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

POSTOPERATIVE ANALGESIC EFFECT OF INTRATHECAL NEOSTGMINE ADDED TO BUPIVACAINE IN COMPARISON WITH BUPIVACAINE ALONE FOR ADULT PATIENTS UNDERGOING LOWER LIMB ORTHOPAEDIC SURGERY AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA, 2017.

(Cohort Study)

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June, 2017

Addis Ababa, Ethiopia

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DATE----------

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Addis Ababa, Ethiopia

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Lists of acronyms

ASA : American Society of Anesthesiologists

BP : Blood Pressure

BN : Bupivacaine Neostigmine Group

BS : Bupivacaine Spinal Group

DC : Data Collector

ETB : Ethiopian Birr

GA : General Anesthesia

Hrs. : Hours

IT : Intrathecal

LA : Local Anesthesia

MIN : Minutes

PONV: Postoperative Nausea and Vomiting

TASH : Tikur Anbessa Specialized Hospital

SPA : Spinal Anesthesia

SPSS : Statistical Package for Social Sciences

VAS : Visual Analogue Scale

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ABSTRACT

Background: Several additives have been suggested to enhance analgesic effect of local anesthetic agents to decrease the adverse effects and increase the degree of satisfaction.

Objective: - To assess postoperative analgesic effect of intrathecal neostigmine added to bupivacaine in comparison with bupivacaine alone for adult patients undergoing Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C.

Methods: -This institutional based prospective observational cohort study was conducted among 60 adult patients scheduled for elective lower limb orthopedic surgery under spinal anesthesia and grouped in to bupivacaine group based on independent decision of responsible anesthetist. Patient‟s vital signs were taken intraoperativley. Postoperatively duration & consumption of analgesia, first analgesia request as well as severity of pain using 100mm visual analogue scale score were assessed over 24hrs. Normality of the data was checked using Shapiro-Wilk test and analyzed using student t test for normal distributed data and chi-square test for categorical data. Non- parametric data was analyzed using Mann –Whitney U test with 95% CI and p- value less than 0.05 is considered as statistically significant.

Results: - Bupivacaine neostigmine group (BN, n=30) compared with bupivacaine only group (BS**,** n=30) which was presented by mean ±standard deviation, time of the first analgesic request in neostigmine and bupivacaine group was (377.60 ± 9.14) and (230.07 ± 17.11) in minute respectively, $p < 0.001$.Morever total amount of tramadol consumption was also significantly different between the two groups that was presented by median (inter quartile range),which was 50(50) mg in neostigmine group vs. 100 (50) mg in bupivacaine group. The visual analogue scale score also reduced at1hr, 2hrs, 3hrs, 4hrs, 5hrs and 6hrs in neostigmine group.

Conclusion and recommendation: -Addition of 25mcg intrathecal neostigmine as an adjuvant to 15 mg bupivacaine for elective lower limb orthopedic surgery increased first analgesia request time, reduced postoperative analgesia consumption and with minimal hemodynamic changes and side effects. We recommend that the use of intrathecal neostigmine combined with bupivacaine for lower limb surgery in our setup.

Key words: - Spinal Anesthesia, lower limb orthopedic surgery, intrathecal neostigmine, postop analgesia.

CHAPTER ONE: INTRODUCTION

1.1 Background

Anesthetists are leaders in the development of pain services in the current era. Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Procedural pain being the acute type has probability of progressing to chronic pain unless intervened properly [2].Postoperative pain is associated with catecholamine release, and the central sensitization issue posed to be among the mechanisms concerned with the persistence of postoperative pain. The aim of good post-operative analgesia is to produce a long lasting, continuous effective analgesia with minimum side effects [3]. Neuraxial blocks have been introduced to produce superior analgesia and decrease the blood loss and the incidence of deep venous thrombosis (DVT), pulmonary embolism, and to minimize the adverse effects of general anesthesia and improve the patients" outcomes. Better pain control may result in an earlier hospital discharge and may improve the patient"s ability in postoperative period [4].
Intrathecal (IT) neostigmine has been used as an adjunct to spinal anesthesia (SA) for the prevention of acute perioperative pain. It has been shown to potentiate opioid analgesia while reducing undesirable side effects such as somnolence and respiratory depression. . Intrathecal neostigmine with bupivacaine caused a prolonged time to the first analgesic request and its use was not associated with any side effects [4, 5, and 6].

Neostigmine is an anticholinesterase agent which increases the acetylcholine concentrations at cholinergic synapses. Spinal neostigmine apparently activates descending pain inhibitory systems that rely on a spinal cholinergic interneuron, probably exacerbating a cholinergic tonus that is already activated during the postoperative period and seems to be extremely efficient for alleviating somatic pain [7].

1.2 Statement of the problem

Postoperative pain is the most important cause of unintended hospital admissions following Spinal anesthesia and a major source of dissatisfaction with perioperative outcome [8]. Spinal anesthesia (SA) is the most commonly used anesthetic technique for lower abdominal surgeries and lower limb surgery. But it has the drawback of short duration of action and lack of postoperative analgesia. Larger dose of analgesic is required to provide pain relief with high incidence of side effects when local anesthetic is used alone for SA [9].

Bupivacaine is the most commonly employed local anesthetic for subarachnoid block, but has limited duration of action. Perioperative hemodynamic status is also a concern [7].Other method of prolonging analgesia is using a continuous epidural analgesia, which is technically more difficult and more costly, which the patients coming to the government hospital may not afford [3]. Opioids, though useful as adjuvants, are associated with undesirable side effects. Hence ideal adjuvants that can be used with bupivacaine for stable intraoperative conditions and prolonging the post-operative analgesia with minimal side effects are being investigated.

Neostigmine is an anticholinesterase agent which increases the acetylcholine concentrations at cholinergic synapses [7].There are controversies concerning effective intrathecal doses of neostigmine with lesser side effects. Some literatures recommend intrathecal neostigmine doses ranging from 25μg to 150 μg while others showed a dose-independent reduction of postoperative analgesia requirement [10] but a dose-dependent increase in the incidence of PONV following addition of various doses of IT neostigmine to bupivacaine [1]. Even the dose as low as 6.25 mcg has been associated with high incidence of PONV. Due to side-effects the dose was substantially decreased [10].According to recent literature the inhibition of acetylcholine enzymatic degradation by neostigmine enhances the descending control of afferent nociceptive stimuli and provide new approach for enhancement of desirable analgesia [11].

Although spinal anesthesia with bupivacaine is routinely done in Tikur Anbessa specialized hospital; there is no previous study about the analgesic efficacy of an adjuvant neostigmine. The aim of this study is to assess postoperative analgesic effect of intrathecal neostigmine added to bupivacaine in comparison with bupivacaine alone for adult patients undergoing lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital

1.3 Significance of the study

Enhancing recovery protocols after surgery to optimize recovery and reduce the length of patient hospital stay, reducing the incidence and severity of intraoperative and postoperative pain is particularly important .Many studies have been performed to compare quality of anesthesia and postoperative analgesic effect of intrathecal neostigmine and bupivacaine in lower limb orthopedic surgery. Most of these studies have been conducted on developed and western populations. The presence of racial, cultural, genetic and socio demographic difference in the perception of pain has been well documented [12]; meanwhile intraoperative & early postoperative pain is a major problem which needs an immediate and sustainable solution. So knowing the effectiveness of intrathecal neostigmine with spinal anesthesia in terms of intraoperative anesthesia quality and postoperative analgesia helps for better outcomes and patient satisfaction. Neostigmine is commonly available drug on the hands of Anesthetist in most theatres both in private and public hospitals in Ethiopia. It can be a good alternative if proved to be effective in preventing postoperative pain. This research can also help as a back ground for future researches on related topic.

CHAPTER TWO

Literature review

Analgesia is one of the main demands of all patients postoperatively [13]. Currently, opioids are widely used for pain relief, but they often provide sub-optimal analgesia with occasional serious side effects which include purities, nausea/emesis, constipation, urinary retention, respiratory depression, undesirable sedation and the development of tolerance/ dependence [13, 14].There are many additives to be used to enhance analgesic effect of neuraxial blocks such as clonidine, magnesium, ketamine, opioids, vasoconstrictor agents and steroids, and neostigmine [6].

Among nonnarcotics, neostigmine was suggested to be more efficacious for somatic than for visceral pain, making it attractive for orthopedic procedures [10].It is reported that the inhibition of spinal cholinesterase by neostigmine produces great Enhancement of endogenous acetylcholine, which is most likely released from intrinsic cholinergic neurons within the dorsal horn of the spinal cord. Intrathecal neostigmine 25µg with bupivacaine caused a prolonged time to the first analgesic request and its use was not associated with any side effects [6].

A prospective randomized comparative study was conducted to evaluate postoperative analgesic efficacy of intrathecal neostigmine in different doses added to bupivacaine by S Gupta, (2009) On 90 patients of ASA CLASS I And II were randomly selected from routine list of gynecology, plastic surgery, general surgery and orthopedics in three different groups. Group I – Received 3ml of 0.5% heavy bupivacaine, Group II – Received 50µg of Neostigmine + 3ml of 0.5% heavy bupivacaine and Group III- Received 75µg of Neostigmine + 3ml of 0.5% heavy bupivacaine. There was no significant difference in onset of sensory or motor blockade in all groups. The duration of sensory blockade in BS Group was 155.6±26, N50 Group 211.2 ±31.7, N75 Group 233.4±34.7. The duration of motor block was statistically significantly prolonged in 75µg as compared to N50 which indicates that motor block could be dose dependent ($P<0.01$). The duration of motor blockade in BS, N50 & N75 Group was 153±16.8, 169.3 ±20.7 and 193.9±24 minutes respectively. The time to first analgesia is longer in neostigmine group than the control Group (BS-138.5±5.1, N50 -183 ±3.3 and N75 -236.2 ±1.6 minutes). The total doses of rescue analgesia required for N75 Group was low as compared to BS Group and N50 Group. In BS group, 1(3.33%) patients had nausea and vomiting, 2(6.66%) had hypotension but there was no bradycardia, tachycardia and sedation. In N50 group, 2 patients had nausea and vomiting, 2

patients had bradycardia, 5 patients had developed hypotension while none had tachycardia, sedation. In N75 group, 9 patients had nausea & vomiting, 8 had bradycardia and 10 had hypotension [15].

A study conducted in *India (2012)* in 50 patients belonging to ASA I and II status and age between18 and 60 years. One group received 2.5 ml of 0.5% hyperbaric bupivacaine (group BS) and second group received neostigmine 50µg with 2.5 ml of 0.5% hyperbaric bupivacaine (group BN). Addition of 50µg neostigmine significantly enhanced the onset of sensory and motor block compared to bupivacaine group, $p<0.05$. Mean time taken for regaining complete motor power was prolonged significantly in Neostigmine group (Group BN=193 minutes) than Bupivacaine group (Group B= 150 minutes). Group BN had prolonged analgesia (300±45 minutes) compared to BS group (200±54minutes) ($P < 0.05$). Hemodynamics was well maintained in the neostigmine group but perioperatively nausea vomiting were noticed in both groups which were statistically insignificant, $p>0.05$ [3].

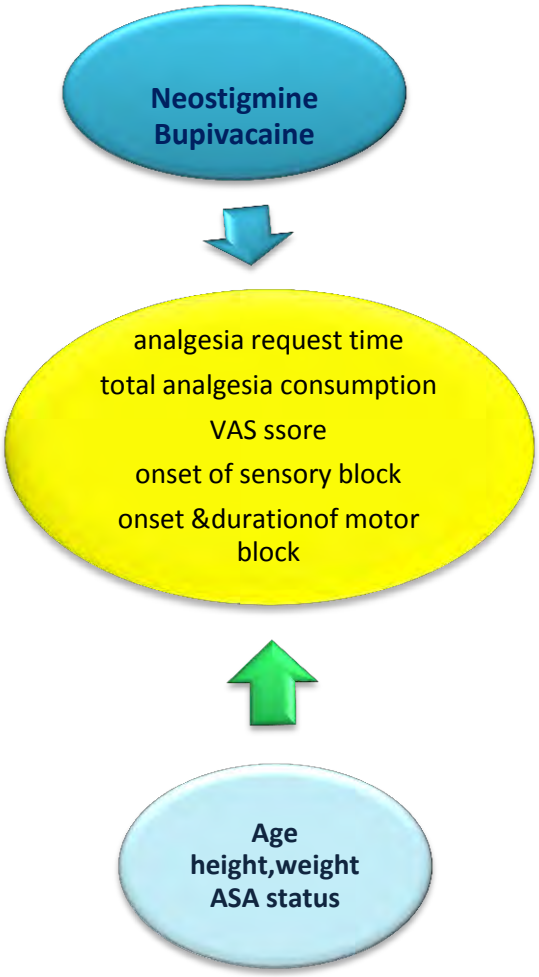
In a prospective randomized double blind study done (2015) on 75 American Society of Anesthesiologist status I and II that received Neostigmine 25µg and MgSO4 50 mg as an adjuvant to 17.5 mg hyperbaric bupivacaine. The mean duration of analgesia was significantly longer in Group N (5.1 h) followed by Group M (4.2 h) and Group C (3.8 h) ($P = 0.0134$). Analgesic requirement was significantly less in Group N followed by Group M and Group C ($P = 0.00232$). The pain score was significantly less in Group M ($P < 0.05$). The incidence of hypotension and vasopressor requirement was lowest (48%) in Group N than in Group M (64%) and Group C 84% ($P = 0.0276$). The incidence of bradycardia and atropine requirement was the lower in Group N than group C.Sedation was observed in 56% patients in Group M compared to 20% in Group N and 8% in Group C ($P = 0.0004$) [9].

Another study conducted in Middle East (2015), on sixty patients 18-80 year with American Society of Anesthesiologists (ASA) physical status I or II, scheduled for femur surgery under spinal anesthesia. There was significantly prolonged duration of motor block in neostigmine

group compared to the control group (221±68 vs. 165±40; P < 0.001). The difference of the mean time to the first analgesic request was also significantly longer in neostigmine group (435±152 vs 289±78; P < 0.001). The total analgesic consumption during the first 12 hours after surgery was devoid of any significant difference between groups N and C (p = 0.41).The two groups were not significantly different in terms of intraoperative and postoperative side effects [6].

Study done in India (2016) on a total of 75 patients, belonging to the American Society of Anesthesiologists (ASA) physical status class I and II were scheduled to undergo lower abdominal and lower limb surgeries were chosen. For the study, patients were randomly allocated into three groups: Group I (control group) were given 12.5 mg of 0.5% hyperbaric bupivacaine, Group II (50 µg group) were given 12.5 mg of 0.5% hyperbaric bupivacaine and 50 µg (0.1 ml) of neostigmine methyl sulfate, and Group III (150 µg group) were given 12.5 mg of 0.5% hyperbaric bupivacaine and 150 µg (0.3 ml) of neostigmine methyl sulfate intrathecaly. The total VAS-P score in group BS (23.12 ± 3.21) was higher than the VAS-P score in group N50µg (18.4 ± 2.92) and group N150µg (16.24 ± 1.85), p<0.05. The total duration of analgesia was significantly prolonged in neostigmine groups (224.40 ± 23.28 min in group BS, 367.60 ± 42.15 min in group N50µg and 625.60 ± 87.70 min in group N150µg) compared to bupivacaine group ,p <0.001. In group BS, the patients required 2.48 ± 0.51 number of analgesics in 24 hours, which was much higher than required in group N50µg (1.92 ± 0.64) and group N150µg (1.32 ± 0.47),p<0.05. The incidence of nausea and vomiting was more with 150µg neostigmine group compared to 50µg neostigmine [1].

2.2. CONCEPTUAL FRAME WORK



CHAPTER THREE: OBJECTIVES

3.1 General Objective

To assess postoperative analgesic effect of intrathecal neostigmine added to bupivacaine in comparison with bupivacaine alone for patients undergoing Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C

3.2 Specific objectives

To compare first analgesic request time between the two groups

To compare postoperative pain severity between the two groups using the VAS

To compare total postoperative analgesic consumption between the two groups

To compare onset of sensory block between the two groups

To compare onset of motor block between the two groups

To compare duration of motor block between the two groups

To compare associated side effects between the groups

CHAPTER FOUR: METHODOLOGY

4.1 Study Area and period

This study was carried out at Tikur Anbessa specialized Hospital, which is located in Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C. Tikur Anbessa specialized hospital is multi-specialist tertiary care teaching hospital in Ethiopia, opened since 1972 and, in 1998 transferred to school by FMOH since then it became a university teaching hospital. TASH is now the main teaching hospital for clinical and preclinical trainings of most disciplines. It is also an institution where specialized clinical services that are not available in other public or private institutions are rendered to the whole nation. It has 1 Blood bank, about 700 beds, it has about 13 operation theatre and more than 900 health professionals in the different specialties dedicated to providing health care services, and the various departments‟ residents under specialty training in the school of medicine also provide patient care in the hospital. As documents in the hospital anesthesia and surgery log book on average 140 elective patients underwent lower limb surgery under spinal anesthesia within two months.

4.2 Study design

Institutional based prospective cohort study was conducted.

4.3 Population

4.3.1 Source Population

All patients who underwent lower limb orthopedic surgery under spinal anesthesia at Tikur Anbessa specialized hospital.

4.3.2 Study Population

All elective patients who underwent lower limb orthopedic surgery under spinal anesthesia and those who fulfill inclusion criteria from January 1 to February 30, 2017 G.C

4.4 Eligibility criteria

4.4.1 Inclusion criteria

All patients scheduled for elective lower limb surgery under spinal anesthesia who gave consent to take part in the study.

4.4.2 Exclusion criteria

Spinal anesthesia using local anesthetics other than bupivacaine, age<18and those who had been American society of Anesthesiologist (ASA) class III& IV, psychiatric problem.

4.5 Sampling Technique and Sample Size Determination

4.5. 1. Sample size determination

According to results from recent study in India [9], the mean duration of analgesia and standard deviation were 308.76 (127.40) when neostigmine is co-administered with bupivacaine but when bupivacaine alone is used 229.52 (59.16) (9), which means μ_1 (308.76), σ_1 (127.40), μ_2 (229.52) and σ_2 (59.16) with an alpha error of 0.05 at a power of 80%, when this value is incorporated into the formula for continuous outcome,

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2)(Z_{\alpha/2} + Z_\beta)^2}{(\mu_1 - \mu_2)^2}$$ Ratio of exposed to unexposed (1:1)

$$n = \frac{(127.4)^2+(59.16)^2}{(308.76 - 229.52)^2} (1.96 + 0.84)^2$$

n =25.

When 20 % of contingency is included for dropouts, total sample of 60 patients or 30 patients per group was required.

4.5.2. Sampling technique

Study participants were selected using systematic random sampling technique. According to the average number of lower limb orthopedic surgery in adults in the last two months (N=140) and sample size (n=60), sampling interval is calculated as: K_{th} = N/n = 140/60 = 2.33.After selecting a random no. every 2nd new study subject was included in the study until the desired number obtained in both groups.

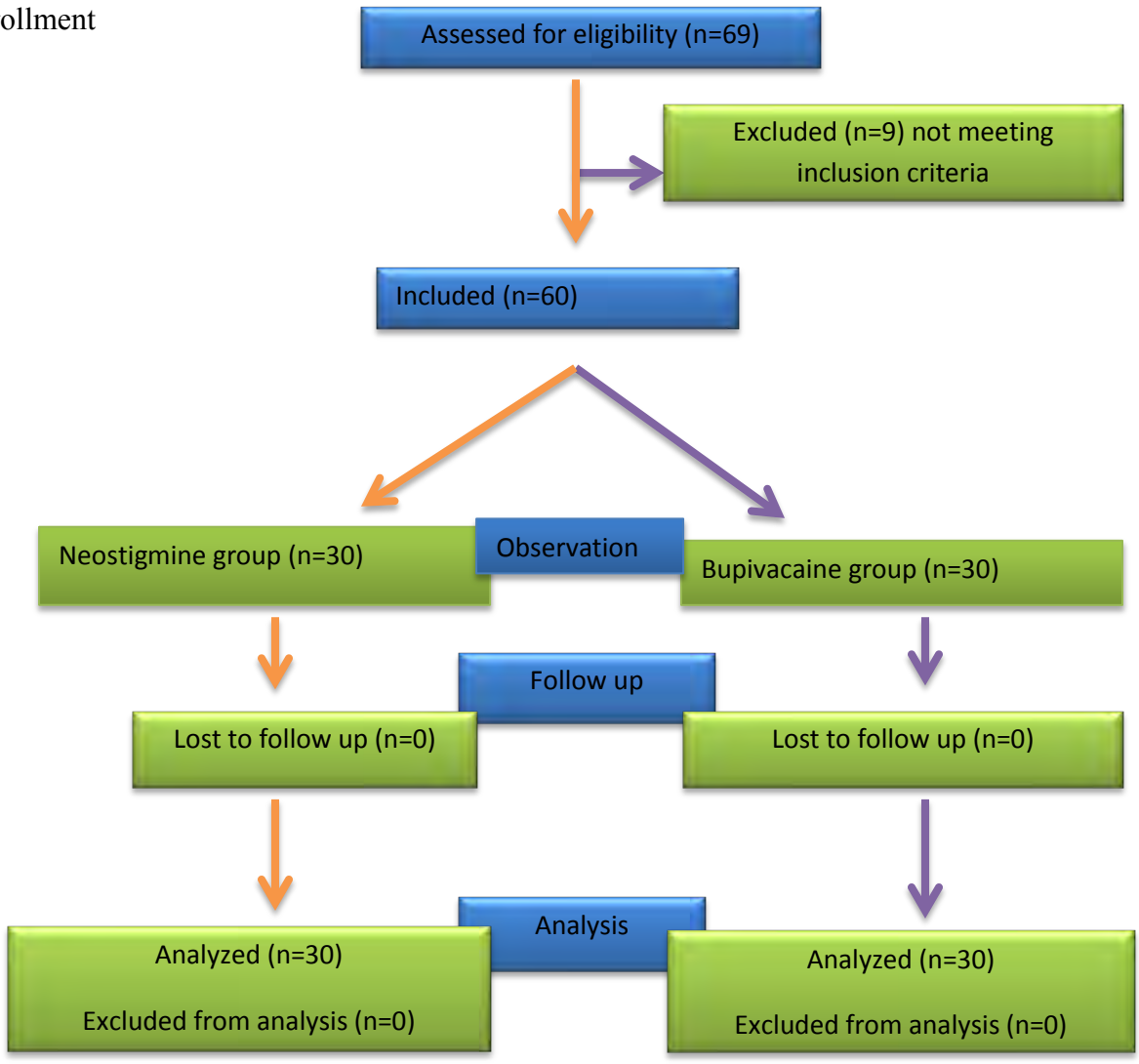


Fig. Consort flow diagram for study subject

4.6 Study variables

4.6.1. Dependent Variables

- First analgesia request time, total analgesia consumption and severity of postoperative pain
- Factor related to SA{ onset of sensory block, onset & duration of motor block}
- Perioperative side effects of SA {nausea/vomiting, hypotension, hemodynamic changes, respiratory depression, and bradycardia}.

4.6.2. Independent Variables

Socio demographic variables {age, sex, weight, height}, duration of surgery, ASA category, type of study drug administered

4.7 Data Collection methods

During each procedure the data collectors have observed intraoperative condition of the patient. Post operatively each patient was interviewed and their charts were also reviewed. Group BN were those patients who had been given 25 mcg of intrathecal neostigmine with 15mg of 0.5% bupivacaine. Another group BS those who were given 15mg of 0.5% bupivacaine only. Intraoperative data was collected by one of the trained data collector. Starting from the immediate postoperative time, presence and scale of pain, time for the first analgesic request as well as analgesics need were assessed by the other trained data collector. These assessments have been done at 1hr, 2hrs, 3hrs, 4hrs, 5hrs, 6hrs, 12hrs and 24hrs for VAS and within 24hrs of postoperative total analgesic consumption were taken. The categories of patients were identified by data collector. Two BSC anesthetists were selected to collect data and one day training was given regarding how to collect data, appropriate use of the data collection instruments and the confidentiality of the collected data. Another MSc anesthetist was assigned to assist and supervise data collectors .Before surgery the concept of visual analog scale (VAS) which consists of 100 mm line with 0 equaling “no pain at all” and 100 equaling “the worst possible pain”, was introduced that was determined by the patient marking their pain intensity.

4.8 Data Quality Control and Assurance

To ensure the quality of data, pretest of the data collection tool (questionnaire) was done on patients by taking 6(10% of sample) respondents (3 BN group and 3 BS group) who underwent lower limb Surgery under spinal anesthesia 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. Then necessary correction was done accordingly on questionnaire for the main study. Data clean up and cross checking, arranging materials sequentially and keeping in a safe and secure place was done before analysis.

4.9 Data analysis and Interpretation

Data was checked manually for completeness and then it was coded and entered into SPSS version 20 computer program for cleaning and analysis. Demographic data were analyzed using student t test (for normal distribution variables) and chi-square test (for categorical variables) as appropriate. The data was tested for normality using Shapiro-Wilk normality test. There was normal distribution data for the time of the first analgesic request, total duration of analgesia, repeated VAS measurements and hemodynamic changes as checked using Shapiro-Wilk test and homogeneity of variance assessed using Levene's test for equality of variances. Therefore, an independent sample t-test was run on the data with 95% confident interval to analyze measurement of time of the first analgesic request, total duration of analgesia time and VAS measurements.

However, total post-operative analgesia consumption was not normally distributed when checked using Shapiro-Wilk test. Therefore, non-parametric Mann –Whitney U test was run on the data as well as 95% confidence interval to analyze with further paired comparison at each time interval. Normally distributed data are presented as mean ± SD whereas not normally distributed data presented as median (IQR) and categorical data presented by frequencies (percentages). A p value < 0.05 was considered statistically significant.

4.10 Dissemination of Results

Copies of the research will be disseminated to college of health science, school of medicine/department of anesthesia, Addis Ababa University student research office, Ethiopian Association of Anesthetists, Ethiopian ministry of health. Finally it will be send to different national and international journals for publication.

4.11 Operational definitions

Hypotension: Defined as when the Systolic blood pressure of below 90mmHg or lower than 30% of starting systolic blood pressure or MAP less than 70mmHg [3,16,17].

Bradycardia: Defined as when the heart rate less than 60 beats/minutes [3, 16].

Respiratory depression: Defined as when the respiratory rate less than 10 breaths per minute and Oxygen saturation less than 90% will be consider [16,17].

VAS: visual analogue scale which is a method of pain assessment determined by the patient making a mark of their pain intensity on a line which is 100 millimeter long [18].

Time for first analgesia request: initial time in which patients need pain treatment postoperatively [19].

Total analgesic consumption: Defined as type and amounts of analgesic drugs given to the patient within 24hrs postoperatively.

Bromage scale: a method of assessing grade of motor block („0"=full movement of hip, knee and ankle; 1=ability to flex knees but no hip movement; 2=unable to flex knees, but no problems with ankle movement; 3=no movement possible with any of the lower extremity joints) [16].

Onset of motor block: The time of reaching to Bromage III [20].

Duration of motor block to recover: when the modified Bromage score is 0 [20].

Onset of sensory block: time elapsed from the end of study solution administration to absence of pinprick sensation at T10 dermatome [21]

Vomiting: expulsion of stomach contents

Nausea: a subjectively unpleasant sensation associated with awareness of the urge to vomit.

4.12 Ethical Consideration

Prior to data collection, this proposal was reviewed by the ethical committee of college of health science school of medicine department of anesthesia. Then after official letter for permission was requested from department of anesthesia, which was given to Tikur Anbessa specialized Hospital

clinical director office. Moreover, the objective of the study was explained to both hospital administration and the patients who were included in the study. Written consent from the patients was asked and Confidentiality of the information was assured by using code numbers than personal identification names and keeping questionnaires locked.

CHAPTER FIVE: RESULTS

Socio-demographic characteristics of the participants

A total of 60 patients (30 patients in each group) were finally involved for data analysis and interpretation of the study. There was no statistically significant difference among the groups with respect to age, sex, weight, height, duration of surgery and ASA status as shown in **[Table1].**

Table1: Demographic and anesthetic base line characteristics between BN& BS group of patients who undergone Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C

Group	BN	BS	p- value
Age in years	34.67±16.63	40.13±19.13	0.242
Sex:- M/ F	24/6	23/7	-
Weight in kilogram	60.50±8.28	60.30±6.98	0.920
Height in meter	1.64±0.08	1.65±0.07	0.647
ASA status :-ASA1	22(73.3%)*	21(70%)*	0.774
ASA2	8(26.7%)*	9(30%)*	
Duration of surgery in minute	133.67±48.22	119.33±35.11	0.204

Category: *= frequency, others in mean ±SD, BN=Neostigmine group, BN=Bupivacaine group, ASA=American Society of Anesthesiologists

Characteristics of spinal anesthesia

There was shorter in onset of sensory block and onset of motor block in BN group than BS group in minutes. The duration of sensor block, motor block and first request for analgesia was prolonged in BN group than BS group in minutes as shown in [table **2**].

Table 2: Characteristic of spinal anesthesia and duration of analgesia between BN& BS group of patients who undergone Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C

Group	BN	BS	p- value
Onset of sensory block (min)	3.90±1.21	9.40±2.14	<0.001
onset of motor block(minute)	5.70±1.34	11.33±2.22	<0.001
Duration of motor block	271.67±11.17	192.30±8.02	<0.001
Time to first request of analgesic (minute)	377.60±9.14	230.07±17.11	<0.001

Values = Mean ± SD, p-value < 0.05 is significant

Postoperative pain VAS score

There was statistically significant difference on VAS score at 1hr, 2hrs, 3hrs, 4hrs, 5hrs and 6hrs among the groups but there was no statistically significant difference on VAS score at 12 and 24hr between BN and BS group as shown in **[table 3].**

Table 3: Postoperative Visual Analogue scale pain scores mean±SD in millimeters over the first 24hrs postoperatively between BN& BS group of patients who undergone Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C.

Groups	BN	BS	P - value
VAS score at 1hrs	0	0.43±0.67	0.001
VAS score at 2hrs	0	0.93±0.94	<0.001
VAS score at 3hrs	0.60±1.04	2.07±1.46	<0.001
VAS score at 4hrs	1.43±1.19	2.33±1.18	0.005
VAS score at 5hrs	1.67±.80	2.57±1.19	0.001
VAS score at 6hrs	2.00±0.98	2.73±0.78	0.002
VAS score at 12hrs	2.87±1.25	2.57±1.10	0.153
VAS score at 24hrs	2.30±0.99	1.87±0.90	0.081

Values are mean ± SD in centimeter

Postoperative total analgesia consumption

Since the postoperative 24hrs of both total diclofenac and total tramadol consumption were not normally distributed as checked by Shapiro-Wilk test, Mann-Whitney U test was used to assess the associations. Patients who received intrathecal neostigmine showed a reduced postoperative total tramadol consumption within 24hrs (BN vs. BS group), described as median (IQR) mg, at 24hours 50(100) vs. 100 (50), $p < 0.001$.Total diclofenac consumption was not statistically significant difference between BN group and BS group within 24 hours (BN vs. BS) described as median (IQR) mg, 75(75) vs. 75(0),p= 0.538 as shown in [**Fig. 1**].

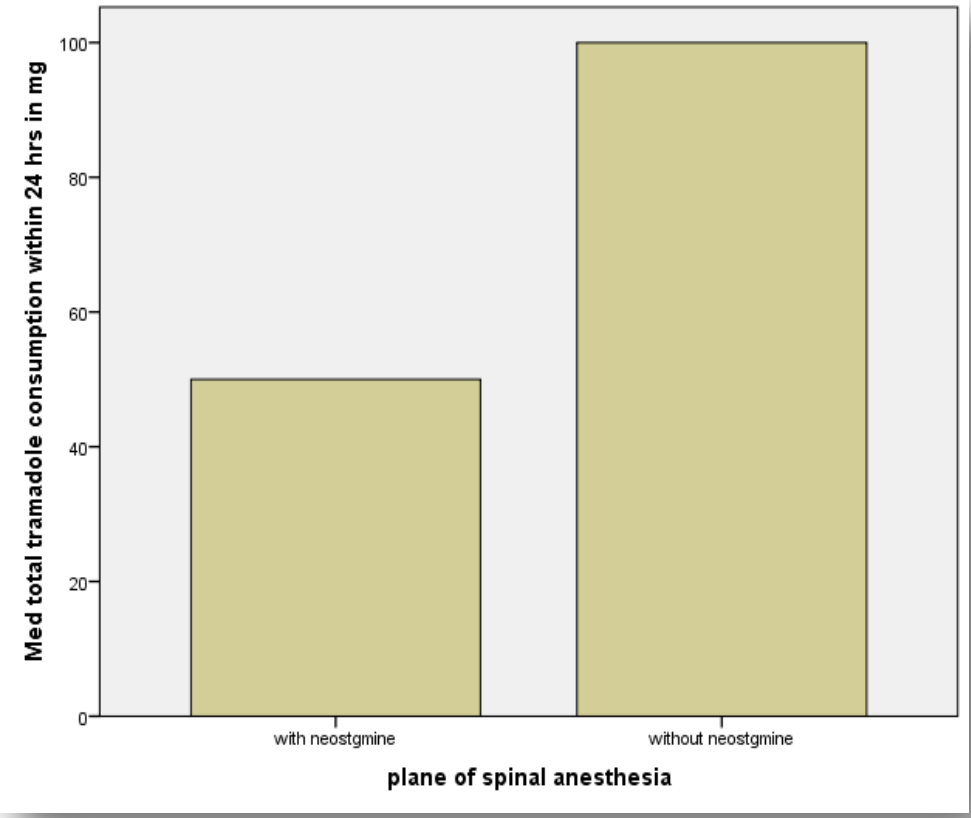
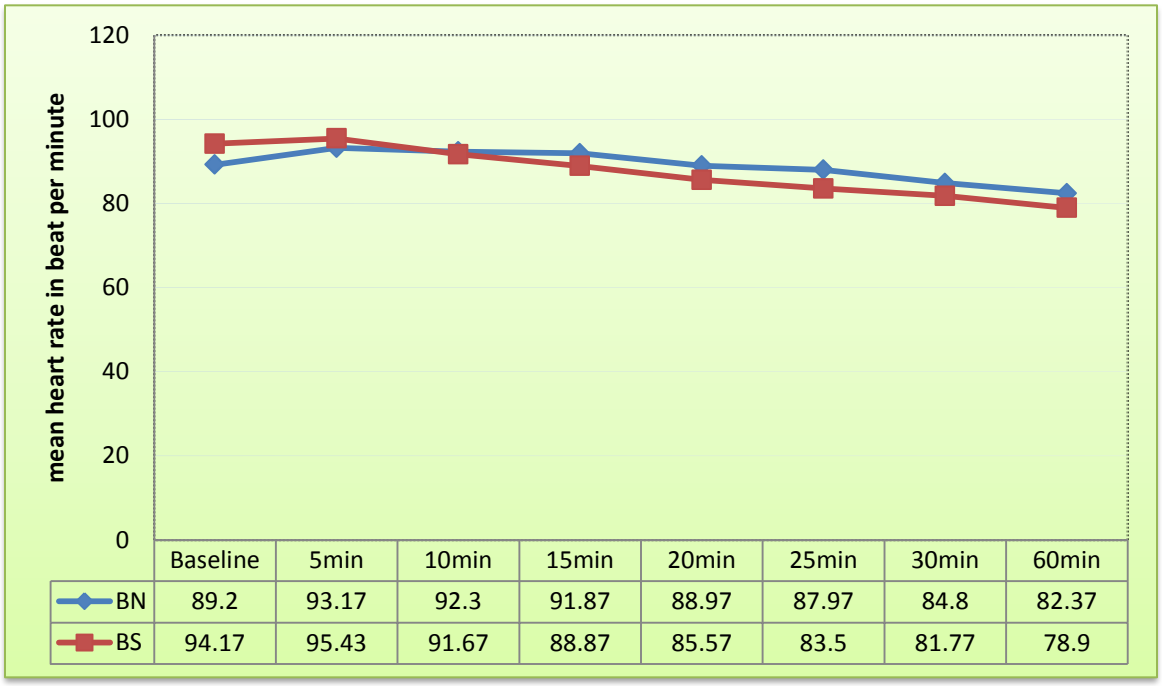


Fig. 1: A bar graph of postoperative total tramadol consumption within 24hrs in each group of patients who undergone lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C.

Hemodynamic parameters

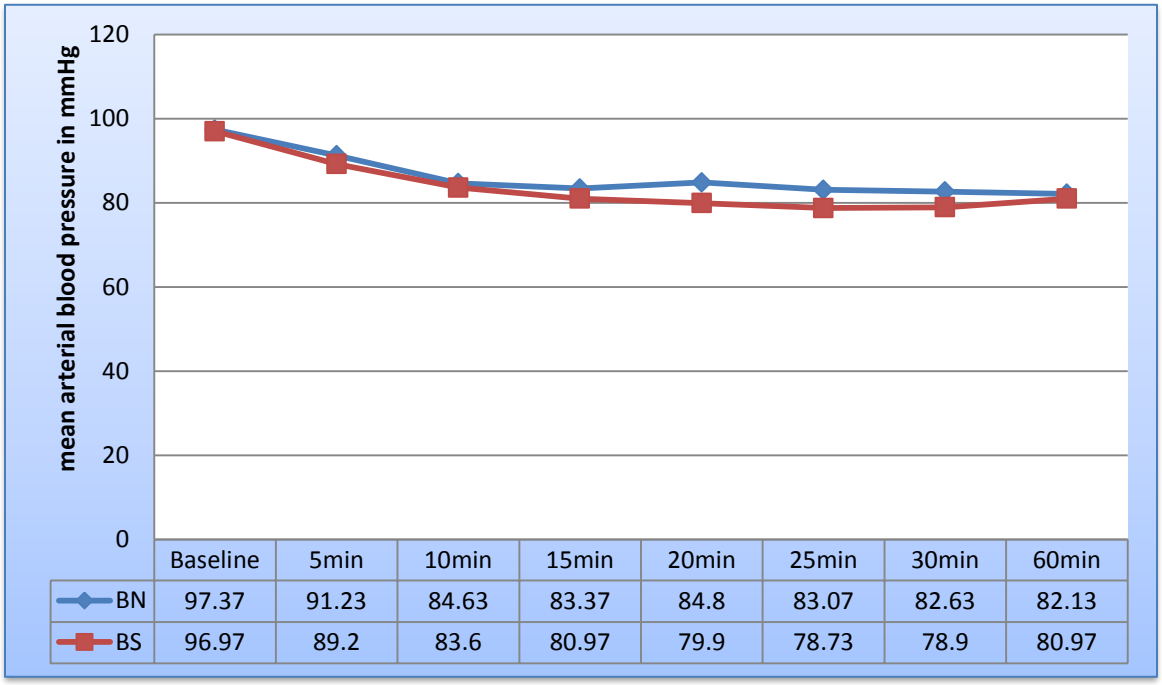
There was no statistically significant difference in mean heart rate at baseline, 5min, 10min, 15min, 20min, 25min, 30min and 60min(p= 0.238, 0.651, 0.898, 0.527, 0.435, 0.269, 0.416 & 0.251 respectively) in both groups as shown in **[Fig.2]**.



	Baseline	5min	10min	15min	20min	25min	30min	60min
BN	89.2	93.17	92.3	91.87	88.97	87.97	84.8	82.37
BS	94.17	95.43	91.67	88.87	85.57	83.5	81.77	78.9

Fig.2: A line graph showing the mean heart rate at various time interval between BN & BS group of patients who had Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C.

There was no statistically significant difference in mean arterial blood pressure at baseline, 5min, 10min, 15min, 20min, 25min, 30min and 60min (p=0.922 ,0.592, 0.808, 0.552, 0.170, 0.197, 0.263 & 0.692 respectively) in both groups as shown in **[Fig.3]**.



	Baseline	5min	10min	15min	20min	25min	30min	60min
BN	97.37	91.23	84.63	83.37	84.8	83.07	82.63	82.13
BS	96.97	89.2	83.6	80.97	79.9	78.73	78.9	80.97

Fig.3: A line graph showing the mean arterial blood pressure at various time interval between BN & BS group of patients who undergone Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C.

Incidence of perioperative complications

No patients developed complications during the early postoperative period. In terms of intraoperative complications, 8(26.7%) patients in BN group & 12(40%) in BS group have developed hypotension and treated with IV fluid. None of them needed vaso-active drugs. But there was no statistically significant difference in both groups. 7(23.3%) patients in BN & 4(13.3%) in BS group developed nausea/vomiting but there was no statistically significant difference in between BN and BS groups as shown in **[table 4].**

Table 4: Incidence of perioperative complications between BN& BS group of patients who undergone Lower limb Orthopedic Surgery at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from January 1 to February 30, 2017 G.C.

Complications	BN group	BS group	p-value
Hypotension	8(26.7%)	12(40%)	0.277
Bradycardia	0	0	
Nausea/vomiting	7(23.3%)	4(13.3%)	0.321
Respiratory depression	0	0	

CHAPTER SIX

Discussion

Effective treatment of pain represents an important component of postoperative recovery. It serves to blunt autonomic, somatic, and endocrine reflexes with a resultant potential decrease in perioperative morbidity. Despite advances in treatment of postoperative pain, many patients still suffer from pain after surgery, probably due to difficulties in balancing postoperative analgesia with acceptable side effects [9].

Lower limb surgeries are performed under spinal anesthesia, as it is easy to perform, single shot technique when compared to epidural and general anesthesia. But its main drawback is that the analgesia is of limited duration. Hence, additives which cause the prolongation of the duration of motor as well as sensory block will be beneficial in reducing the morbidity of the patients in the postoperative period [22]. Several studies suggest neostigmine as an effective adjuvant to prolong the duration of the subarachnoid block and spinal analgesia with better hemodynamic stability [23].

Many studies showed that there is synergism between intrathecal neostigmine with local anesthetic agents. Considerable evidence exists to implicate the role of cholinergic agonists and anticholinesterase agents in the spinal inhibition of nociceptive transmission [11]. Intrathecal administrations of neostigmine produce antinociception, which is mediated by spinal muscarinic and nicotinic receptors in animals and human beings [1, 6]. It produces analgesia by releasing of NO [6] and inhibiting the metabolism of acetylcholine [1, 24] and binding to M1, M2, M3 and M4 muscarinic and to nicotinic receptors [10]. Whereas local anesthetic agents/bupivacaine act by blocking voltage gated Na+ channels in spinal cords [25, 26].

In this study the demographic characteristics (age, sex, weight, height), duration of surgery and ASA status were not statistically significant between the groups which was supported by many studies, $p>0.05$ [7, 15, 22]

In regard to our study, patients in the BN group had a significant longer time for the first analgesic request compared to BS group, (377.60 ± 9.14) versus (230.07 ± 17.11) in minutes respectively with p<0.001. Study done in Middle East showed that analgesia request time in BS Group was 289±78 minutes and 435±152 minutes in BN Group [6]. In the above study, analgesia request time was longer than in our study. This might be due to high dose of bupivacaine (4ml) they used compared to our study. Our result was consistent with study conducted in Saudi [23] even though patient characteristics, type of procedure and duration of surgery were different from our study.

Another study in India showed that first analgesia request time was shorter in their study than in our study even though there were similar sample size and high dose of intrathecal neostigmine (50mcg) used [27]. This might be due to experience (perception) of pain is affected by genetics, cultural and social factors in different ethnicity across the world.

With regard to our study there was significantly reduced mean VAS score for the first 6hrs in BN group than BS group with p-value < 0.05. Our finding was consistent with randomized trial by Bhat M. et al [27]. This similarity might be related with the wear off analgesic effects of spinal anesthesia in bupivacaine group and the synergistic effect of intrathecal neostigmine with bupivacaine in BN group continued since the duration of intrathecal neostigmine is expected to stay 6 hours [3]. After 6 hour there was no significant difference in mean VAS scores between BN & BS groups, p>0.05 [9] since both groups were treated with diclofenac and tramadol as well as wear of action of intrathecal neostigmine.

Patients in BN group had reduced postoperative total tramadol consumption within 24hrs compared to BS group, p < 0.001. Our finding was consistent with a randomized study conducted by Joshi-Khadke S, et al showed that intrathecal neostigmine decreased tramadol requirements in the first 6hrs with p- value = 0.001 [9]. The reason might be patient in BN group had prolonged duration of analgesia than patient in BS group. Diclofenac requirement was not statistically significant, p>0.05 [9].

In our study the onset of highest sensory analgesia had statistically significant difference between BN and BS group (3.90±1.21 vs. 9.40 ± 2.14 respectively) in minutes, p <0.001. A study done by solainppan B, et al showed that significant time difference for onset of highest sensory analgesia, which was 1.60± 0.49 minutes in BN group versus 2.77 ± 0.13 minutes in control group [22].Relatively longer onset of sensory in our study than the above study. These might be due to high dose of neostigmine (50mcg) in the above study. But a study done by Gupta S et al found that the mean time to reach peak sensory level was earlier with bupivacaine group than neostigmine group in seconds [15].

Intrathecal administration of Neostigmine, by increasing spinal levels of acetylcholine, may augment motor block as a result of axonal conduction block from spinal Bupivacaine. Many lower-extremity surgical procedures require muscle relaxation, and spinal Bupivacaine alone provides only modest motor block [3].
Onset of motor blockade was statistically significant between BN and BS groups (5.70 ± 1.34 versus 11.33 ± 2.22 respectively) in minutes and all patients had grade III motor block in our study. Study by Solaiappan B, et al found significant time difference for onset of motor block, which was 1.61± 0.32 minutes in BN group and 1.94 ± 0.11 minutes in control group [22]. Relatively longer onset of motor block in our study than the above study, these might be due to high dose of neostigmine (50mcg) in the above study. But a study conducted in 2009 by S Gupta et al showed that the mean time to onset of motor blockade was earlier with bupivacaine group than neostigmine group in seconds [15].

In our study there was a prolonged motor block in BN group than BS group (271.67 ±11.17 vs.192.32 ±8.02 respectively) in minutes. Study‟s by Bhat M, et al motor recovery in group BN was 220.3 ±9.70 minutes and in Group BS was 189.83 ± 5.64 minutes which was significant but shorter duration of motor block than our study [27]. This might be due to small dose of bupivacaine they used, (12.5mg of 0.5% Bupivacaine) compared to our study.

Cholinergic sites in the brainstem and thoracic and cervical spinal cord may involve in mediation of perioperative nausea/vomiting side effect [3]. Accumulation of acetylcholine at chemoreceptor trigger zone [15] and rostral/ cephalic spread of Neostigmine to brainstem site [1,

3, 4, 7] is proposed to be the cause for nausea and vomiting. In our study 7(23.3%) patients in BN group & 4(13.3%) patients in BS group have developed nausea/vomiting which was statistically insignificant, p>0.05 [6].This might be due to most of the patients were in sitting posture while administering the drug that prevents the cephalic spread of neostigmine[3,7]. But Study"s by Bahr D, et al the incidence of nausea/vomiting in BN group was 20(40%) and in BS group was 6(12%), which was significant [23].The incidence is higher than our result, these might be large dose of neostigmine they used or variation in type of procedure .

Intrathecal administration of Neostigmine causes an amplification of action acetylcholine released at preganglionic sympathetic neurons resulting in increase in heart rate and blood pressure[1,3].In our study there were no statistical significant difference in mean heart rate and mean arterial blood pressure at various time intervals in both groups, which was similar finding with Bhat M, et al (27). In our study there were no cases of bradycardia in both groups (6). However, study by Bhar D, et al showed that the incidence of bradycardia was 10% in control group and 6% in BN group with no statistically significant variation in the group (23). The above study is not similar to our data serious. These might be due to case selection difference (our cases were lower limb surgery compared to the above studies which were abdominal hysterectomy).

In terms of intraoperative hypotension our study showed that 8(26.7%) patients in BN group & 12(40%) in BS group have developed hypotension and treated with IV fluid. None of them needed vaso- active drugs. Study by Pandey V, et al found that 4(16%) patients in BS group and 3(12%) patients in BN groups had hypotension that required rapid infusion of crystalloid [1]. But study done by Bhar D, et al, patients in the BS group (36%) had significantly more hypotensive than BN group (16%) [23]. Even if our study is not statistically significant it is clinically important in our setup, since we do not have vaso- active drugs like ephedrine and phenylephrine to treat hypotension during spinal anesthesia. So Intrathecal neostigmine directly stimulates preganglionic sympathetic neurons in spinal cord and can counteract/prevent the hypotension caused by intrathecal injection of bupivacaine [3, 15, 23].

In our study none of the patients developed respiratory depression (spo2< 90%) which was supported by many studies [1, 6, 15, 27].

Strength of the study

Subjects were homogeneous (orthopedics patients) which play its own roll to have more representative results. There were adequate sample sizes with the planed, estimated and fixed period of time.

Limitation of the study

Anesthesia management differs from anesthetist to anesthetist depending on seniority. It was difficult to have a truly blinded data collector. Because during data reviewing, they can easily identify in which group the study subjects belong, so this can be means for bias.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

Conclusion

The result of our study shows that the uses of intrathecal neostigmine with bupivacaine for orthopedic surgery would increase first analgesia requested time and reduces severity of pain as well as total analgesia consumption. Not only these but also it improves the quality of anesthesia, good hemodynamic stability, no ventilator depression, intraoperative and post-operative analgesia.

Recommendation

We recommend intrathecal neostigmine with plain bupivacaine to improve intraoperative quality of anesthesia and early postoperative analgesia for orthopedic surgery. We recommended further randomized control trial in order to avoid bias and to asses exact severity of pain.

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Annexes

Annex I: -Information sheet to get permission for the research

Introduction

This information sheet is prepared to explain the research project that you are asked to join by a group of research investigators. The research team includes MSc students, one senior advisor and two BSc Anesthetists for data collection.

Name of Principal investigator: - Kassaw Moges (2nd year MSc Student)
Advisor's name: - Sr Betelihem

Name of sponsor: - Addis AbabaUniversity

This information sheet is prepared by the above mentioned investigator.

Risk

There is no any risk or harm that the patient will face by participating in this research. Any personal information registered in the book will not be copied and transferred to other bodies. No need of writing participants‟ name but by a code. Every piece of information will be kept confidentially. No individual information will be transferred.

Benefits

There is no incentive or payment to be gained by taking part in this project. The information collected from this research project will be kept confidential and only accessed the researcher and research assistant only. This research project will be reviewed and approved by ethical committee of Addis Ababa University.

Annex II: - Consent form

Dear participants

The aim of this study is to assess quality of anesthesia and postoperative analgesic effect of intrathecal neostigmine with bupivacaine during SA for lower limb orthopedic surgery at Tikur Anbesa specialized hospital, 2017. You are selected to participate in this study by chance. The study will involve various intimate and private life questions. In order to achieve the objective of the research, we are requesting your participation. There are questions for you to answer politely and there is no need to put your name on the questionnaire; no individual response will be reported. Your response will be completely confidential. It is your full right to accept or refuse to give answer for questions. However; your honest answer to those questions will help us to assess and understand the effect. So; we are requesting you to give honest response and keep participation. Are you willing to participate? A/ Yes, signature_____, B/ NO (Thank you very much for your help). For any farther question, please contact the investigator.

Name: Kassaw Moges

Tel: +251920594753

Mail:kassawmoges53@gmail.com

Annex III

የመጠይቅ ፈቃድ

የተከበራችሁ የጥናቱ ተሳታፊዎች

የዚህ ጥናት ዋና አላማ በ2009ዓ.ም በጥቁር አንበሳ ሆስፒታል አጥንት ክፍል ተኝተዉ ከወገብ በታች በሚሰጥ ማደንዘዣ ቀዶ ጥገና የሚደረግላቸው ታካሚዎች በቀዶ ህክምና ወቅት እና ከቀዶ ህክምናዉ በኃላ የሚደርስባቸዉን ህመም በመገንዘብ የሚደረግ ጥናት ነዉ::በአጋጣሚ እርስዎም በዚህ እንዲሳተፉ ተመርጠዋል::የዚህ ጥናት ጥቅም እርስዎ በሚሰጡት ምላሽ መሰረት መረጃዎችን በማሟላት በሚገኘዉ ዉጤት መሰረት መረጃዎችን በማጠናቀር ውጤቱን እየተሰራበት ካለው ጋር ማገናዘብ እንዲቻል ነዉ:: ጥናቱ በትክክል አላማውን እንዲመታ የእሶን ድጋፍ እንጠይቃለን::የማንኛውም ግለሰብ ስም አይመዘገብም እንዲሁም ሀሳቡ ብቻውን ይፋ እንዲዎጣ አይደረግም ሙሉ በሙሉ በሚስጥር የተጠበቀ ነው::በጥናቱ መሳተፍ አለመሳተፍ የራስዎ መብት ብቻ ነዉ::ግልፅ የሆነ ምላሽንና ከልብ የመነጨ ተሳትፎዎን እንዲሰጡን በአክብሮት እንጠይቃለን::ለመሳተፍ ፈቃደኛ ነዎት ? ሀ/ አዎ ፊርማ _____ ለ/ አይደለሁም

ለመሳተፍ ፈቃደኛ ስለሆኑ እናመሰግናለን::

Date ____/___/____

Check list

ADDIS ABABA UNIVERSTY

COLLEGE OF PUBLIC HEALTH AND MEDICAL SCIENCE

SCHOOL OF MEDICINE DEPARTMENT OF ANESTHESIA

A data collection format to assess postoperative analgesic effectiveness of intrathecal neostigmine and bupivacaine, in Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia from January 1, to February 30, 2017.

Instructions:

A. Fill the blank space provided.

B. Encircle the alternatives when necessary.

C. Check the questions for completeness.

Part 1. Section I: Socio-demographic and basic characteristics of the patient (chart review):

1.1. Patient MRN_____ 1.2. Age (in year) _____

1.3. Sex: A. Male B. Female 1.4. Body weight _____ Kg

1.5. ASA category (ASA 1, 2) 1.6.Height

Part 2.Preoperative assessment for SA including (Document review) :

2.1. Plan of spinal anesthesia A. With neostigmine B. Without neostigmine

2.2. Base line HR _____ bpm 2.3. Base line BP_____ mmHg

2.4. Base line RR & spo2_____bpm & %

Part 3. Question related to spinal anesthesia and surgery

3.1. Spinal injection to incision starting time (minutes)_____

3.2. Level of motor blocks (In Bromage scale) & onset of time _____

3.3. Any additional analgesic drug given intraoperative_____

3.4. Duration of surgery_____ (minutes)

Part 4.Value of hemodynamic parameter after spinal anesthesia intra operatively:

4.1. At 5 minutes A.HR_____ bpm B.MAP_____ mmHg

4.2. At 10 minutes A.HR_____ bpm B.MAP_____ mmHg

4.3 .At 15 minutes A.HR_____ bpm B. MAP_____ mmHg

4.4. At 20 minutes A.HR_____ bpm B.MAP_____ mmHg

4.5. At 25 minutes A.HR_____ bpm B.MAP_____ mmHg

4.6. At 30 minutes A.HR_____ bpm B.MAP_____ mmHg

4.7. At 1h/r A.HR_____ bpm B.MAP_____ mmHg

4.8. At 2 h/r A.HR_____ bpm B.MAP_____ mmHg

4.9. At 3 h/r A.HR_____ bpm B.MAP_____ mmHg

Part5. Question related to intraoperative complications

5.1. Does hypotension occur intraopratively (<30% from baseline)? A. yes B. No

5.2. Does bradycardy occur intraoperatively? (HR<60bpm A. yes B. No

5.3. Does respiratory depression occur (spo2<90or RR<9bpm? A. yes B. No

5.4. Does nausea& vomiting occur intraoperativly? A. Yes B. No

Part6. Question related to pain and postoperative condition of the patient?

6.1. Severity of pain visual analogue scale postoperatively

No pain worst pain

At 1 hr. _____ (in millimeters)

At2 hrs. _____ (in millimeters)

At 3 hrs. _____ (in millimeters)

At 4hrs. _____ (in millimeters)

At 5hrs. _____ (in millimeters)

At 6hrs. _____ (in millimeters)

At 12hrs. _____ (in millimeters)

At 24hrs._____(in millimeters)

6.2. Total and type of analgesia consumption within 12 hours after patient arrive in the recovery is (_____)

6.3. Initial Analgesia request time _____ (in minutes) till after the patient arrived in the recovery.

6.4. Time of motor regressions to Bromage scale 0_____ (in minutes)

Name of data collector_____ Status/profession _____

Signature_____

Name of supervisor_____ status/profession_____

Signature_____

Thank you!!!