developed shivering with p value 0.941. None of the patients in BD and BF group developed pruritus. However, 1(3.4%) patient in BM group developed pruritus which is mild and didn't need treatment.

Table 6 Incidence of intraoperative complications between groups at study hospital in study period.

Intraoperative complications	**Spinal anesthesia adjuvants**			**P value**
	BD	BF	BM	
Nausea	2(6.9%)	3 (10.3%)	6(20.7%)	0.258
Vomiting[#]	0(0%)	0(0%)	2(6.9%)	0.326
Shivering	8(27.5%)	7(24.1%)	7(24.1%)	0.941
Pruritus[#]	0(0%)	0(0%)	1(3.4%)	1

NB: Values are presented as: Number (%): chi-square and Fisher exact (#) test was used; $p<0.05$ was taken as significant

CHAPTER SIX: DISCUSSION

Adequate management of postoperative pain allows early mobilization of patients after orthopedics surgery thus preventing the associated co-morbidities. Despite advance in treatment of postoperative pain many patients still suffer from pain after surgery, probably due to difficulties in balancing postoperative analgesia with less side effects(7).

Lower limb surgeries are commonly performed under spinal anesthesia; as it is simple to perform by single shot technique compared with epidural and peripheral technique. However its main drawback is a short duration of analgesia, hemodynamic instability and higher usage of postoperative analgesia(34). Therefore, different types of drugs are used as adjuvants to target different phases of pain pathway from perception to central modulation. Administering of intrathecal adjuvants with spinal anesthesia provide hemodynamic stability along with prolongation of postoperative analgesia and less side effect(52).

Studies have shown that opioid was the most commonly used adjuvants with local anesthetics for spinal anesthesia; by providing prolonged analgesia with fewer central and systemic undesired effects than administered systematically. It potentiates the anti-nociception of local anesthetics by G protein coupled receptor mechanism. Opioids bind competitively to specific receptor to induce pain relief by hyperpolarization of afferent sensory neuron(13,14). Intrathecal administration of morphine has been shown to improve postoperative pain due to hydrophilic nature; that make it less absorbed into surrounding tissue(53). Intrathecally administered fentanyl has a contribution to improved analgesia during intraoperative and postoperative period in orthopedics surgery(54). Steroid like dexamethasone was commonly investigated in the last decade for its effect as adjuvant to LA in neuraxial as well as peripheral nerve block(52).

This study was mainly undertaken to find the analgesic effects of dexamethasone, fentanyl and morphine as adjuvant after administration with hyperbaric bupivacaine for patients undergoing elective lower limb orthopedics surgery under spinal anesthesia.

In our study the demographic characteristics (age, sex, and BMI), ASA status, preoperative diagnosis, duration of surgery and surgeon experience were comparable among groups, $p>0.05$.

In regard to our study, there was no significance difference on NRS score at 2^{nd} and 24 hours after surgery between groups. This might be due to analgesic effects of spinal anesthesia that

continue in all three groups who had the same value of NRS score at 2 hours. The median or inter quartile range NRS score at 4 and 6 hour was significantly higher in fentanyl added group compared to dexamethasone and morphine added group. That might be due to higher lipophilic nature of fentanyl that made quick absorption into surrounding tissue and early completion of analgesic duration. Similarly our study was supported by Yesuf KA et al(24) and Refika K et al(48) they were used 25µg fentanyl and 0.1mg morphine with 12.5mg heavy bupivacaine for cesarean section and knee replacement surgery respectively. The median or inter quartile range NRS score at 8 hours was significantly higher morphine group. Our finding was comparable with a study done in Japan by Massaki Machino et al(45) the pain score was higher at 8hour. That might be completion of analgesic effects of intrathecal morphine; that warns to initiate first analgesia after procedure with p-value < 0.05. At 12 hours after surgery; the higher pain score was recorded in dexamethasone and morphine group. That might be complete wear off analgesic effect in both groups. Our finding supported by Salmah G and Choy Y(44), and Saracoglu A (39)they shows higher pain score at 12 hour in morphine group after surgery.

Regarding to our study, patients in BD and BM group had significantly prolonged time for first rescue analgesic request compared to patients in BF group; (702. ±72.09), (667.07±75.3), and (367.9±65.64) in minute respectively. Study done by Salmah G et al used 25µg fentanyl and 0.1mg morphine with 1.8ml of 0.5% heavy bupivacaine was (297.4 ± 112.0) minutes in BM and (197.7 ± 60.0) minutes in BF group(44). In the above study, analgesia request time was shorter compared to our study; that might be due to small dose of morphine and bupivacaine was used for intrathecal blockade. Our study also supported by a study done in India by using 4mg dexamethasone and 25µg fentanyl with 12.5mg heavy spinal bupivacaine for elective orthopedics surgery; their result shows first rescue analgesic request time was significantly prolonged in dexamethasone group(10). Our study agreed with a study done in Turkey which uses 0.1mg morphine and 25µg fentanyl with 12.5mg heavy spinal bupivacaine for knee replacement surgery; which showed time to first analgesia request after surgery was prolonged in BM group(5.9±1.3) hour compared to BF group(2.6±0.6) hour (48). That might be due to usage of large doses of morphine and bupivacaine in our study; which delays analgesic request time more than above studies. Our study was also consistent with a study done by Karaman S et al(46) by using 0.2mg morphine and 25µg fentanyl with 10mg heavy bupivacaine for cesarean section shows prolonged analgesic request time (20.5±6.7) hour for morphine and (4.2±3.9) hour

for fentanyl group. That could be due to almost similar doses of morphine and fentanyl used for adjuvant; however analgesic duration was prolonged in morphine group due to less lipid solubility of morphine. In contrast to our study; a study done in Taiwan by Khezri M et.al on comparison of 25µg fentanyl and 15mg heavy spinal bupivacaine lower limb surgery showed that; time for first analgesic request was significantly prolonged in BF group (699.375 ± 79.80minute)(40). That was more delayed compared to our study; it might be due to quality of surgical care in developed country. Study done by Qi X et al by using 0.1mg intrathecal morphine with 10mg bupivacaine for cesarean section showed that; analgesia request time in Group BM (n= 40) was 16.78±5.9 hour(47). In the above study, analgesia request time was longer than in our study even dose of morphine and bupivacaine was lower. This might be due to large sample size of the study group. In contrast to a pervious study in India on comparing the effectiveness of 5µg dexmedetomidine versus 0.2mg morphine with 15mg hyperbaric bupivacaine for infraumbilical surgeries; the first analgesic request time was shorter in Morphine groups (232.50±45.45 min) (55). That might be due to including all surgical procedures below umbilicus as the same nociceptive category even though there is known scientific difference on pain perception between different surgical procedures.

Regarding to our study median tramadol consumption was significantly lower in BD group 50(45-80) compared to 75(55-100) in BF and 70(55-80) in BM group. Karaman S et al(46) and Amhimmid A et al(56) support our finding; they shows there was less opioid consumption after using 0.2mg morphine, 25µg fentanyl and 4mg dexamethasone with 12.5mg bupivacaine for sub-umbilical surgery. That might be due to prolonged analgesic effect of dexamethasone by reducing acute inflammatory mediator release from tissue injury that has important role in surgical pain. Delayed analgesic duration in morphine might be staying in CSF for longer time and provide longer duration of analgesia during intrathecal blockade; that results less dose of analgesic request postoperatively.

In this study we found that there was no significant difference in intraoperative mean atrial blood pressure reduction and mean heart rate at all intended time interval between groups after intrathecal injection of drugs p (>0.05). This might be due to reduced dose and hyperbaric nature of given local anesthetics made it denser than CSF and less cephalic spread from injected site that results less sympathetic blockade. Good hydration of fluids during intraoperative period and technique of administration and positioning after injection plays its own role. Similar findings

were observed by Saracoglu A et al that compare hemodynamic and analgesic effectiveness of 25µg fentanyl and 0.2mg morphine with 12.5mg heavy intrathecal bupivacaine for elective cesarean section(39). Refika K et al(48), also shows similar finding to our study where they use 12.5mg heavy bupivacaine with 25µg fentanyl and 0.1mg morphine intrathecally for postoperative pain management during elective total knee replacement surgery. Kaur H et al(10), also shows similar finding to our study where they used 25µg fentanyl and 4mg dexamethasone with 12.5mg heavy spinal bupivacaine for elective lower limb orthopedics surgery. Our results had similar finding with the above studies since dose of adjuvants and bupivacaine were relatively equal with them.

The results of our study showed that, the analgesic duration was significantly shorter in BF group compared with BD and BM group; 3.48±0.2, 5.72±0.52 and 5.74±0.43hour respectively. This might be due to the hydrophilic and highly ionized nature of morphine; highly lipid soluble nature of fentanyl. However analgesic duration of intrathecal dexamethasone is not well known. Some study suggests reduction of regional blood flow; thus, may slow local anesthetic absorption and prolonged pain free period. Similar finding was observed by Mohammad S et al by using 4mg dexamethasone and 12.5mg heavy spinal bupivacaine during cesarean section for postoperative analgesia(36). Kaur et al also showed similar finding on comparing 4mg dexamethasone and 25µg fentanyl with 12.5mg heavy bupivacaine for elective orthopedics surgery (10). Aliakbar N et al (12), Subrata D et al (31) also support our study by using 8mg dexamethasone to 15mg heavy spinal bupivacaine for elective orthopedics surgery. Similar finding was observed by Salmah G and Choy YC by using 0.1mg morphine and 25µg fentanyl with 10mg heavy bupivacaine for prolonging analgesic duration for cesarean section(44). Refika K et al also shows similar finding with our study by using 0.1mg morphine versus 25µg fentanyl with 12.5mg heavy bupivacaine for total knee replacement surgery(48). Our finding was also comparable with Karaman S et al(46); they used 0.2mg morphine with 15mg bupivacaine prolongs analgesic duration compared to 25µg fentanyl during lower limb surgery under SA. Our study also supported by a study done in Ethiopia by Yesuf k et al(24) on duration of analgesia by using 25µg fentanyl and 10mg bupivacaine for cesarean section.

Recent study in our country by Ebrie AM et.al also shows similar findings with our study in duration of analgesia and first analgesic request time; 260.3±40.3 min and 294.6±99.5min respectively by using 25µg fentanyl with 10mg heavy bupivacaine for cesarean section. Median

VAS score at 2nd, 4th and 12 hour was consistent with our study in BF group(25). However, our study shows shorter onset time for sensory block; that might be due to slightly high dose of bupivacaine was injected with fentanyl.

In our study we observed faster minutes of onset of sensory block in fentanyl group (1.38±0.3) and dexamethasone (1.22±0.32) than morphine group (4.25±0.99). This might be due to less ionic nature of fentanyl that made easily absorbable by neural sheath. Chavan G *et.al* also shows similar findings in onset of sensory and motor block by using 15mg bupivacaine with 25µg fentanyl for cesarean section, shows faster onset of sensory and motor block in fentanyl group(57). That might be due to highly lipid soluble nature of fentanyl. In contrast to our finding a study done in India compares analgesic effectiveness of 4mg dexamethasone versus 25µg fentanyl as additive with 12.5mg bupivacaine shows prolonged minute for onset of sensory block for BD (6.85±1.21) and BF group (7.65±1.25). However duration of motor block was consistent with our study(10). That might be due to small dose of bupivacaine was used compared to our study.

In our study 8(27.5%) in BD group, 7(24.1%) in BF group and 7(24.1%) in BM group developed shivering. Our finding on shivering was supported by evidence observed by Beni-hashem N et al (12) in BD group (9/25) during orthopedics surgery and in BD group (7/30) by Ismaiel N et al(33) during C/S; they used 8mg dexamethasone with 12.5mg bupivacaine for orthopedics surgery and cesarean section. Our study also consistent with the finding by Kaur H et al(10) by using 4mg dexamethasone and 25µg fentanyl with 12.5mg bupivacaine for orthopedics surgery. In our finding only 1(3.4%) person developed pruritus which was happened in BM group. This might be the anti- inflammatory effects of dexamethasone and most study focuses on postoperative complication which may change number of patients who developed unwanted effect of drug. Our study was supported by Gupta R et al(58) and Kaur H et al(10); which shows there was no patient developed pruritus in fentanyl and BD group; however pruritus was common in BM group in most studies(59,60). In our study 2(6.9%) in BD, 3(10.3%) in BF and 6(20.7%) in BM group developed nausea and 2(6.9%) person in BM group developed vomiting intraoperatively; that was consistent with the study done by Shah O and Bhat K(60) and Ahmed M et al(35).

6.1 Limitation of the study

It was challenging to manage the intrathecal injection rate, which varied from anesthetist to anesthetist. During data evaluation, it was feasible to figure out which participants belonged to which group, which could be a source of bias. The majority of the research selected for comparison were randomized controlled trials. It was difficult to conduct trials comparing dexamethasone and morphine for spinal anesthesia.

6.2 Strength of study

Participants were homogenous (elective lower limb orthopedics patients) which play its own roll to have a more representative result. The variables on Sociodemographic distribution and perioperative factors are comparable between groups, so the differences observed are possibly due to exposure factor. There was adequate sample size with planned, estimated and fixed period of time.

6.3 Conclusion

We conclude that; the use of intrathecal dexamethasone and morphine as adjuvant with 15mg heavy bupivacaine for lower limb orthopedics surgery is effective in controlling the intraoperative and early postoperative pain management, prolonged first analgesia request time and decreases severity of postoperative pain and opioid consumption with less side effect on the study patients.

6.4 Recommendation

We recommend the use of 4mg dexamethasone and 0.2mg morphine with 15mg heavy spinal bupivacaine as appropriate to improve intraoperative and immediate postoperative pain management during elective lower limb orthopedics surgery as a multimodal analgesia in resource limited area.

- **Anesthetist**

We also recommend anesthetist to use 0.5% heavy spinal bupivacaine with 4mg of dexamethasone as alternative adjuvants of choice for 0.2mg morphine during spinal anesthesia for lower limb orthopedics surgeries in a resource limited area.

- **Researcher**

We also recommend researchers to do further randomized control trial with adequate sample size and follow up period in order to avoid bias and to assess the exact severity of pain and first analgesic request time.

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ANNEX ONE: INFORMATION SHEET

Title of the study: Comparing the effectiveness of fentanyl, dexamethasone and morphine as adjuvants to intrathecal bupivacaine for postoperative pain relief in elective lower limb orthopedics surgery at Addis Ababa public hospital 2022/2023. Prospective cohort study

Principal investigator (PI): - Ali Dimma (BSc, MSc student in advanced clinical anesthesia)

Advisor/s: Ms. Selamawit Shiferaw (BSC, MSC Lecturer of Anesthesia)

Mr. Ashenafi Seifu (BSC, MSC Lecturer of Anesthesia)

Name of organization: - AAU, HSC, School of Medicine, Department of anesthesia

Name of sponsor: - Addis Ababa University

Source of Budget: - Addis Ababa University

Introduction

This information is prepared with the aim of comparing the effectiveness of intrathecal dexamethasone, fentanyl and morphine on spinal bupivacaine as part of prolongation of postoperative analgesia for lower extremity orthopedics procedure.

Objectives:

The aim/goal of this study will be to compare the analgesic effectiveness of dexamethasone, morphine and fentanyl as adjuvants to spinal bupivacaine to manage postoperative pain in elective lower limb orthopedic surgery at public hospital in Addis Ababa. The finding of this study is expected to be used by decision makers, MOH, EAA, Pediatric surgery department, department of anesthesia and health practitioners of the University to change modifiable factors.

Procedure

This study will include all elective adult lower limb orthopedic patients coming for operation cases during the study period.

They will be selected as part of the study participants who will have willing to participate in the study and willing to have consent.

Duration: The study will be conducted from December 1, 2022 to February 28, 2023.

Benefits, Risk or Discomfort

There will be no direct benefit to study participants and we will not to give you new drugs, but your participation is likely will help us in determining the effect of morphine, fentanyl and dexamethasone when added to bupivacaine for spinal anaesthesia. Ultimately, this will help all stakeholders to work on the gaps and the result of this study will be used for further improvement of the analgesic service. There is no risk of participating in this study

Confidentiality: The information collected from the study subjects will be kept confidential and stored in the file, without their name by assigning a code number to each. Any personal formation recorded will not be copied and transferred to other bodies.

Right to refusal or withdraw

Study subjects will have full right to refuse from participating in this study.

Person to contact

For any questions or concerns you can contact the principal investigator using the following addresses:

Name Ali Dimma (primary investigator)

Telephone: - +251916424019
Email: - alidimma34@gmail.com

AHRI/ALERT IRB committee: -Phone office: - +251 118 342742

SPMMC IRB COMMITTEE: - Phone office 251 112 732639

AAU IRB: Phone office 251 115 52 59 50

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AHRI / ALERT IRB □□□ □□□□ □□: 251 118 342742.

SPMMC IRB committee: 251 112 732639

AAU IRB: 251 115 52 59 50

ANNEX TWO: CONSENT FORM

Consent form

Hello! My name is Ali Dimma I am anesthetist and I work in TASH and members of the research team and I am here to ask you some questions and to collect some important information from your chart. Your name will not be listed out, that means your confidentiality will be kept. If you are willing to participate in this research to compare effectiveness of intrathecal dexamethasone, fentanyl and morphine with bupivacaine in patients undergoing lower extremity procedure under spinal anesthesia for post-operative analgesia which I will appreciate the contribution you will made to this research. So, I would like to ask you, if you are willing to participate in this research. I understood about the objectives of the research and the roles I will have in the research. However, your honest response to those questions will help us to asses and understand the effect. Therefore, we are requesting you to give honest response and keep participation. Would you agree to participate in the research?

A) Agree B) Dis agree signature----------

Name of data collector……. Signature……. Date……. /……/…...

Thanks for taking part in the study!!!

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ANNEX THREE: PATIENT DATA

Data collection tools/questioners

1. Socio demographic information

101	Age of the patient	
102	Gender	A. Male. b. female
103	BMI	
104	ASA status	a. ASA1 b. ASA2

2. Preoperative patient condition

201	Diagnosis	
202	Baseline vital sign	a. BP_____ b. PR_____ c. RR_____ d. Spo2

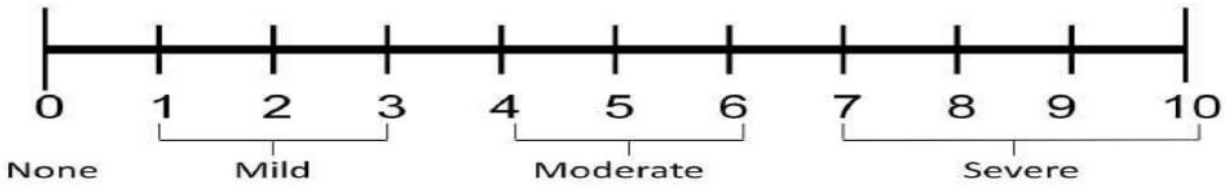
3. Intraoperative patient condition

301	Spinal anaesthesia drug given	a. Dexamethasone 4mg with 15mg bupivacaine. b. Fentanyl 25µg with 15mg bupivacaine. c. Morphine 0.2mg with 15mg bupivacaine	
302		Onset of sensory block(minute)	
303		Onset of motor block	
304		Time to achieve grade 3bromage scale	

	Parameter	Time interval after spinal anesthesia(min)						
		5M	10 M	15 M	30 M	60 M	90 M	120 M
305	MAP							
306	HR							
307	Does nausea occur intraoperatively?	Yes No						
308	Does pruritus occur intraoperatively?	Yes No						
309	Does vomiting occur intraoperatively?	Yes No						
310	Does shivering occur intraoperatively?	Yes No						
311	Surgeon experience	1. R3 2. R4 3. Senior						
312	Duration of pain free period(hour)							
313	Duration of surgery(minute)							

4. Postoperative patient condition

401. Severity of pain scoring using NRS



At 2hour…… (In cm)

At 4hour…… (In cm)

At 6hour…… (In cm)

At 8hour……. (In cm)

At 12hour……. …. (In cm)

At 24hour……. …. (In cm)

402. Duration of motor blockade (minute)……

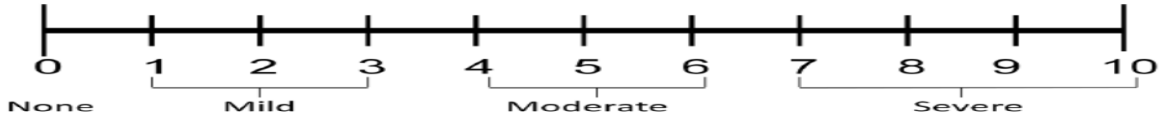
403. Time for first analgesic request post operation (hour)…….

404. Total dose of analgesic drug given in 24 hours (mg)…….

405. Types of analgesics given postoperatively within 24 hours after the patient arrived in recovery/ward

A. tramadol ----------mg
B. diclofenac ----------mg
C. Others…….mg

ANNEX FOUR. THE NUMERIC RATING SCALE (NRS)

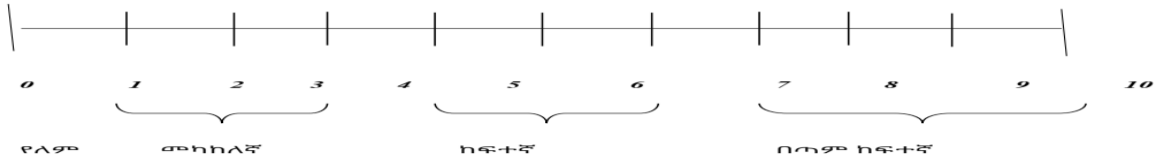


The scale was taken 6 times within 24 hours. Patients was asked to rate their pain; pain was assessed and recorded at every 2 hours after surgery until 8hr and 12 and 24hour postoperatively.

The patient was asked one of the following questions:

A. What number on a 0 to 10 scale would you give your pain right now?

B. When the explanation suggested above is not sufficient for the patient, further explanation or conceptualization of the scale will be done



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ANNEX FIVE: MODIFIED BROMAGE SCALE

Modified Bromage Scale

0: No motor loss,

1: Inability to flex the hip,

2: Inability to flex the knee and

3: Inability to flex the ankle.

ANNEX SIX: DATA ACCURACY CHECK SHEET

S.No.	Tools	Yes	No
1	Are the Inclusion criteria /exclusion criteria done appropriately		
2	Are all questions on Sociodemographic data filed appropriately?		
3	Are all questions on preoperative period data filled appropriately?		
4	Are all questions on intraoperative period data filled appropriately?		
5	Are all questions on postoperative period data filled appropriately?		

6	Did the postoperative analgesic drugs filled with appropriate type of drug, time and dose		
7	Did the SOP followed strictly		

ANNEX SEVEN: DECLARATION

Assurance of principal investigator

I, the undersigned, MSc in clinical anesthesia student declare that this thesis is my original work in partial fulfillment of the requirement for the degree of Master in clinical Anesthesia.

Name of the student: Ali Dimma

Signature ---------- date----------

Approval of the primary Advisor

Name of the primary advisor: Ms. Selamawit Shiferaw. (BSc, MSc in clinical anesthesia)

Date _____ Signature _____

ANNEX EIGHT: ASSURANCE OF INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific, ethical conduct of the research project and for provision of required progress reports as pre terms and conditions of the research and publications office of Addis Ababa University.

Name of the student: _____ Date: _____ Signature: _____

Approval of the advisor (s)

Advisors

1. _____ _____ _____

Name Signature Date