Addis Ababa University

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Department of Anesthesia

ANALGESIC EFFECT OF INTRATHECAL NEOSTIGMINE + BUPIVACAINE, MORPHINE + BUPIVACAINE AND BUPIVACAINE ALONE AMONG POSTOPERATIVE PATIENT WHO UNDERGONE LOWER EXTREMITIES ORTHOPEDICS PROCEDURE AT ASELLA REFERRAL AND TEACHING HOSPITAL, SOUTH WEST ETHIOPIA, 2019

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TITLE

ANALGESIC EFFECT OF INTRATHECAL NEOSTIGMINE + BUPIVACAINE, MORPHINE + BUPIVACAINE AND BUPIVACAINE ALONE AMONG POSTOPERATIVE PATIENT WHO UNDERGONE LOWER EXTREMITIES ORTHOPEDICS PROCEDURE AT ASELLA REFERRAL AND TEACHING HOSPITAL, SOUTH WEST ETHIOPIA, 2019

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Executive summary

Background: Spinal anaesthesia is a commonly used regional technique for lower abdominal and lower limb surgeries. Bupivacaine is the most commonly employed local anaesthetic for sub arachnoid block. Perioperative hemodynamic status and post-operative pain relief are important issues with Bupivacaine. Different studies have been conducted to establish best adjuvants to overcome these demerits and so as to enhance bupivacaine induced post-operative analgesia and provide a stable intraoperative condition.

Objective: To compare analgesic effectiveness of intrathecal morphine + bupivacaine + neostigmine bupivacaine and bupivacaine alone for a patient who undergone lower extremities orthopedics procedure

Methodology: In this institutional based prospective cohort study, 102 patients with American Society of Anesthesiologists (ASA) class I or II status, age≥18 who undergone lower extremities orthopedics were grouped into bupivacaine 12.5 with morphine(0.2mg) n=34, bupivacaine 12.5mg with Neostigmine (50mcg), n=34 and Bupivacaine alone group (15mg) based on the decision of responsible anesthetist. Data collection method includes preoperative chart review, intraoperative observation and postoperatively patient interview and chart review. Postoperatively duration & consumption of analgesia, first analgesia request as well as severity of pain using 10cm NRS score were assessed over 24hrs.
The data were entered into EPI INFO and transport to SPSS version 22 for analysis of variable using one-way ANOVA, kuruska-walih H rank test, and chi square.

Results: There was significant difference in maximal level of sensory block, time to maximum sensory and motor block among the three groups. The morphine group had longer time to first rescue analgesics than the neostigmine and bupivacaine group ($P < 0.05$). Overall 24-hr NRS pain scores were significantly higher in the bupivacaine group v/s the morphine and neostigmine groups ($P < 0.05$)

Conclusion and recommendation: Morphine 0.2mg produce prolonged postoperative analgesia with few side effects than neostigmine and bupivacaine alone.

Key Words: Spinal anesthesia, neostigmine, morphine, bupivacaine and pain

Acronyms

ASA	American society of anesthesiology
BP	Blood pressure
CSEA	Controlled spinal epidural anesthesia
CSF	Cerebrospinal spinal fluid
DVT	Deep venous thrombosis
MAP	mean arterial pressure
NRS	Numerical rating scale
PONV	Postoperative nausea and vomiting
PR	Pulse rate
SpO2	Oxygen saturation
SD	Standard deviation
TKR	Total knee replacement

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Chapter 0ne: Introduction

1.1 Background information

Orthopedic surgical procedure is one the most commonly performed procedure worldwide with the highest number in sub Saharan Africa commonly due to trauma. Although there is no documented evidence or study in Ethiopia lower extremity orthopedic procedure such as open reduction and internal fixation, Nailing, Sequesterectomy, amputation, wiring, plating and tendon repair are commonly performed procedure.

Orthopedic procedures have been reported to have the highest incidence of pain compared to other types of operations. If it is not adequately treated, it can cause shallow breathing, atelectasis, retention of secretions, increase risk of deep venous thrombosis (DVT) and later increases the incidence of post-operative morbidity and leads to delayed recovery and hospital discharge.(1, 2)

Management of acute post-operative pain has received keen attention in recent years with considerable concurrent advancement in the field. Despite this advancement, post-operative pain continues to be ~~a~~ challenging and is often inadequately treated, leading to patient anxiety, stress, and dissatisfaction.(1)

Regional anesthetic techniques may lead to blockade or reduced pain ranged from several hours to several days.(3) Better pain control may result in an earlier hospital discharge and may improve the patient's ability of early ambulation in postoperative period. In addition, regional anesthesia is usually easy to administer and the drugs are readily available.(4)

Lower extremity Orthopedic surgical procedures are commonly performed under spinal anesthesia. Bupivacaine is the most commonly employed local anaesthetic for sub arachnoid block. Perioperative hemodynamic status and post-operative pain relief are important issues with Bupivacaine. However, the relatively short duration of bupivacaine to cover post-operative pain is one limitation. (5)

Several adjuvants have been used to extend and enhance the effect of bupivacaine such as ketamine, clonidine, adrenaline and commonly opioids; however all of those drugs are no free of side effects.

Different studies have been conducted to establish best adjuvants to overcome these demerits and so as to enhance bupivacaine induced post-operative analgesia and provide a stable intraoperative condition.

Neostigmine is an anticholinesterase agent, which inhibits the hydrolysis spinal neurotransmitter such as acetylcholine, as a result acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated and increase threshold for electrical stimuli. Spinal Neostigmine apparently activates descending pain inhibitory systems that rely on a spinal cholinergic interneuron.(6)

Intrathecal neostigmine produces analgesia in animals and humans, but its side effects, including nausea and vomiting, limit its use in clinical practice.(4, 7) Nevertheless, studies have shown that small doses of neostigmine (50 µg) can enhance sensory anesthesia with few side effects when combined with small-dose bupivacaine spinal anesthesia.(4) Thus, it is conceivable that the combination of Intrathecal neostigmine 50 µg neostigmine and local anesthetic might improve the quality of spinal anesthesia and prolong postoperative analgesia with few adverse effects.

Another Intrathecal adjuvant drugs are Opioids. Opioids are commonly chosen for pain relief. Intrathecal and epidural administration of Opioids is frequently used to provide postoperative analgesia without sensory or motor blockade. Unfortunately, neuroaxial opioids are associated with adverse side effects, in particular, delayed respiratory depression.(8) The most commonly used opioids are morphine, fentanyl and tramadol. opioids such as morphine provide excellent selective spinal analgesia because of small volume of distribution and slow clearance from the spinal cord.(3) However, slow spinal cord penetration and prolonged duration in cerebrospinal fluid (CSF) caused by hydrophilicity also results in slow onset, prolonged duration of action, and risk of delayed respiratory depression from rostral spread in CSF.(7)

1.2 Statement of the problem

Pain has both sensory and emotional components that interact to produce an overall pain experience. Unrelieved pain after surgery can interfere with sleep and physical functioning and can negatively affect patient wellbeing on multiple levels.

Good pain control is important to prevent negative outcomes such as hypertension, myocardial ischemia, arrhythmias, respiratory impairments, DVT and poor wound healings. In addition to the significant personal suffering and social burden that result, considerable financial expense is incurred, both directly in extra healthcare costs (9, 10).

Uncontrolled acute pain is associated with the development of chronic pain with reduction ~~of~~ in quality of life. Pain after orthopedic procedure is a severe form, if it is left untreated or not adequately treated, can cause shallow breathing, atelectasis, retention of secretions, increase risk of DVT and later increases the incidence of post-operative morbidity and leads to delayed recovery and hospital discharge. (11)

Despite years of advances in pain management, the mainstay of postoperative pain therapy in many settings is still systemic opioids and NSAID. All opioids have significant side effects that limit their use and NSAID are not adequate for surgical pain management as a single agent. The most common side effects of opioid is respiratory depression that could result in hypoxia and respiratory arrest, In addition, nausea, vomiting, pruritus, and reduction in bowel motility leading to ileus and constipation are also side effects of these medications(12).

Although spinal anesthesia is ideal form of anesthetic technique it is limited to cover post-operative pain. When bupivacaine alone is used for spinal anesthesia patient feel pain with in short period of time after spinal anesthesia is given and analgesic request is within the first 2 hours.

Several studies have shown that small doses of neostigmine (50 µg) can enhance sensory anesthesia with few side effects when combined with small-dose bupivacaine spinal anesthesia. Similarly, intrathecal morphine with bupivacaine is another alternative method of achieving prolonged post-operative analgesia however it still remains controversy effectiveness of this drug at different doses with minimal side effects.

This hospital based prospective cohort study was designed to assess the effectiveness neostigmine (intrathecal 50mcg) added to 12.5 mg Bupivacaine in comparison with Morphine (0.2mg) added to 12.5 mg Bupivacaine with bupivacaine alone (15mg) for effectiveness of post-operative analgesia in patients undergoing lower extremity orthopedic procedure under spinal anesthesia in Arsi university hospital, south west Ethiopia.

1.3 Justification of the study

Despite advances and modern anaesthetic and surgical techniques and increasing attention on postoperative pain control it still remains challenges for clinical care providers.

In the current era of minimally invasive surgery combined with enhanced recovery protocols to optimize recovery and reduce the length of patient hospital stay, reducing the incidence and severity of Pain is particularly important.

Intrathecal (IT) and epidural administration of opioids is frequently used to provide postoperative analgesia without motor blockade. Unfortunately, neuroaxial opioids are associated with adverse side effects, in particular, delayed respiratory depression.

3–5μg/kg IT neostigmine produces analgesia in animals and humans, but its side effects, including nausea and vomiting, limit its use in clinical practice. Nevertheless, studies have shown that small doses of neostigmine (50 μg) can enhance sensory anesthesia with few side effects when combined with small-dose bupivacaine spinal anaesthesia and neostigmine less than (50 μg) has less analgesic effect. Similarly, intrathecal morphine with bupivacaine is another alternative method of achieving prolonged post-operative analgesia however it still remains controversy when they are used at different doses with minimal side effects.(13)

Neostigmine and morphine are 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 prolonging postoperative analgesia with less side effects which is treatable and acceptable according to our setup

Although several studies done in western countries on similar topic; the result of those study might not be generalized to our populations beside difference in the perception of pain has been well documented. This study will also be the first in its kind in Ethiopia and can provide opportunities for further studies on related topic.

Chapter two: Literature review

The success of surgical procedure is conditioned by many factors. Poor pain control; has deleterious effects on organ systems and may lead to pathophysiological changes in the pulmonary/cardiovascular system, neurologic change. And also delay wound healing and prolong hospital discharge.

Severe pain after surgery remains a major problem, occurring in 20–40% of patients. Despite numerous published studies, the degree of pain following many types of surgery in everyday clinical practice is unknown(14).

There are several methods for postoperative pain control. One recently introduced methods of postoperative pain management is using of adjuvant drugs for spinal anaesthesia some these adjuvant drugs are Opioids such as morphine, pethidine, fentanyl and anticholinergic such as neostigmine

Different studies in different county have been conducted to determine analgesic effect of morphine and neostigmine when used with bupivacaine.

As study done in Taiwan by M Alkan and his colleague's comparing bupivacaine with saline, bupivacaine with morphine and bupivacaine with neostigmine ~~and~~ reported there were no significant difference in maximal sensory block among the three groups of patients. However, the duration of complete analgesia was significantly prolonged in the neostigmine and morphine groups, and the duration of complete analgesia in the morphine group was prolonged relative to the neostigmine group.

The mean time until the first dose of diclofenac was longer for patients in the morphine and neostigmine groups, on other hand the overall 24-hr VAS score was significantly higher for patients in the saline group than in patients in the morphine and neostigmine groups with No significant differences in the incidence of dizziness or anxiety.(15)

However M Alkan et al reported increased frequency and severity of nausea and vomiting in the neostigmine and morphine group compared with the saline group, however Pruritus occurred more frequently in the morphine group than in the neostigmine and saline groups.(15)

According to study done in Kenya there were no significant differences between the groups those take morphine, neostigmine and saline in terms of hemodynamic parameters. In the first 12 hours postoperatively, in the neostigmine group, there was a significant decrease in HR compared to its baseline values, while a significant increase in MAP was observed in the saline group. However, there was no difference between the groups, and clinical bradycardia requiring treatment was not observed in any of the cases. These results suggest that neostigmine can be used in the epidural space, even at a relatively high dose of 10 µg /kg. The results indicate that epidural administration of 10 µg/kg neostigmine has no significant effect on hemodynamic parameters.(16)

According to study done by Didem Onk and Tülin Akarsu Ayazoğlu in 2016, the first analgesic request was significantly longer in morphine and neostigmine groups than in saline group. As this Indian study the time of postoperative analgesic requirement was significantly longer in patients who received

morphine 0.2mg when compare with those with saline. Addition of morphine to bupivacaine produced prolonged effective anaesthesia and postoperative analgesia compared to addition of fentanyl to bupivacaine without producing undue adverse effects in companied-spinal epidural anesthesia (CSEA).(17)

In other study the morphine group had lower pain scores than did the fentanyl group and the saline group the 2nd, 6th, 12th, and 24th hours. And in the 2nd, 6th, and 24th hours the morphine group was also found to have fewer patients who required additional analgesics than did the fentanyl group.(18, 19)

Another research done by Seyed Hamid and Reza Faiz, the sensory block onset time and motor block onset time (knee flexion time) were not significantly different among the groups, whereas the time to complete motor block was significantly longer in group that take neostigmine and motor block recovery time were significantly different among groups. The maximum sensory levels were T4 in both group of morphine and group of neostigmine. Nausea and vomiting is more common in neostigmine and bupivacaine group while itching is more in morphine group. and the homodynamic status was not significantly different across the study among the three groups.(19)

According to research done in India dose-independent reduction of postoperative analgesia requirement and dose-dependent increase in the incidence of PONV has been demonstrated using various doses of Intrathecal neostigmine with bupivacaine. The addition of 1-5 mcg neostigmine intrathecal (IT) to 100 to 200 mcg morphine doubled the duration to first rescue analgesic in the patients undergoing major gynecological surgeries without increasing the incidence of adverse effects. Moreover, the risk of delayed respiratory depression with the use of neuroaxial morphine is a great concern. 1mcg/kg IT neostigmine would augment the analgesic efficacy of IT fentanyl and bupivacaine, without increasing the incidence of untoward side effects [9]. As total knee replacement (TKR) surgery involves severe pain in the postoperative period and the study in this subset of patients. The addition of a low dose of neostigmine (50 mcg) increased the duration of effective analgesia by 78%. All patients who received IT neostigmine in combination with IT bupivacaine required less epidural top ups in 24 hrs.

Patients receiving neostigmine had a significantly prolonged duration of motor block and sensory block compared to the control group. The difference of the mean time to the first analgesic request was also significantly longer in neostigmine group when compared with saline group. The total analgesic consumption during the first 12 hours after surgery was significant difference between groups Neostigmine and saline .The two groups were not significantly different in terms of intraoperative and postoperative side effects.(18, 19)

The adverse effect of neostigmine depends on dose of neostigmine added to bupivacaine. Nausea and vomiting incidence depends on the dose. Neostigmine greater than 75mcg significantly produce nausea and vomiting which if resistant to ant emetics. Hemodynamic state (pulse rate blood pressure), respiratory depression and pruritus of the neostigmine and control group are comparable .(13)

Research hypothesis

Pain intensity scale are different in patient who receive morphine and neostigmine compared to those who receive bupivacaine alone for postoperative pain management.

HO1: There is no statistically significant difference in NRS between groups.

HA1: There is statistically significant difference in NRS between groups

HO2: There is no statistically significant difference in time to analgesic request between groups.

HA2: There is statistically significant difference in time to analgesic request between groups.

HO3: There is no statistically significant difference in analgesic consumption between groups.

HA3: There is statistically significant difference in analgesic consumption between groups.

Conceptual frame work

This conceptual framework is developed by referring different literatures related to analgesic effectiveness of morphine and neostigmine as compared to bupivacaine alone for lower extremity orthopedic procedure surgery in order to indicate relationships between variables. It represents set of interrelated concepts that represent an image of association between postoperative pain and factors affecting postoperative pain. This structure will provide guidance for the study.

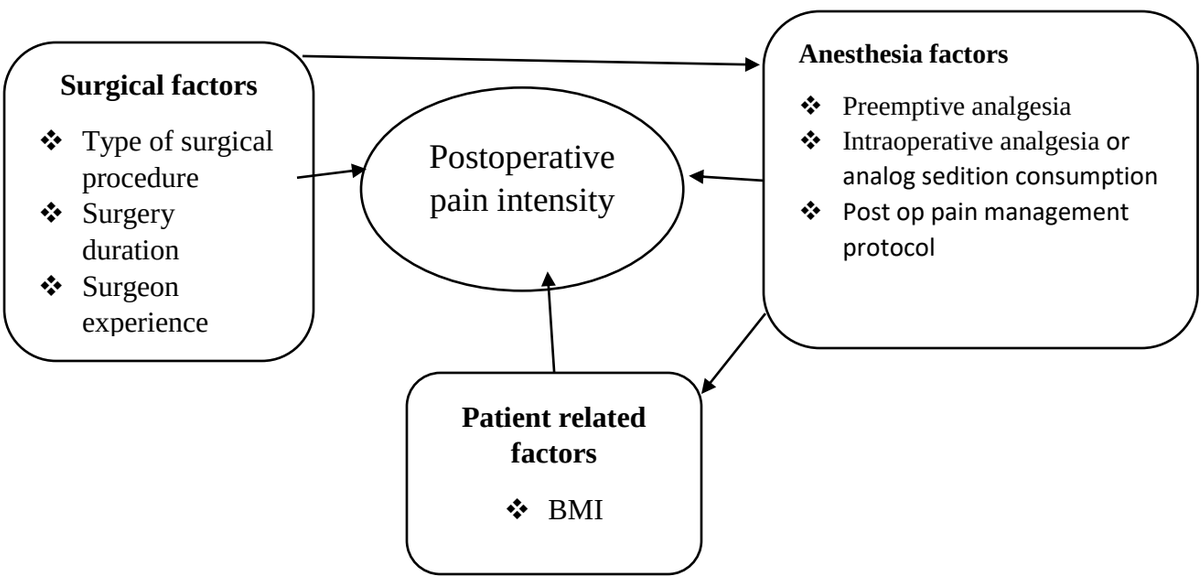

Fig 1 conceptual frame work

Chapter three: Objective of the study

3.1 General objective:

To compare analgesic effectiveness of intrathecal morphine and neostigmine for a patient who undergone lower extremities orthopedics procedure in Asella referral and teaching hospital.

From September 2018 to June 2019

3.2 Specific objective:

To compare numeric rating scale (NRS) score between groups

To compare time to first analgesic request in groups

To compare total analgesic consumption between groups over 24 hours

Chapter four: Methodology

4.1 Study area: This study was conducted in **A**sella referral and teaching hospital which is found in Asella town Oromia region, south west Ethiopia. Asella referral and teaching hospital has 5.2 million catchments area. Based on the annual report of Asella referral and teaching hospital operate 9500 patients annually. 750 of them are lower extremities orthopedics procedure, which needs regional anaesthesia. Asella referral and teaching hospital has five fully functional operation rooms and one for ophthalmology.

4.2 Study design and period: An institutional-based prospective cohort study was employed from September 2018 to June 2019.

4.3 Population

4.3.1 Source population: All patients greater than 18 years who undergone lower extremity orthopedics procedure under spinal anesthesia at Asella referral and teaching hospital.

4.3.2 Study population: All patients who undergone lower extremity orthopedics procedure under spinal anesthesia during study period those fulfill the inclusion criteria.

4.4 Study variables:

4.4.1 Dependent variable:

Pain severity (measured by: NRS score),

Time to first analgesic request

Total postoperative Analgesic consumption in 24 hours).

Variables related to spinal anaesthesia (level of sensory block, onset of sensory block, grade of motor block, onset of motor block).

Variables related to incident of postoperative side effect (nausea/vomiting, hypotension, bradycardia, shivering and Pruritus.

4.4.2 Independent variables:

- Socio demographic characteristics: age, sex and BMI
- Duration of surgery
- Type of surgical procedure
- ASA physical status
- Perioperative fluid given
- Type of given drugs

4.5 Operational definition

Hypotension;-Defined as when the Systolic blood pressure of below 90mmHg.(20)

Bradycardia; - When the heart rate less than 50 beats/minutes.(20)

Postoperative pain: the presence of pain in the postoperative period was defined as a patient as having pain and any pain score other than zero starting from recovery within 24 hours.

Numerical pain rating scale (NRS): is a valid ~~is a~~ method of pain assessment where patients are asked to score their pain ratings on a scale of 0–10, corresponding to current and worst pain experienced over

the 24 hours. The median value was used to represent patient's level of pain(21). Figure 2: Adopted from the National Initiative on Pain Control™ (NIPC™)

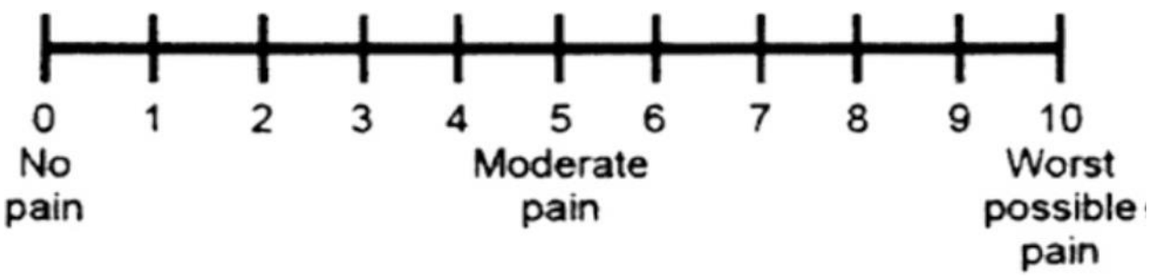

Figure 2: Adopted from the National Initiative on Pain Control™ (NIPC™)

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

Total post-operative analgesia consumption: total dose and type of medication given in mg within the first 24 hour starting from admission to recovery room.

Post-operative nausea and vomiting: when a patient's experience at least one episode of either nausea or vomiting within 24 hours.

Motor block was assessed by the modified Bromage score:

0: No motor loss;

1: Inability to flex the hip;

2: Inability to flex the knee; and

3: Inability to flex the ankle(22)

4.6 Inclusion and exclusive criteria:

4.6.1 Inclusion criteria: All ASA class I and II patients, age between 18-65 yrs. scheduled for lower extremities orthopedics procedure under spinal anesthesia included in the study.

4.6.2 Exclusive criteria: Emergency surgeries, patient pre-medicated with anti-pain with in 12 hour before anesthesia, patient refusal of follow up, inadequate or failed spinal anesthesia, drug dose given other than morphine 0.2mg with bupivacaine 12.5mg, neostigmine 50 mcg with bupivacaine 12.5mg and bupivacaine 15mg, patient anti-pain intraoperative if patient sedated intraoperative and any regional block done in addition to spinal anesthesia

4.7 Sample size and sampling technique

The primary endpoint of our study was compare pain by numeric rating scale (NRS) score between groups for 24 hours after the surgery. After review the study done in Taiwan we found that with α=0.05 and β=0.1 and 90% power and Mean one (morphine) =4.2 and SD = 0.2, Mean two (neostigmine) =4.7 and SD=0.3 and mean three(bupivacaine) =5.7 and SD= 0.4 [18].

$Z_{\alpha/2}$= 1.96 for error of 5% (95% confidence level)

Z_{β} = 1.28 for 90% power

μ_1 =4.2 and SD = 0.2

μ_2 =4.7 and 0.3.

Using comparison of two mean formula; $n= (z_{\alpha/2}+ z_{\beta})^2 (\sigma_1^2+\sigma_2^2)/ (\mu_2-\mu_1)^2$

$N1 = (0.3^2 +0.2^2) (1.96+1.28)^2 / (4.7-4.5)^2$

n1 = 34.

$n2 = (0.3^2 +0.4^2) (1.96+1.28)^2 / (4.7-5.7)^2$

$n2^{=}$ 10.8

$n3= (0.2^2 +0.4^2) (1.96+1.28)^2 / (5.7-4.5)^2$

n3= 7.54

Using largest sample size for all groups; **102** participants those fulfill inclusion criteria was included in the study since there are three groups.

4.71 Sampling procedure: Systemic random sampling technique was used to select study participants by using skip interval of "K". Data was collected for five month. During this period 300 were operated. K =N/n=3. When the selected "K" fails to fulfill the inclusion criteria the next case was taken.

n = total sample size

K = skip interval

N = Total study population

The first study participant was selected by lottery method. Anesthetist decides the group of the patients depending on the drug he/ she used. In Asella referral and teaching hospital some anesthetist use 15mg bupivacaine and others use 12.5mg bupivacaine with additives.

Depending on this the groups were:

Group N (neostigmine group): participants those take 12.5mg bupivacaine with50 mcg neostigmine.

Group M (morphine group): participants those take12.5mg bupivacaine with 0.2mg morphine

Group B (control group): participant those take15mg bupivacaine alone

4.8 Data collection technique and patients

After providing training for data collectors, data was collected using pretested questionnaires with multiple close-ended questions on respondents, chart review and observetion. All patients scheduled for elective lower extremities orthopedics procedure those fulfill inclusion criteria was assessed before surgery by history taking, and chart review following informed consent. On the morning of the surgery, the data collector instructs the patient on how to self-report pain using the eleven point NRS score 0 to 10. Anesthetist in charge filled Sociodemographic and intraoperative variables and the other data collector who is unaware of group allocation collected the remaining postoperative data.

On arrival of the patients to the operative theater, and after application of the routine hospital monitoring protocol, HR, noninvasive blood pressure, and SPO2 has been recorded

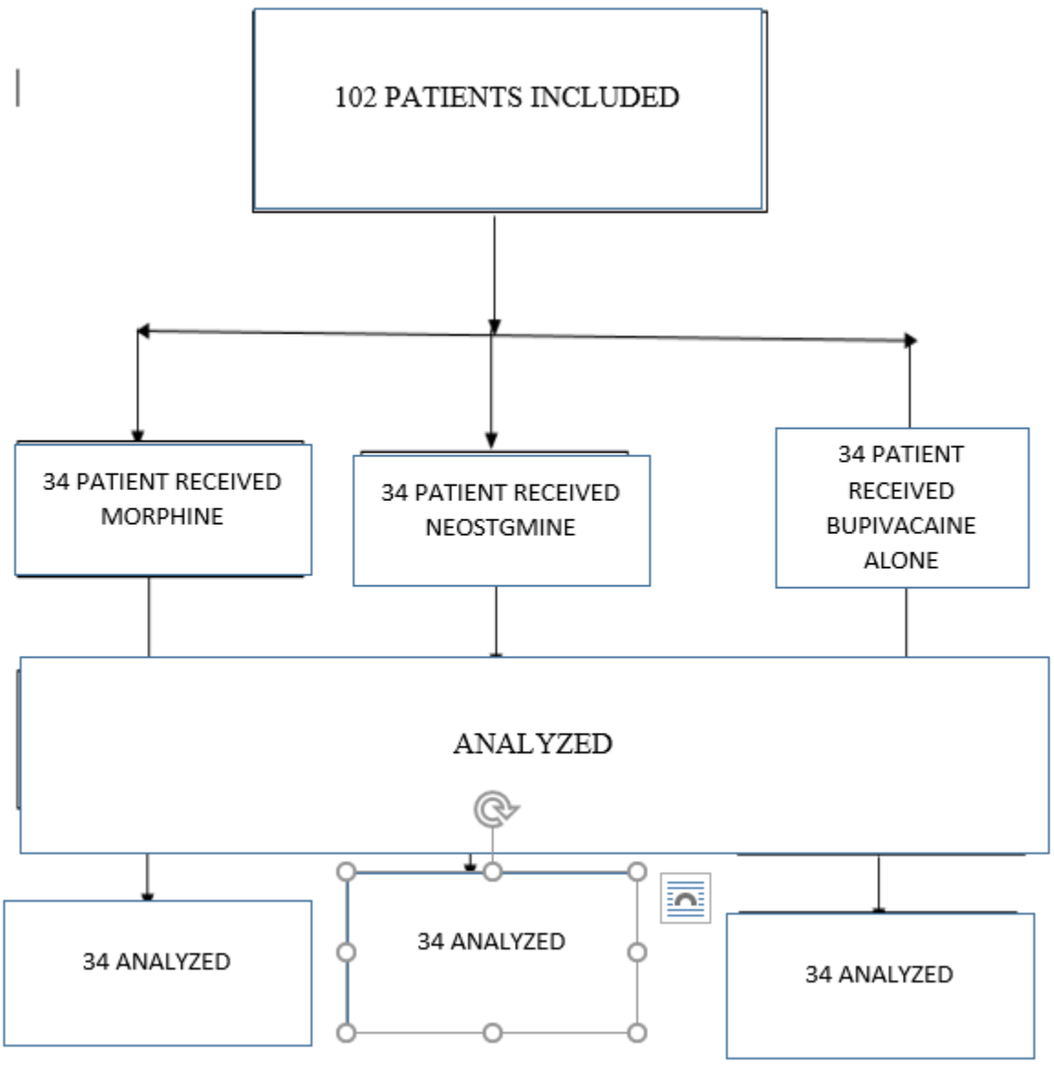

Figure 3: Enrollment chart for patients scheduled for orthopedic procedure

4.10 Data quality control

To ensure quality of data, pretest of the data collection tool (the questionnaire) was done on 10 patients who were not be included in the main study and the collected data was checked out for the completeness, accuracy and clarity and cross checking was done before analysis.

Patients were explained how to rate severity of pain on NRS and Training was given for data collectors and supervisor for one day on how to approach study subjects and on how to use data collection tool. Supervised by principal investigator and supervising MSc anesthetist.

4.11 Data analysis and interpretation

Data were entered into Epi-info 7 and transported to SPSS V 22 for analysis. The data were tested for normality using histogram and Shapiro–Wilk normality test and homogeneity of variance by Levene's test of homogeneity of variance. Normally distributed and continuous data were analyzed using one way

analysis of variance (ANOVA) with post hoc analysis for multiple test and non-normally distributed data were analyzed using kuruska-walih H rank test.

The comparisons of categorical parameters were analyzed using chi-square test or Fisher's exact test with post hoc as required. Data were presented as mean ±SD for normally distributed, median ± IQR for no normally distributed and categorical data were presented as numbers and frequencies (percentages). P-values <0.05 was considered statistically significant.

4.12 Ethical consideration

Ethical clearance was obtained from the department ethical clearance committee before the start of the study. Permission was also obtained from the concerned bodies of Asella referral and teaching hospital administration and Arsi Zonal Health Department. The purposes and the importance of the study were explained and verbal as well as written informed consent was obtained from each participant. Confidentiality was maintained at all levels of the study by avoiding identifiers and using codes to identify patients. The participant's involvement in the study were on a voluntary basis, participants who are not willing to participate in the study and those who wish to quit their participation at any stage were informed and allowed to do so without any restrictions.

4.13 Dissemination plan

Results will be submitted to AAU Department of anesthesia and presented orally. To help in future interventions the result will be communicated to governmental teaching institution. In addition, effort will be exerted to publish the paper and disseminate it via presentation on different national and international conference

CHAPTER FIVE: RESULTS

5.1 Demographic and preoperative Characteristics

Total number of patients involved in this study was 102. The three groups of patients in the study did not differ significantly with regard to age, sex, BMI and duration of surgery (Table I)

Table I: Sociodemographic characteristics of the patients in Asella referral and teaching hospital 2019 G.C

	Group N(n = 34)	Group M(n = 34)	Group B (n = 34)	p- value
Age (years)	40.7±13.5	40.1±13.9	37.5±10.2	0.537
Gender (M/F)	18/16	24/10	21/13	0.325
ASA status: - ASA I/II)	29/5	30/5	32/2	0.49
BMI (kg/m^2)	21.3±2.2	22.0±2.4	21.7±2.6	0.560

Values are presented as Mean ± SD, (n, %) = number and percentage.

Preoperative fluid, baseline vital sign are not statically significant between the group.

Table II: Preoperative baseline vital sign of the patients in Asella referral and teaching hospital 2019

	Group N(n = 34)	Group M(n = 34)	Group B (n = 34)	p- value
Preoperative fluid	894.1±125	932.3+106	926.4+121	.359
Baseline SBP	128.9±17.1	128.8+17	124.6+11	.436
Baseline PR	77.1±11.5	80.5±12.2	79.5±11.7	.465
Baseline RR	15.7±1.8	16.1±2.1	15.6±1.9	.555
Baseline SPO2	93.8±5.2	94.7±1.6	94.5±1.3	.523

SBP=systolic blood pressure PR=pulse rate RR=respiratory rate SPo2= oxygen saturation

Values are presented as Mean ± SD

5.2 Intraoperative patient management

Using one way anova, there was significant difference in the onset and maximal sensory block amongst the three groups of patients. The time to achieve grade three Bromage motor blocks was shorter in bupivacaine alone group different between the groups.(table III)

Duration of the procedure was not significantly between the group and intraoperative fluid given was significantly different between the morphine and bupivacaine alone group. But, there is no significant difference between neostigmine and bupivacaine and neostigmine and morphine group.

Table III: Characteristic of intraoperative spinal anaesthesia in Asella referral and teaching hospital 2019

	Mean of the group			P value		
	Group N n = 34)	**Group M (n = 34)**	**Group B (n = 34**	**Group N v/s M**	**Group N v/s B**	**Group M v/s B**
Duration of procedure	135±25	112±23	111±27	0.89	.84	1
Fluid given in ml	1974±322	1700±362	2670±504	1	.20	.04
Onset of max. sensory block	13.71±4.5	8.72± 3.4	7.44±2.7	.00	.00	.48
Maximum level of sensory block	6.94±1.3	6.44±1.1	5.55±1.2	.28	.00	.01
Time to achieve Bromage grade 3 motor block	11.61±2.4	8.05±2.3	6.11±1.5	.00	.00	.01

N=neostigmine M=morphine B=bupivacaine v/s= versus

Values are presented as Mean ± SD in minute

Compared with neostigmine and morphine group systolic blood pressure was significantly lower in the bupivacaine alone group (table IV) throughout the procedure which was analysed by

chi square test Table IV Intraoperative hemodynamic parameters of the patients in Asella referral and teaching hospital 2019G.C

	Mean of the group			P value		
	Group N n = 34)	**Group M (n = 34)**	**Group B (n = 34**	**Group N v/s M**	**Group N v/s B**	**Group M v/s B**
Baseline SBP	129 ±17	128±17	124±11	1	0.78	0.80
SBP at 5 min	124±14	122 ±15	109±12	1	0.00	0.00
SBP at 10 min	120 ±15	119±14	102 ±13	1	0.00	0.00
SBP at 20 min	117±16	115±12	97±13	1	0.00	0.00
SBP at 30 min	114±13	113 ±13	99.5± 11	1	0.00	0.00
SBP at 40 min	114±14	114±11	102±10	1	0.01	0.01
SBP at 50 min	114±13	114±10	107±9	1	0.01	0.02
SBP at 60 min	116±13	115±11	105±25	1	0.01	0.04
Pulse rate						
Baseline PR	76±8	78±9	78±7	0.61	1	1
PR at 5 min	76±14	77±12	72±10	1	0.36	0.15
PR at 10 min	72±13	74±11	68±10	0.96	0.43	0.04
PR at 20 min	68±14	74±11	65±12	0.14	0.99	0.01
PR at 30 min	67±13	73±10	66±11	0.10	0.07	0.07
PR at 40 min	66+13	73±10	68±9	0.03	0.99	0.02
PR at 50 min	67±12	74±9	71±9	0.08	0.98	0.48
PR at 60 min	68±12	74±9	71±9	0.07	0.81	0.75

Values are presented as Mean ± SD SBP=systolic blood pressure PR= pulse rate

Pulse rate were significantly different between the group N and M and group M and B at different time intraoperatively. Group N and group M are significantly different at 40 minute and group M and N are significantly different at 20 and 40 minute intraoperatively.

Mean pulse rate of N and B alone group were lower than mean of M group (table IV).

Using chi square test, transient hypotension occurred at various times in groups M and B, and the difference was significant at 20 minute intraoperative (table V)

Table V: Intraoperative hypotension and bradycardia in Asella referral and teaching hospital in 2019G.C

Time interval	Group			P value
	Neostigmine	Morphine	Bupivacaine alone	
Hypotension				
At 5 min	0(0%)	0(0%)	1(2.9%)	0.99
At 10 min	0(0%)	1(2.9%)	4(11.7%)	o.12
At 20 min	0(0%)	1(2.9%)	926.7%)	0.01
At 30 min	0(0%)	2(5.8%)	4(11.7%)	0.162
At 40 min	0(0%)	1(2.9%)	0(0%)	0.99
At50 min	0(0%)	0(0%)	1(2.9%)	0.99
At 60 min	0(0%)	0(0%)	2(5.8%)	0.327
Bradycardia				
At 5 min	0(0%)	0(0%)	0(0%)	constant
At 10 min	1(2.9%)	0(0%)	3(8.8%)	0.89
At 20 min	0(0%)	0(0%)	1(2.9%)	0.32
At 30 min	2(5.8%)	0(0%)	0(0%	0.32
At 40 min	1(2.9%)	0(0%)	0(0%)	1
At50 min	1(2.9%)	0(0%)	0(0%)	1
At 60 min	0(0%)	0(0%)	0 (0%)	constant

Values are presented by observed value and the % within the group

Transient bradycardia occurred at various times in groups which is higher in group N and B when compared with group M. Though here is no significant difference between the groups (table V)

Adverse effects observed in the study shown on the figure3. The frequency of nausea and vomiting were significantly increased in the neostigmine group compared with the morphine and bupivacaine alone group at P value 0.01. Pruritus occurred more frequently in the morphine group than in the neostigmine and Bupivacaine alone groups at P value 0.00 which was analysed by chi square test

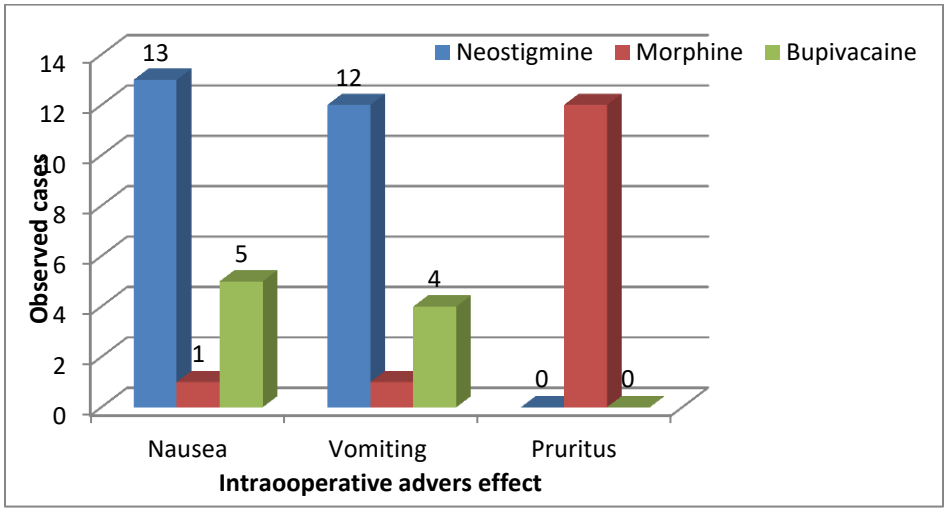

Figure III: intraoperative complication at Asella referral and teaching hospital in 2019 G.C

5.3 Postoperative patient condition

Compared with the bupivacaine alone group, the duration of complete analgesia was significantly prolonged in the neostigmine and morphine groups, and the duration of complete analgesia was prolonged in the morphine group compared to the neostigmine group. The mean time until the first dose of diclofenac was longer for patients in the morphine and neostigmine groups when compared with patients in the bupivacaine group, and also prolonged in the morphine group relative to the neostigmine group which was analysed by chi square test.

Table V: postoperative time to first analgesia request and total analgesia consumption in Asella referral and teaching hospital in 2019G.C

	Mean of the group			P value		
	Group N n = 34)	**Group M (n = 34)**	**Group B (n = 34**	**Group N v/s M**	**Group N v/s B**	**Group M v/s B**
Time to first analgesia request	8.53±2.9	11.94±3.8	3.35±2.5	0.00	0.00	0.00
Total analgesia consumption						
Pethidine	2.9±54	2.98±47	15±70	1	0.01	0.01
Tramadol	146±64	108±55	234±110	0.02	0.00	0.00
Diclofenac	54±12	41±12	93±23	1	0.14	0.03

Values are presented as Mean ±SD in hour and mg

Pethidine and diclofenac consumption was not significantly different between group N and group M and significantly different from group B at P value 0.012. Diclofenac consumption was not significantly different between group N and group B at P value0.144.

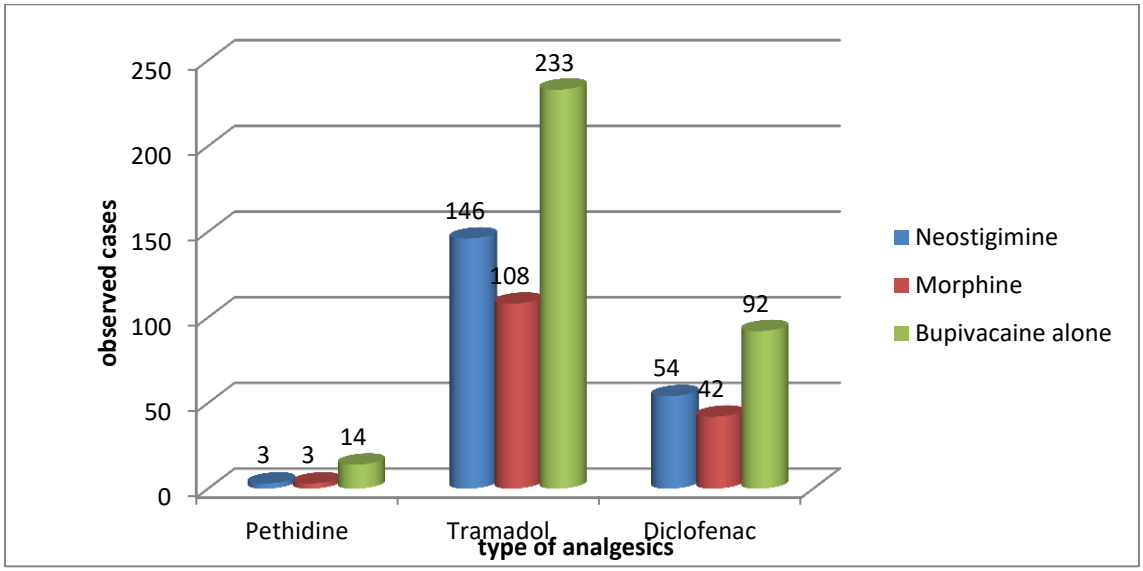

Figure IV Postoperative analgesic drug consumption within 24 hour at Asella referral and teaching hospital in 2019 G.C

The overall NRS score was significantly higher for patients in the bupivacaine alone group than in patients in the morphine and neostigmine groups at three and six hours (figure). And after which no significant difference was noted among the three groups.

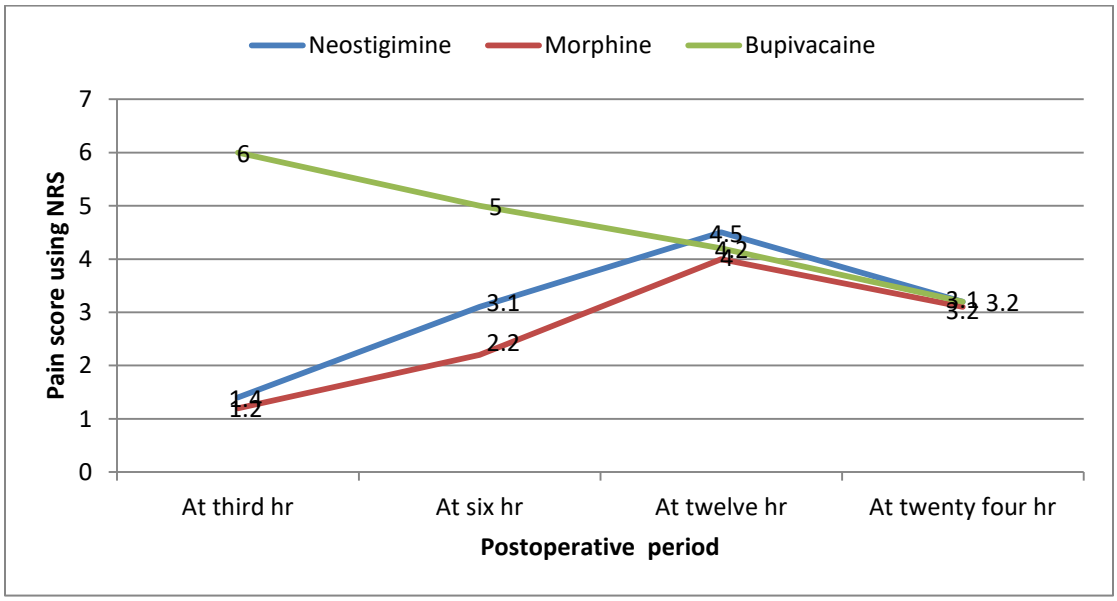

Figure V: Postoperative pain score using numerical rating scale within 24 hour at Asella referral and teaching hospital in 2019 G.C

Postoperative nausea and vomiting has no significant difference between the groups. However; pruritus was significantly different in morphine group when compared with neostigmine and bupivacaine alone group at P 0.03(figure VI) which was analysed by chi square.

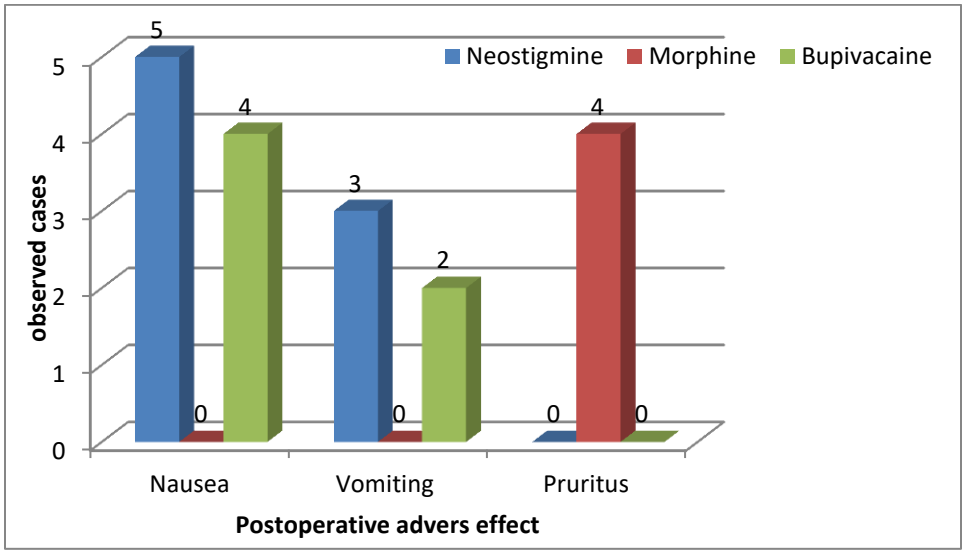

Figure VI: Postoperative adverse effect within 24 hour at Asella referral and teaching hospital in 2019 G.C

CHAPTER SIX: DISCUSSION

The aim of good postoperative analgesia is to produce a long lasting, continuous effective analgesia with minimum side effects. Multimodal analgesia protocol may increase analgesic effectiveness. Severe pain can be treated with intravenous opioids and NSAIDs, epidural local anesthetics and/or opioids, peripheral nerve blocks, or different combinations of drugs. (22)

Hence, an intrathecal additive to these local anaesthetic forms a reliable and reproducible method of prolonged postoperative analgesia. This technique being simple and less cumbersome has gained a wide acceptability. Commonly used intrathecal additives to local anaesthetic include Opioids, Clonidine, and Neostigmine.(5)

The purpose of this study was to compare the duration of complete analgesia, total analgesic consumption and severity of pain using NRS among morphine with bupivacaine, neostigmine with bupivacaine and bupivacaine alone groups.

Based on the data found in present study patients in the groups did not differ significantly with regard to age, sex, BMI and duration of surgery. Preoperative patient blood pressure, pulse rate oxygen saturation and fluid given are not significantly different between the groups

There was significant difference in the onset of sensory block between the group neostigmine, morphine and bupivacaine with mean 13.7±4.5, 8.7±3.4 and 7.44±2.7minute rrespectively. Neostigmine produces analgesia indirectly when administered intrathecal through inhibition of endogenous spinal neurotransmitter which cause delayed onset and activate inhibition of descending pain pathway This result of the study is slightly higher than result of neostigmine, morphine and bupivacaine with mean 7.4, 6.3 and 6 minute respectively from previews study done by Yoganarasimh in 2012 and significantly hither the result of research done Seyed in 2015.(5, 23). The difference may be due to baricty of bupicaine and the position of the patient after spinal anaesthesia is given. Maximal level of sensory block amongst the three groups of patients is different between the group neostigmine, morphine and bupivacaine with mean 6.9±1.3, 6.4±1.1 and 5.55±1.2 minute respectively. The time to achieve grade three Bromage motor blocks was ~~is~~ prolonged with group N relative to group M and group B which is in line with the result from research done by Yoganarasimh in India in 2012.(5)

Mean SBP of group bupivacaine is significantly lowered compared to neostigmine and morphine group at all measure from 5 minute to 60 minute. Although there was hypotension of SBP occurred at various times in group's morphine and group bupivacaine there was no statistically significant difference between the groups and no one patients are treated by vasopressor intraoperative. Mean of intraoperative pulse rate of group neostigmine and group bupivacaine is not significantly different in the study result, which is not similar with the result of research done by Vesenka in India(24). Bradycardia is observed more in neostigmine and bupivacaine group. Five patients from the neostigmine group and four patients from bupivacaine group were treated by one dose of 0.5mg atropine intraoperative.

The incidence of intraoperative and postoperative nausea and vomiting were significantly more neostigmine and bupivacaine alone groups compared to the morphine group even though the incidence is decreased in postoperative period. This may be associated with neostigmine easily spread up to brainstem through cerebrospinal fluid and activate medulla and chemoreceptors and bupivacaine 15mg resulted in more hypotension which can cause nausea and vomiting. Pruritus was observed more commonly in the morphine group. Intraoperative and postoperative 35% and 12% has complained pruritus in the morphine group which is nearly similar with 41% of the patient complained pruritus in previous studies done by D Bhar in 2016 and Ping-Heng in 2001.(15, 25)

We found that IT group neostigmine and group morphine prolonged postoperative analgesia time. The mean time for first analgesic requested in the neostigmine, morphine and bupivacaine were 8.53$\pm$2.9hr 11.94$\pm$3.8hr and 3.32$\pm$2.5hr respectively. Compared with the group morphine and neostigmine the time for first request for analgesic in the bupivacaine group were shorter and relatively neostigmine group hour is shorter than the morphine group. The difference come from the duration of action of bupivacaine, which is 4 to 8 hour. This result is in line with the result of neostigmine, morphine and bupivacaine with mean 7.8$\pm$3, 10$\pm$5 and 4.5$\pm$1.2of research done by Tan in 2001.6(15)

In the first 12-hour NRS pain scores was significantly higher in the group bupivacaine relative to the group of neostigmine and group of morphine, and slightly higher in neostigmine group

than the morphine group after which all group have similar NRS. This observation is nearly similar with the result of research done in Ping-Heng Tan MD in Taiwan in 2001.(5, 25, 26)

When the additional analgesic requirements of the three groups were compared, it was found that total analgesia used in 24hrs postoperative is more in bupivacaine group. Pethidine, tramadol and diclofenac consumption of bupivacaine group was significantly higher than group of neostigmine and group of morphine. The diclofenac consumption was 54±12, 41±12 and 93±23mg in neostigmine, morphine and bupivacaine respectively; which is slightly less than the result (75, 75 and 150mg in neostigmine, morphine and bupivacaine group respectively) of previous stud done by Ping-Heng in 2001.(25). The difference may be the analgesic drug used postoperative was not controlled in our case.

Limitation

The current study has certain limitations, lack of control over the confounding factor like incision size and type of procedure even though most variables are comparable between groups. Participation of different orthopedic surgeon and anesthetist even though practice variability was handled by standard of practice. Lack of standard pain management protocol in the study hospital was especially during postoperative period was among limitation we encountered during data collection.

Conclusion and recommendation

Adding of morphine has prolonged postoperative analgesia effect and has less NRS than the neostigmine and bupivacaine alone when used as adjuvant for spinal anesthesia with bupivacaine. Also addition of neostigmine to bupivacaine has prolonged postoperative analgesia effect when compared to bupivacaine alone..

Using morphine as adjuvant for spinal anesthesia with bupivacaine is better for country like Ethiopia is better until further RCT and patient satisfaction research is done

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Annex one: 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 research investigators.

The research team includes MSc students, two senior advisor from AAU and three anesthetist for data collection.

Name of Principal investigator: - Ayele Bekele

Advisor's name: -:- Adugna Aregawi(Assistant proffesor)

Lemlem Getachew(BSc,Msc in anesthesia)

Name of sponsor: - AAU

Name of organization: - AAU, Health science college, anesthesia department

This information sheet is prepared by the above-mentioned investigator.

Risk Procedure

The aim of the research is not to give you new drugs. But following what will happen during the procedure after spinal anaesthesia. We do not record your name and identification number.

Risk/ Discomfort

By participating in this research project, you may feel that it has some discomfort; especially you may waste about 30 minute. We hope you will participate in the study for the sake of the benefit of the research result. There has no any risk to you for participating in this research project.

Benefits

If you participate in this research project, there may not be direct benefit to you but your participation is likely to help us in determining the effect of morphine and neostigmine when added to bupivacaine for spinal anaesthesia. Ultimately, this will help all stakeholders to work on the gaps and improve the quality

Annex two: Consent form

Dear participant:

This is a research designed to compare effectiveness of intrathecal morphine and neostigmine with bupivacaine in patients undergoing lower extremity procedure under spinal anesthesia for post-operative analgesia. As a chance, you were included in the study. So, we kindly request your involvement in the study and honest response to achieve the objective of the study. Your response completely confidential and you have full right either to refuse a single question or leave the study. 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 willing to participate in the study please? YES/NO

Thanks for taking part in the study!!!!

For further question ask investigator

Tel: - 0931252112

E-mail- bekeleayele5@gmail.com

Amharic Version Questionnaire Consent Form

Annex three:

Annex: Questioner

Annex 1: Data collection tools/questioners

1. Socio demographic information

1.	Age of the patient	_____
2.	Gender	a. Male. b. female
3.	BMI	

2. Preoperative patient condition

1	Diagnosis	_____
2	ASA classification	a. ASA 1 b. ASA 2
3	premeditation drugs	----------
4	Base line vital sign	a. BP_____ b. PR_____ c. RR_____ d. Spo2_____

3. Intraoperative patient condition

1	Spinal anaesthesia drug given	a. Neostigmine with bupivacaine b. Morphine with bupivacaine c. Bupivacaine alone								
2	Vital sign	Time	5min	10min	20min	30min	40min	50min	60min	
		BP								
		PR								
		RR								

		Spo2									
3	Shivering	0. No shivering; 1. Muscular activity in only 1 muscle group 2. Muscular activity in more than 1 muscle group 3. Shivering involving the whole body.									
4	Maximum level of sensory block	_____									
5	Time to achieve maximum sensory block	_____-									
6	Time to achieve grade 3bromage scale	_____									
7	Nausea and	0: no 1: yes									
8	vomiting	0: no 1: yes									
9	Duration of procedure	_____									
10	Total intraop. Fluid										

4. Postoperative patient condition

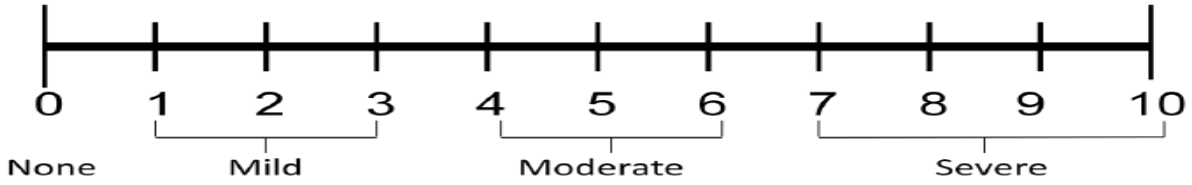
1	Vital sign	Time after operation	immediately	1 hrs	3hour	6 hour	12hour	24 hour
		BP						
		PR						
		RR						
		Spo2						
		Immediately after the operation is completed in PACU		1hout	3hour	6hour	12hour	24hour
2	Pain score using visual analog	_____						

	scale							
3	Time for first analgesic request post operation	_____						
4	Total dose of analgesic drug given in 24 hrs							
5	Nausea	a. No b. yes						
6	Vomiting	a. no b. yes						
7	Pruritus	a. no b. yes						

Appendix four: The numeric Rating scale (NRS)

English version

The numeric Rating scale (NRS)



The scale was taken 4 times within the first24 hours. Patients was asked to rate their pain was assessed and recorded at 0 min (immediately on acceptance of patient at recovery room) and 0-3, 3-6, 6-12, 12-24 hours post-operatively.

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:

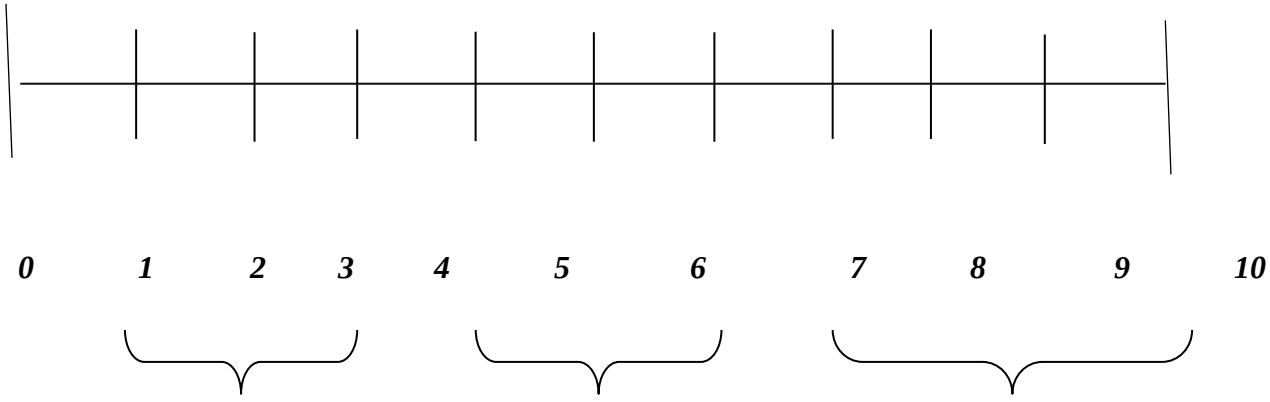
0 = No Pain

1-3 = Mild Pain (nagging, annoying, interfering little with ADLs)

4–6 = Moderate Pain (interferes significantly with ADLs)

7-10 Severe Pain (disabling; unable to perform ADLs)

The numeric Rating scale (NRS)



መለኪያዉ በ 24 ሰአት ዉስጥ 5 ጊዜ የ ሚለካ ሲሆን ታካሚዎች የሚሰማቸዉ የህመም መጠን በየ 6 ሰአት ልዩነት እንዲያሳዩን እንጠይቃለን

ታካሚዎች የሚከተሉትን ጥያቄዎች ይጠየቃሉ፤-

ሀ . አሁን ከተገለጹት ቁጥሮች ማለትም (0-10) ባሉት ዉስጥ የእርስዎ የህመም መጠን ስንት ላይ ነው

ለ. ከላይ የተገለጸዉ በቂ ካልሆነ ተጨማሪ ማብራሪያ ይሰጡታል ፡

0 ህመም የለም

1-3 መካከለኛ ህመም (መነጫነጭ፣መርበሽ፣ወ.ዘ.ተ)

4-6 ከፍተኛ ህመም (ከ ህመሙ በተያያዘ ስራን በ አግባቡ አለመስራት)

7-10 በጣም ከፍተኛ ህመም (እለታዊ ትግባራትን ማከናወን አለመቻል)