ADDIS ABABA UNIVERSITY

COLLAGE OF HEALTH SCIENC

SCHOOL OF MEDICINE

DEPARTMENT OF ANESTHESIA

Effect of Low-Dose Intravenous Ketamine on Postoperative Pain after Cesarean Section following under Spinal Anesthesia in Zewditu Memorial Hospitals, Addis Ababa, Ethiopia, 2021, a prospective observational cohort study

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Declaration

I, the undersigned declare that this thesis is my original work in partial fulfillment of the requirement for the Master of Science degree in anesthesia. I aware that plagiarism will not be tolerated and quoted materials had been appropriately referenced.

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This thesis work has been submitted for examination with my/our approval as Advisors and tutors on the Master of Science degree in anesthesia.

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Finally I like to give appreciation to our study data collectors and authors of articles.

List of Abbreviations/Acronyms

AAU = Addis Ababa University
ASA = American Society of Anesthesiologists
CD = Cesarean Delivery
BMI = Body Mass Index
Cm = Centimeter
CNS = Central Nerve System
C/S = Cesarean Section
Ho = Null Hypothesis
HA = Alternative Hypothesis
HR = Heart Rate
Hr. = Hour
IQR = Interquartile Range
MAP = Mean Atrial Pressure
MD = Mean Difference
Mg = Milligram
NMDA = N-Methyl-D-Aspartate
NRS = Numeric Rating Scale
PCA = Patient Controlled Analgesia
SA = Spinal Anesthesia
SD = Standard Deviation
SPSS = Statistical Package for Social Sciences
VAS = Visual Analog Scale
WMD = Weighted Mean Difference
WHO = World Health Organization

Abstract

Background: Cesarean section is common obstetric procedures worldwide. Following cesarean delivery, mothers experience moderate to severe pain since postoperative analgesia of spinal anesthesia is limited by duration of local anesthesia drug used. Analgesic effect of local anesthesia agents could be extended by adding adjuvants like neostigmine, opioid and low dose of intravenous ketamine.

Objective: This study was assess effect of low-dose intravenous ketamine on postoperative pain following cesarean section with spinal anesthesia in Zewditu Memorial Hospital, Ethiopia, 2021

Method: Sixty pregnant mothers planned for elective cesarean delivery under spinal anesthesia were involved in this prospective cohort study at zewditu memorial hospital. Participants were selected by systematic random sampling technique. Numerical rating scale pain score, time to request first analgesia and total analgesia consumptions were recorded in first 24 hours. Independent sample t- test, Mann–Whitney *U*-test and a chi-square was used for analysis based on distribution of data.

Result- Numerical rating scale pain score at 1^{st} and 2^{nd} hour after surgery was significantly different between the groups with $p \leq 0.05$. But pain score at 6^{th}, 12^{th}, 18^{th} and 24^{th} insignificant. Time to request first analgesia was significantly longer in exposed than Non-exposed group with $p < .0001$.The median(range) of tramadol consumption in 24 hour was 100(100_100) for exposed and 150(100_150) for non-exposed which was significant difference between both groups with (p- value < .0001). But, diclofenac consumption was not significantly different ($p = .576$).

Conclusion and Recommendation: Low dose intravenous ketamine (0.25mg/kg) before skin incision was extended postoperative first analgesia request by average of 45.5minutes and decrease total analgesia consumption in 24 hours. Based on this we recommend use of low dose ketamine as a part of postoperative pain treatment.

Key words: cesarean section, postoperative pain, Intravenous ketamine

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1. Introduction

1.1 Background

Giving birth is a natural phenomenon which wants preventive and supportive measures. Normal vaginal delivery is to mothers who are able to deliver, otherwise, cesarean delivery may performed in cases delivery is difficult or in cases risk for both mothers and fetus[1,2]. Cesarean delivery is widely done obstetric surgery when done with medical indication is a lifesaving operation and play important role in decreasing maternal mortality[3,4,5].

Even though WHO recommend rate of cesarean section between 10 % and 15%, caesarean delivery rate is progressively increased in both developed and developing country [4,6]. Reason for rising of cesarean delivery rate is concept of cesarean delivery as safe procedure, despite of health related risk and financial crisis[3]. Cesarean section can negatively affect mothers' physical, psychological, social and environmental life quality after delivery and post operation pain is the common adverse event after cesarean delivery[7].

postoperative pain intensity can affected by some factors such as preoperative pain, depression, preoperative anxiety, type of anesthesia, analgesics and time of surgery were some factors[8,9]. Pain following cesarean section has many complications such as respiratory insufficiency, cardiac complication, coagulation problems, urine retention and delaying gastric emptying[10,11,12]. Postoperative pain prevention and shortening in bed duration of the parturient and supporting to ambulate as fast as possible after the operation reduce the general complications[11].

There are different medication to reduce postoperative pain. Depend on patient's preference, health profession select the most suitable drugs for each patient. Most of health institutions use narcotics for controlling post cesarean section pain. However, narcotics have many adverse events such as respiratory depression, addiction, drug adaptation, nausea, and vomiting[11,13,14,6]. So, health profession generally chooses non-narcotics painkiller for decreasing post surgery pain.

Uncontrolled pain cause persistent nociceptive and neuropathic pain which patients feel and opioid-induced hyperalgesia partially mediated through N-methyl-D-aspartate (NMDA) receptors[15]. Many researches have explore the effect of sub-dose ketamine together with other

drugs in decreasing post surgery pain[11],[16]. Sub-anesthetic dose of ketamine can antagonize the NMDA receptor-mediated pain sencitazation[17,18].

Many researchers reported function of N-methyl-D-aspartate (NMDA) receptor in nociceptive pathway and pain processing, such as central plasticity, increasing pain severity and decrease pain threshold[19,20]. Ketamine is an N-methyl-D-aspartate (NMDA) receptor inhibitor that causes antipain by desensitization of stimulated N-methyl-D-aspartate receptor, so by blocking pain signal in central nerve system[21,22].

Low-dose ketamine also decline the activity of brain structures that respond to noxious stimuli[17]. It has effects on opioidergic receptors and stimulates monoaminergic descending inhibitory pathways at supraspinal sites causing in antinociception, all of which mediate analgesic effects[17,23]. Ketamine is a single iv anesthesia agent that has antipain effect. The antipain effect of this agent used at low doses (0.1 - 0.8mg/kg) by antagonizing NMDA receptors, that block central nerve system pain transfer, which important in preventing postoperative pain[11].

Low dose ketamine before skin incision safeguard to avoid the altered afferent input processing which increase postoperative pain and reduce postoperative pain and use as prophylaxis against anxiety response to operation[24,25].

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1.2 Statement of problems

Giving birth by Cesarean delivery is the most common operation over the world. Worldwide systemic review of cesarean delivery from eighteen different countries in 2015 showed that overall cesarean section rate has been 42.5%, which varied between 65.84% in the private sector and 33.99% in the public sector[26]. According to the 2016 Ethiopia Demographic and Health Survey, the rate of cesarean section (21.4%) in Addis Ababa which was much higher than the acceptable cesarean section rate (10–15 %) in WHO's guidelines[27].

Following this high rate cesarean section, mothers experience moderate to severe pain in the acute postoperative period. Study done in Brazil 2016 shows the occurrence of moderate to severe post cesarean delivery pain was 78.4%[8]. Another cross-sectional study in Brazil 2017 reported the prevalence of immediate postoperative pain post cesarean delivery corresponded to 92.7%. The strongest pain was 6.6 (sd=2.2) and the "weakest" pain 3.3 (sd=2.0) which exaggerated by movements[28].

According to study in university of Gondar Comprehensive Specialized Hospital, Gondar 2019 the incidence of moderate to severe post-operative pain after cesarean section was 85.5% within the first 24 postoperative hours[29]. Prevalence rates of chronic pain after cesarean delivery are between 6.8 to 18.3%. About 80% of mothers have pain at surgery site which can stay up to 12 months[30].

Following poor postoperative pain control parturient may lose sleep, functional activity impairment, increased risk of developing chronic pain and psychological injuries and affect mother to child bounding. Also may develop systemic complications such as cardiac arrhythmia, atelectasis, thrombosis, myocardial ischemia, ileus, and urinary retention. In addition to personal health crisis, it affect socioeconomic such as high economic cost and lost job. Therefore, great attention should be given to postoperative pain management[29].

Commonly opioids and NSAIDs are used to manage postoperative pain after caesarean section. But due to varies adverse events of these drugs, especially opioids, such as nausea, vomiting, and delaying gastric motility[31]. So those adverse effects have negative impact on pain management and have major contribution behind high rate inadequate postoperative pain control now a day. Therefore, analgesics with less adverse effect and better advantage. Nowadays, there are some types of adjuvants which alleviate pain with less complications or adverse effects but require

more studies to approve their efficacy[13]. ketamine blocking multiple pain pathways at lower drug dosages reduces the incidence and severity of adverse effects of the multiple drugs used[23].
The aim of this study was to assess effectiveness of low-dose intravenous ketamine on postoperative pain following cesarean section under spinal anesthesia.

1.3 Significance of the study

Managing postoperative pain associate with parturient satisfaction, increasing mother-newborn bond, early mobilization, shortening hospital stay and cost. Postoperative pain is ranked from mild to severe and commonly managed with single analgesic agent which cannot cover different pain pathway or pain fiber. Multimodal analgesic drugs should be used to block multiple pain pathways and decreasing adverse events of sedative drugs[32]. The best post cesarean section pain management is local analgesia such as epidural analgesia, Trans-abdominal plane block and Illio inguinal illio hypogastric nerve block[33,34].
Due to shortage of epidural kit and trained person, those alternative is not practiced at all in most health institutions including our study area. So in most institutions postoperative pain is inadequately treated by low potency opioids and non-steroidal anti-inflammatory drugs. In addition to inadequate to relief moderate to severe pain their adverse effects are a lot. Due to numerous side effects, it sounded that maternal pain treatment with these drugs had to be declined[35,36]. Persistent nociceptive and opioid-induced hyperalgesia which some part mediated by NMDA receptors may not easy to manage opioid or NSAID.
Recently many researchers have explored the use of N-methyl-D-aspartate (NMDA) receptor inhibitor. ketamine is strong NMDA receptor inhibitor for treat and reduction of post cesarean section pain[37]. Inhibition of NMDA receptor by ketamine shows decreasing acute pain to chronic pain and significantly reducing narcotic consumption. Also reducing narcotics induced hyperanalgesia without affect hemodynamic and respiratory status, makes ketamine attractive for analgesic[18].

We haven't got a single published paper on effect of low dose ketamine following spinal anesthesia for postoperative pain control in Ethiopia. So the result of this study have role in reduction of post cesarean section pain, which has been left undermanaged due to many reasons, especially in resource limited institutions.

2. Literature review

2.1 Post cesarean section pain rate

Management of post cesarean section pain is important parts of humanity and care for mother give new life. Inadequate pain management increase postoperative complication to both mothers and new born child. Despite of advanced multimodal analgesic method development, pain following cesarean section still challenging.

Prospective cohort study done in Brazil 2016 used numerical pain scale score showed the occurrence of moderate to severe post cesarean delivery pain was 78.4%[8]. Another cross-sectional study in Brazil 2017 on 1062 parturients by numerical Pain Rating Scale (NPRS) score reported 84.7% of them had moderate to worst pain with total of 92.7% (95% CI: 90.9 – 94.2) postoperative pain[28].

Study done in south Africa, 2016 used visual analogue scale pain score reported moderate to severe post cesarean section pain incidence was 87%[38]. Study done in Ethiopia University of Gondar 2019 on 290 parturient measured with numerical rating scale (NRS) reported post cesarean section pain ranked moderate to severe was 85.5% within the first 24 hours[29].

2.2 post cesarean section pain treatment

Study done by pain physician in 2008 worldwide reported opioids were widely prescribed medicine for controlling pain with many adverse events such sedation, nausea, vomiting, delaying gastric emptying, hyperalgesia, immunologic and hormonal change postoperative pain is undertreatemt[14].

Study done in United States of America, 2000 reported Nonsteroidal anti-inflammatory agents are commonly used for postoperative pain and inflammation. However NSAID drugs are less potent for major surgery than opioids and related with adverse effects such as gastric ulcer, gastric bleeding, renal impairment, change liver function and platelet impaired[39].

Another retrospective cohort study done in USA ,2013 on g 319,898 patients from 380 hospitals reported 95% of postoperative pain was controlled by opioid with 12.5% develop opioid related side effects including nausea, vomiting, delay bowel motility, over sedation, somnolence, respiratory complications and till life loss[40].

2.3 ketamine for post cesarean section pain

Ketamine is inhibitor of the N-methyl-D-aspartate (NMDA) receptor that antagonize central sensitization and has a pre-emptive analgesic effect to reduce post cesarean pain.

Systemic review done in Northern Europe 2015 reported that postoperative pain severity 2 hour after surgery were significantly lower in group took ketamine than control group. The first time to ask antipain was also significantly extended in exposed parturient than control parturients; the WMD was 49.36 min; But incidence like maternal nausea, vomiting and psychomimetic effects was similar between both groups[41]. Another Prospective cohort study in Singapore 2009 shows first 24 hour after cesarean delivery pain incidence was about 77.4%[42].

A review of total 20 RCT done in Shanghai, china 2020 which include 1737 parturient undergone cesarean section reported that pain score after surgery in the ketamine group was significantly lower than that of control group. Time to request first analgesia was significantly prolonged in the exposed than that of the control group (MD, 72.48 minutes. Also Iv ketamine shows reduction of morphine consumption than control group[43].

RCT done in Iran, 2010 showed sub-anesthetic dose of iv ketamine before skin incision had no significant advantage for postoperative pain and analgesic consumption after surgery. But, morphine dose during the first 2 hours postoperative was reduced in the ketamine group than to control group. Two parturients in the ketamine group develop hallucination, nausea or vomiting than control group[20]. Another study done in Iran 2011 reported that sub-anesthetic dose 0.15mg/kg iv ketamine does not show reduction of pain severity score after cesarean delivery[44]. RCT done in Iran 2014 showed there was not significant statistical difference on average VAS (F = 0.15, P = 0.70). Diclofenac suppository and mean time for the first opioids have not statistical difference also (respectively; P = 0.76, P = 0.87)[13]. Study done in Iran 2014 showed that the subcutaneous prescription of low dose ketamine (0.5 mg/kg) as antagonist of NMDA receptor pre and post-surgery can decrease the postoperative pain during the first 12 hours in comparison with experimental group. In addition, the subcutaneous consumption of ketamine perioperative the surgery can not only prolonged the analgesia request time but also decrease total analgesic consumption when compared with control group[45].

RCT conducted in Iran 2015 reported that the pain scores were higher for the control group compare to exposed group (p<0.001) and the difference time to request first antipain request was significant between the two groups[11]. According to study conducted in Iran,2019 there was a

significant difference for the first analgesia request time between the ketamine and control groups ($P < 0.001$)[46].

A comparative study done in turkey 2005 on effects of low-dose iv ketamine together with spinal bupivacaine for caesarean delivery shows that the first postoperative request for analgesia was higher in the ketamine ($P = 0.001$) group than control group. Pain rating scores were higher in control ($P = 0.034$) group than ketamine group at the 90th minute. At 150th minute VAS was greater in the control group than ketamine ($P = 0.02$) groups. In the ketamine group, VAS was decreased compare to control ($P = 0.044$) groups at 180 min. Also opioid consumption in first 24hour was significantly decreased in the ketamine group than control group ($P = 0.0001$)[24].

Study RCT done in Nigeria 2011 on analgesic effects of small dose intravenous ketamine together with spinal bupivacaine for caesarean delivery shows that the first postoperative request for analgesia was higher in the ketamine group (193.44 ± 26.53 min) than in control group (140 ± 22.34 min) ($P < 0.001$). Analgesia request time was more prolonged in ketamine group than in control group. Total opioid consumption in ketamine group was 84.0±9.76 mg while for control group was 106.5±7.16 mg which significantly different, $p=0.002$[47].

Another study conducted in Nigeria 2012 on analgesic effects of sub-anesthetic dose iv ketamine together with spinal bupivacaine for caesarean section shows that the first postoperative request for analgesia was higher in the ketamine (209 ± 14.7 min) compare to control group (164 ± 14.1 min) ($P < 0.001$). Pain rating scores decreased in ketamine group than in control group for 120 min postoperative ($P = 0.022$). Diclofenac consumption in first 24hour was higher in control group than ketamine group ($P < 0.001$)[23].

Another RCT done in Uganda 2017 reported the time to first analgesia request time was extended in the ketamine group 210 (90–270) than control group 180 (90–360) with $p = 0.002$. First day after surgery NRS pain scores was stronger in control group 5(3– 7) than ketamine group 7(3–9) with $p = 0.001$. Total diclofenac consumption was higher in placebo group(150mg) than ketamine group (used up to 75mg) with (p value $= 0.053$)[48].

Study Hypothesis

Ho_1: There is no difference in post operation numerical pain rating scale between expose group and control group.

HA_1: There is a difference in post operation numerical pain rating scale between exposed and non-exposed groups.

Ho_2: There is no difference in first analgesia request time between exposed and non-exposed groups.

HA_2: There is a difference in first analgesia request time between both groups.

Ho_3: There is no difference in sum of analgesic used in the first 24 hours between the study groups.

HA_3: There is a difference in sum of analgesic used in the first 24 hours between the study groups.

3. Objectives of the study

3.1 General objective

To assess effect of low-dose iv ketamine on postoperative pain following cesarean delivery under spinal anesthesia in Zewditu Memorial Hospital, Ethiopia, 2021.

3.2 Specific objective

To compare postoperative pain severity by numerical rating scale pain score between exposed and non-exposed groups

To compare first analgesia request time after surgery between the groups

To compare 24 hour analgesia used between both groups.

4. Method and material

4.1 Study area

The study was conducted at Empress Zewditu Memorial Hospital, one of the government hospital located in kirkos sub city wereda 08, Addis Ababa, Ethiopia. The hospital was built by non-governmental organization but changed to public in 1976E.C. currently, the hospital is governed under ministry of health. It gives services in different specialty: in general surgery, obstetrics, gynecology, neurology and plastic surgery. It has total 128 beds which about 46 beds for obstetrics, gynecologic and postnatal ward. Also the hospital has 7 major operation room which 2 of them for cesarean delivery. It has 3 post anesthesia care unit. In this hospital there are an average of 10 new born per day. Out of these one fourth are delivered by cesarean section.

4.2 Study design and period

Institutional based Prospective observational cohort study design was conducted from January 25_ April 25, 2021

4.3 Population

4.3.1 Source population

All pregnant mothers who were give birth by elective caesarian section under spinal anesthesia at Empress Zewditu memorial Hospital during study period.

4.3.2 Study population

All eligible pregnant mothers who underwent elective caesarian delivery under spinal anesthesia in the study period.

4.3.3 Study participants

Selected pregnant mothers who underwent elective cesarean section under spinal anesthesia at Empress Zewditu Memorial hospital during study period.

4.4 Inclusion and exclusion criteria

4.4.1 Inclusion criteria

- ✓ Pregnant women with single (not twins) term who are candidate for elective cesarean section under spinal anesthesia group in ASA class II,

4.4.2 Exclusion criteria

- ✓ Patients who have respiratory complications
- ✓ ketamine allergy
- ✓ changes in anesthesia
- ✓ high blood pressure
- ✓ high intracranial pressure
- ✓ history of seizure
- ✓ number of spinal anesthesia attempt above one
- ✓ patients take other analgesia pre or intraoperativly

4.5 Study variable

4.5.1 Dependent variable:

- Numerical rating pain scale
- First analgesia request time.
- Sum of analgesics used in first postoperative day

4.5.2. Independent variables

- Sociodemographic characteristics**:**
  - Patients' age
  - Educational status
- Preoperative clinical characteristics:
  - Weight
  - Height
  - BMI
  - Parity
  - Number of previous C/S
  - Base line vital sign
- Anesthesia related:
  - premedication
  - Dose of local anesthesia both volume and baricity
  - Site of lumbar puncture
  - Spinal needle type and gauge
  - Preload in ml
  - Intraoperative fluid given
  - Intraoperative vital sign
- Surgery related:
  - Duration of surgery
  - Intraoperative blood loss
  - Time of recovery arrived

4.6 Sample size and sampling technique

4.6.1 Sample size

Sample size was calculated from study done in Nigeria 2011 by notice first analgesia request time postoperatively due to it gives maximum sample size than other left objectives[47]. The study find was 4.22±2.6 hour for ketamine group and 2.33±2.2 hour for control group. By supposing equal sample size in both exposed and non-exposed group, sample size was calculated as follows.

$$n_1 = n_2 = \frac{(\sigma_1^2 + \sigma_2^2)(Z_{\alpha/2} + Z_{\beta})^2}{(\mu_1 - \mu_2)^2}$$

$$\text{Where } n = \frac{(2.6^2 + 2.2^{2)}(1.96+0.84)^2}{(4.22 - 2.33)^2}$$

$$= \frac{(11.6)(7.84)}{(1.81)^2}$$

$$= 91/3.28$$

$$n_1 = n_2 = 27.74 \sim 28$$

After adding 10% attrition rate the total sample is N = 62 patients

N = total sample size

n_1 = number of patient under spinal anesthesia exposed group

n_2 = number of under spinal anesthesia non-exposed group

Z= 95% confidence interval =1.96

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

σ_1 – Standard deviation for time to first analgesia request of exposed group

σ_2 - Standard deviation for time to first analgesia request non-exposed group

μ_1 - Mean for first analgesia request exposed group

μ_2 - Mean for first analgesia request non-exposed group

4.6.2. Sampling technique

From situational analysis of three consecutive months Empress Zewditu memorial hospital gave services for 114 elective cesarean section under spinal anesthesia. Sixty two patients was involved in the study using systematic random sampling technique. Thus, to obtain every k^{th} patient into the study, K=114/62 ≈ 2. Therefore, by considering a consecutive patient scheduled to undergo elective C/S under spinal anesthesia, every 2^{nd} patient was selected to be included into the study. The first patient was selected using lottery method from scheduled patients to indicate where to start our sampling. Then after, every 2th patient from the random start number was included into the study until the sample size were achieved.

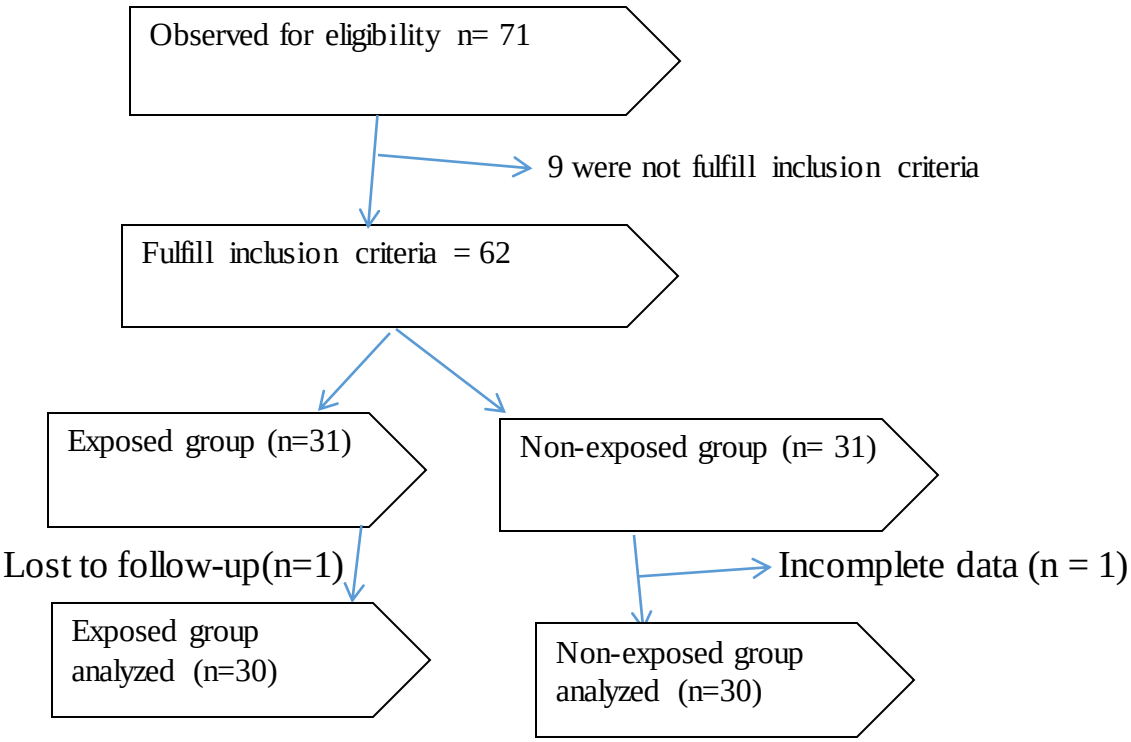

Figure 1: schematic shows patients enrollment in the research

4.7 Data Collection Tool and Procedure

Data collectors were trained before data collection by a principal investigator.

Three trained BSc anesthetists for data collection and one MSc anesthetist for supervision were assigned. Anesthesia service given by BSc and MSc anesthetists in hospital. Some anesthetists give 10mg intravenous ketamine after spinal anesthesia for prevention of shivering, anxiety and pain. To make uniform, anesthetists in hospital were informed to depend on patient's weight while they give ketamine (0.25mg/kg) following spinal anesthesia before data collection period. Data was collected using pre-tested questionnaires with consent form prepared in English and in Amharic (consent and numerical pain rating scale score). Patients scheduled for elective cesarean section and volunteer to participate in study were trained by data collector on how to self-report pain using the eleven point NRS score (0 to 10) on the morning of surgery. Sociodemographic data such as: age, weight, height, parity, educational status and base line vital sign were taken preoperatively. Preload fluid volume and premeditations were recorded. Site of lumbar puncture, volume and baricity of local anesthesia, gauge of spinal needle was documented. Only a single attempt for lumbar puncture at patient sitting position was included. After spinal anesthesia given by assigned anesthetist data collector document time of spinal anesthesia given, dose of ketamine (in mg) if given, skin incision started time, duration of surgery, intraoperative vital sign every 5minutes till surgery end. Also intraoperative fluid used and blood loss was documented. Time of patient arrived to recovery was recorded. patient vital sign, pain intensity at 1^{st}, 2^{nd}, 6^{th}, 12^{th}, 18^{th} and 24^{th} hours, time to first analgesia request and analgesia consumption were documented. Assigned supervisor check the completeness of data every day and further by investigator.

4.8 Data quality assurance

To have confident the quality of data, training and orientation was given on necessary issues for data collector. Pre-tested questionnaires on 10% of sample size in study area were prepared in English. The result of pretest not included final analysis. Completeness of data was checked by investigator.

4.9 Data processing and Analysis

Data completeness rechecked and coded, then entered and cleaned using Epi Info version 7 and transported to statistical package for social sciences (SPSS) software version 26 for analysis. The distributions of data were tested using the Shapiro-Wilk normality test and homogeneity of variance was checked by Levene's Test for equality of Variances. Numeric data showed in mean ± SD and median(IQR). The difference between the groups were analyzed by independent sample t- test for normally distributed numeric data and Mann–Whitney U-test for non-parametric numeric data. Frequency and percentage were used for categorical data and comparison by using chi-square. a p-value of less than 0.05 was considered as statistically significant. Data were presented by text, table and graph.

4.10 Operational Definition

Analgesia: any group of drugs used to relief pain.

ASA classification: American Society of Anesthesiologists classification of patient physical status based on presence or absence coexisting diseases and limitation activity to predict morbidity and mortality of the patients(**refer annex V**).

Baseline vital sign: vital sign taken before spinal anesthesia delivery.

Duration of surgery: Time from start of skin incision to end the operation.

Exposed group: participants who were take 0.25mg/kg iv ketamine after spinal anesthesia.

Non-exposed- participants who did not take 0.25mg/kg iv ketamine after spinal anesthesia.

Numeric Rating Scale: pain severity assessment tool that patients report their pain by rating from 0-10(11point scale) with assuming that 0 shows no pain and 10 shows the most unexplained pain[49].

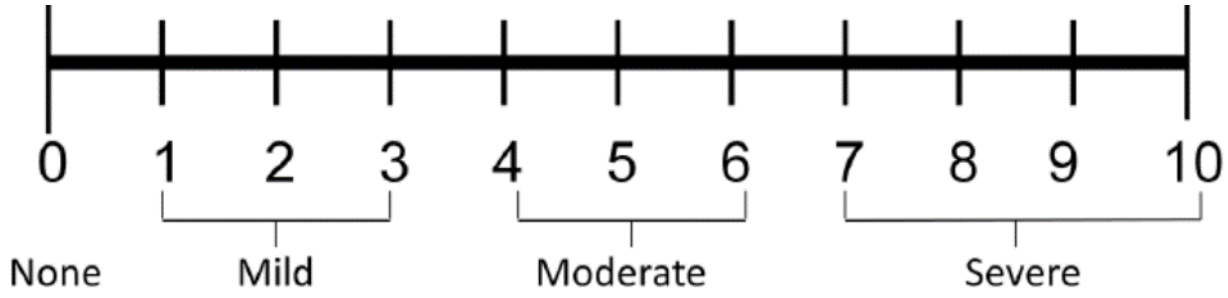

Figure 2. Taken from the National Initiative on Pain Control™ (NIPC™).

Premedication: medication given before induction of anesthesia for different purpose.

Spinal Anesthesia: Injection of local anesthetic into the cerebrospinal fluid in the spinal canal to block sensory and motor sensations before they reach the central nervous system. It is used mainly during surgery on the lower abdomen and legs.

Time to First Analgesia Request: A time from spinal anesthesia given to first time patient ask for analgesia in minutes.

Total Analgesia Consumption: Sum of antipain dose given in first 24hr post surgery in mg.

4.11 Ethical Consideration

Ethical clearance was taken from ethical Review Board of Addis Ababa University (AAU). Permission and letter of cooperation for the zewditu memorial Hospital obtained from department of anesthesia and submitted to hospital. Objective of the study was explained and permission obtained from the clinical service coordinator of the hospital. After discussed the importance of study both verbally as well as in consent form with participants. Voluntarily involved participants data was collected using code to identify the participant by avoiding any patient identifier to maintain confidentiality of the participants.

4.12 Result Dissemination Plan

The finding of the study will be submitted in a form of a thesis to AAU College of Health Science, Department of anesthesia. The result will be publicly defended following submission. Copies will be provided to relevant stakeholders. Efforts will be made to present the results in scientific conferences and to publish in reputable journals.

5. Result

5.1 Socio demographic and preoperative clinical characteristics

A total of 60 parturient (30 in each group) were analyzed with response of 97%. One patient data from each group was excluded due to incomplete data from non-exposed and lost follow up from exposed group. The mean ± SD) age of exposed and non-exposed patient's was 29.63±5.611 and 29.43±4.272respectively. No significant difference between both groups in patients' weight, height, BMI, parity and previous cesarean section. Most parturient were diploma holder in both non-exposed and ketamine groups (46.67% and 50%, respectively) followed by those can read and write. No significant difference between both groups in patients' base line vital sign.

Table1: Patients' socio demographic and preoperative characteristics

Variables	**Exposed group** n =30	**Non-exposed group** n =30	P value
Age in year	29.63±5.611	29.43±4.272	.877*
Weight(kg)	70.33±6.48	72.03 ± 6.78	.325*
Height(cm)	165±0.06	167±0.05	.301*
BMI	25.47±1.77	25.87±1.97	.414*
Parity	2(0_3)	2(0-4)	.905#
No. previous c/s	1(0_3)	1(0_3)	.562#
educational status: - read and write - diploma - degree	8(26.67%) 15(50%) 7(23.30%)	11(36.67%) 14(46.67%) 5(16.67%)	.766•
Base line HR	84.87±6.892	86.10±6.326	.473*
Base line MAP	79.40±4.288	78.5±4.876	.451*

NB: * = Independent t test, #= Mann-Whitney test, ● =chi-square, Data present mean±standard deviation, median(interquartile range), frequency(percentage) as needed. Kg_kilogram, cm_ centimeter, BMI_ body mass index, No_number, ASA_ American society of anesthesiologist, HR_heart rate, MAP_mean arterial pressure. Independent sample t-test, Mann-Whitney and chi- square test was used by considering p-value < .05 was statistically significant.

5.2 Anesthesia and surgery characteristic

All parturients in both groups premeditate with 10mg intravenous plasil. Preloaded fluid volume was similar for both exposed and non-exposed groups. No significant deference in lumbar puncture site, spinal needle gauge, intraoperative fluid given and blood loss between both exposed and non-exposed. The duration of operation was also not statistically different between both groups.

Table2: Anesthesia and surgery characteristic

Variables	**Exposed group** n = 30	**Non-exposed group** n = 30	P- value
Premedication: plasil 10mg iv	30(100%)	30(100%)	
Preload fluid median(IQR) in (ml)	600(400_800)	600(500_800)	.563[#]
Site of LP. b/n L3/4 L4/5	9(30%) 21(70%)	7(23.3%) 23(76.7%)	.559•
Spinal needle gauge 24	100%	100%	
Bupivacaine: isobaric (0.5%) Volume (12.5ml)	100% 100%	100% 100%	
Intraoperative fluid given median (IQR) in ml	2000(1800 _ 2400)	2000(2000_2500)	.284[#]
Intraoperative blood loss	325(300_500)	325(250_500)	.419[#]
Duration of operation(minute)	33.77±0.589	34.67±0.611	.293[*]

NB: * = Independent t test, #= Mann-Whitney test, ● =chi-square, result put in frequency(percentage), median(IQR), Mean ± SD, IQR_ Inter quartile range, SD_Standard deviation: independent sample t- test, Mann Whitney test and X^2 was used, p- value < 0.05 taken as significant.

5.3 Base line and Intraoperative mean atrial blood pressure (mmhg)

An independent sample t test was used to compare mean atrial pressure at different time interval between groups. Intraoperative minimum mean atrial blood pressure was recorded at 15th minutes in both exposed and non-exposed groups (74.87 and 74.71, respectively). At all-time interval there was no significance difference recorded MAP through operation between both groups with $p > 0.05$.

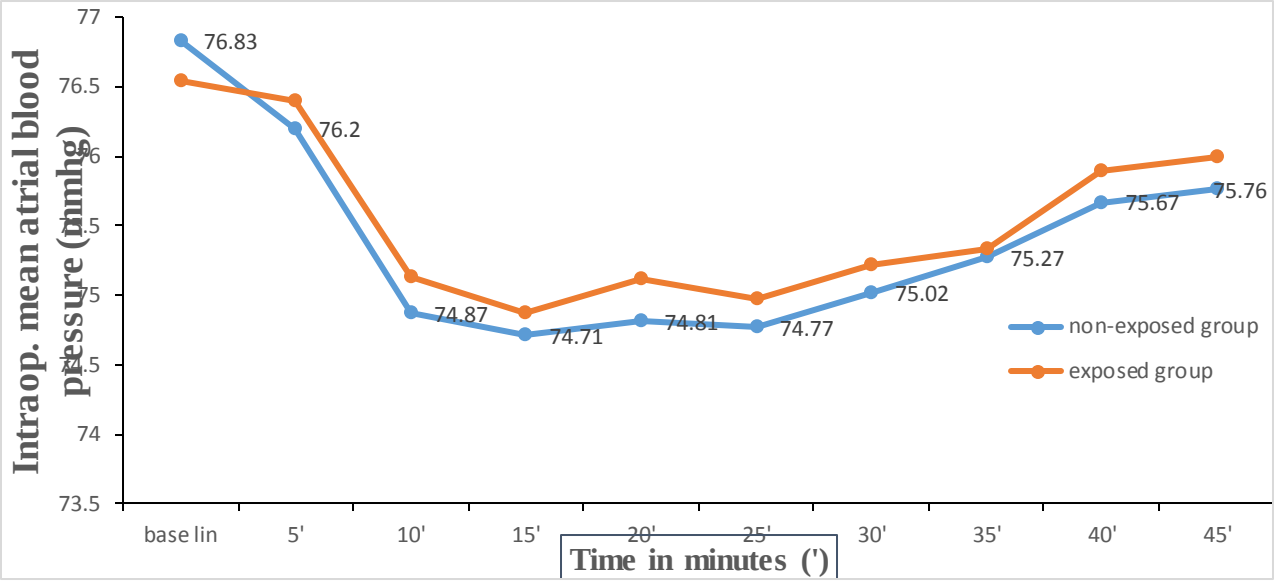

Figure 3: Line graph shows intraoperative mean atrial blood pressure between exposed and non-exposed groups

5.3 Comparison of pain intensity between exposed and non-exposed groups.

The median(range) of postoperative numerical rating scale pain score was significantly higher in non-exposed group compered to exposed group at 1 and 2 hour after operation. But no significant at 6^{th}, 12^{th}, 18^{th} and 24^{th} hour post surgery. The highest numerical rating scale pain score was recorded at 12 hour after operation in both groups. Mann-Whitney U test was used to compare pain severity between exposed and non-exposed, p-value < 0.05 considered as statistically different.

Table3: Median(range) of postoperative pain Severity in 24hours

variables	**Exposed group** n=30	**Non-exposed group** n=30	p-value
Postop. NRS at 1^{st} hr. median(IQR)	0	0(0_1)	.040
Postop. NRS at 2^{nd} hr. median(IQR)	0	2(0_3)	.000
Postop. NRS at 6^{th} hr. median(IQR)	3(1_5)	3(1_6)	.326
Postop. NRS at 12^{th} hr. median(IQR)	4(1_6)	4(2_6)	.642
Postop. NRS at 18^{th} hr. median(IQR)	2(1_4)	2(1_4)	.395
Postop. NRS at 24th hr. median(IQR)	2(1_3)	2(1_4)	.569

NB: IQR- Interquartile range, hr. _ hour, NRS- Numerical pain rating scale

5.4 Comparison of time to first request analgesia and total analgesia consumption between exposed and non-exposed.

The median(range) time to request first analgesia was significantly higher in exposed group192.5(140_210) than non-exposed 146(130_160) with p-value < .0001.

Sum of tramadol dose used in first postoperative day was lower in exposed group 100(100_100) mg compare to non-exposed 150(100_150) in mg with p < .0001. But, diclofenac consumption difference was not significant with p =0.576.

Mann-Whitney test was used assuming p- value < .05 significantly different.

Table4: Time to first analgesia request and total analgesic consumption in 24 hour

Variable	**Exposed group** n = 30	**Non-exposed group** n = 30	p-value
First time request for analgesia in minute **median(IQR**)	192.5(140_210)	146(130_160)	< .0001
Postoperative analgesic consumption median(IQR)			
Tramadol iv in mg	100(100_100)	150(100_150)	< .0001
Diclofenac im in mg	75(75_150)	75(75_150)	.576

NB: im_ intramuscular, iv_ intravenous, mg- milligram, IQR- interquartile range: Mann-Whitney test used

6. Discussion

Postoperative pain is a big challenge for mothers giving birth under cesarean section that wants close approach to avoid postoperative pain and its complications. Balanced(multimodal) analgesia is best option to treat postoperative pain by combination of opioid and non-opioid painkillers that act on different site. These also protective for patients to reduce opioid complications and opioid related hyper-analgesia[39,34].

Our study result showed that low dose (0.25mg/kg) iv ketamine immediate after spinal anesthesia reduces post cesarean section pain at 1 and 2 hour after surgery, prolong time to request first analgesia and total tramadol consumption in 24 hours compered to non-exposed group without side effects difference. In line with our finding, another studies reported low dose ketamine decrease postoperative pain severity, extend time to request first analgesia and reduction of total analgesics consumption[11,23,24,41,47,48].

Our study finding showed median(range) postoperative pain severity scores by using NRS was statistically significant at 1st and 2nd hour postoperative that lower in exposed group than non-exposed with p-value = .040 and < .0001 respectively. This result match with study done in Turkey, 2005 showed mean±SD of postoperative pain severity used VAS pain score was significant at 60 minutes that 2.4±0.8 in control group and 0 in ketamine group and at 120minutes that 3.1±1.0 for control group and 1.4±0.8 in ketamine group[24].

Research conducted in Nigeria, 2012 also in line with our result that reported measured postoperative pain severity used visual analogue scale pain scores were significantly lower in in ketamine group than control group at 60minutes and 120minutes after operation[23]. Systemic review of twelve studies done in northern Europe, 2015 reported visual analogue scale pain scores at 2 hour after surgery were significantly lower in ketamine group than control group with test for overall effect: Z = 2.35 (P = 0.02)[41].

In contrary to our result study done in Iran, 2011 reported that postoperative visual analogue scale pain score was not significantly difference between ketamine and control groups in first 24 hours[44]. This difference may due to ketamine doses difference we used 0.25kg/mg while they used 0.15mg/kg, study design and sample size difference (60 vs 120).

Another Study done in Chicago, USA (2011)also not in line with our study that reported median (range) of post-surgery pain severity was not significant between both groups which 9 (8–10)in ketamine group and 9 (8–10) in control group with $p > 0.55$[22]. Arguments may secondary to dose difference in our study 0.25kg/mg ketamine was used while they used 10mg for all patients and they used fentanyl additive to spinal bupivacaine while in our study bupivacaine alone.

Another our study finding showed the median(range) time in (minutes) to first analgesia request was significantly prolonged in exposed group 192.5/3.21hr,[95% CI: 2.33_2.35] than non-exposed group 146/2.43hr [95% Cl: 2.2_2.7] with $p<.0001$. In line with our result, study done in Uganda, 2017 showed the median (range) time (in minutes) to first analgesia request was Significantly longer in the ketamine group [210 (90–270)] than control group [180 (90–360)][48]. Similarly RCT done in Nigeria, 2012 math with our study result that showed first analgesia request time was significantly higher in ketamine group(209±14.7min) than control group(164±14.1)[23].

Our study result also in line with study in Nigeria, 2011 reported The time to first analgesic request was higher in ketamine (4.22±2.6) hour group than placebo group was [47]. Also study done in Turkey, 2005 match with our finding that showed time to first request for analgesia was significantly longer in the ketamine (197 min) compared to the control group (144 min)[24]. Another study in Iran, 2015 reported that there were significant differences between the ketamine and control groups in the time to first request for analgesia 1.36±0.48 and 2.76±1.28 in hour respectively[11].

In contrary to our result, study done in Iran, 2014 showed time to analgesic request was 5.8 (3.6)hr in ketamine and 6 (5.5)hr in the control group which was not significant difference between the groups[13]. The difference may secondary to difference between doses of ketamine, in our study we used 0.25mm/kg while they used 0.2mg/kg and different study design. Another study conducted in Chicago, 2011also not in line with our study that showed time to the first analgesia request was 684 (337, 1031)minutes in ketamine group and 760 (346, 1174)minutes in control group that was not significant difference between groups[22]. The difference may due to ketamine doses difference, time of injection ketamine injection, in our study bupivacaine was used alone for spinal anesthesia while they used additive 15µg fentanyl, also sample size difference (60 patients vs. 188patients).

In present study tramadol consumption in 24 hour was significantly higher in non-exposed group 150(100_150) compare to exposed group 100(100_100) in mg. However, diclofenac consumption difference was not significant [75(75_150), for both groups]. This result match with study done in Nigeria (2011) that reported the total tramadol consumption in first 24hrs (mg) 84.0±9.76 in ketamine group and 106.5±7.16 3.68 control group that was significant and total diclofenac consumption was equal in both groups (150mg) that was not significant[47].

Another study conducted in Iran, 2002 also match with our study result, morphine consumption in 24hours was lower in the ketamine group (6.25±3.42 mg) than in the control group (17.73±4.08) in mg. If opioid converter factor morphine to tramadol used 1:10[50]. In Contrast to our study finding, study conducted in Uganda, 2017 showed diclofenac consumption was significantly lower in ketamine 75 (75–150) than control group 150 (75–150) in mg, but, total tramadol consumption was not significant[48]. This difference may due to pain control protocol difference, study design and sample size.

Study conducted in Korea university of Soonchunhyang, 2013 also not in line with our result that report total analgesia consumption was not difference between ketamine and control group[51]. This may due to pain management protocol difference in their study area fentanyl and ketorolac while in our study hospital tramadol then diclofenac was pain management protocol.

7. Strength and Limitation

7.1 Limitation of study

Time to surgery end to patients arrive recovery was not recorded.

Lack of similar study before

Studies used for comparison were randomized clinical trial are some of our study limitations.

7.2 Strength of study

Study participants were homogenous (elective pregnant mothers) one factor cause difference between groups. Groups were comparable in terms of socio demographic distribution and perioperative factors, the difference observed might be secondary to the exposure factor. Study was not done on ketamine for postoperative pain, this make study as base for future study in our county further.

8. Conclusion and Recommendation

8.1 Conclusion

We conclude that low dose intravenous ketamine (0.25mg/kg) following spinal anesthesia before skin incision decrease 1and 2hr pain severity after operation with extended postoperative time to request first analgesia by average of 45.5minutes and reduce total analgesia consumption in first 24hr.

8.2 Recommendation

Based on present finding we recommend:

For anesthetists we recommend the use of low dose ketamine immediate after spinal anesthesia before skin incision as a part of post cesarean section pain management.

For researcher we recommend additional randomized control trail study.

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Annexes

Annex I: Information sheet

This questionnaire is designed to assess effectiveness of low dose ketamine for postoperative pain following cesarean section under spinal anesthesia in Zewditu Memorial Hospitals, Addis Ababa, Ethiopia, 2021. I am going to conduct on effect of low dose ketamine for postoperative pain following spinal anesthesia patients undergoing elective cesarean section. There is no risk to take part in the study, all information is confidential. Their names will not keep in the form. Their participation in the study will be voluntary: They are not obliged to participate and may discontinue at any time. Moreover, this research thesis is approved by Ethical review board of AAU and college of health science, department of Anesthesia.

Annex II. Consent Form

Hello! Good morning/afternoon? My name is _____ I am here today to collect data on effectiveness of low dose ketamine for postoperative pain following spinal anesthesia in Zewditu Memorial Hospitals, Addis Ababa, Ethiopia, 2020/2021. The objective of this questionnaire is to assess the effect of low dose ketamine for postoperative pain following spinal anesthesia in Zewditu Memorial Hospitals, Addis Ababa, Ethiopia, 2021.

Your correct and genuine response or answer to the questions can make the study achieve its goal. Therefore, you are kindly requested to respond very voluntary with patience. The questionnaire may asked as needed. We assure you that this study is surely confidential, thus writing your name is not needed. Are you willing to participate in answering the questionnaire? Yes!

Go to the next page.

ጤና ይስጥልን እኔ_____እባላለሁ፡፡ከቀዶ ጥገና ወሊድ በኋላ ለሚመጣው ህመም ማስታገሻ ዘዴዎች ላይ የሚሰራ ጥናት መረጃ ሰብሳቢ ነኝ:: ጥናቱ ለእርሶ ምንም አይነት የገንዘብ ጥቅም አያስገኝም ነገርግን የጥናቱ ውጤት በህክምና ዘርፍ ላይ ያሉትን ችግሮች ለመቅረፍ እና የታካሚዎችን ደህንነት የሚያረጋግጡ ህጎች እንዲስተካከሉ እና ሥራ ላይ እንዲውሉ የበኩሎን አስተዋፅዖ ያበረክታሉ፡፡ ስምዎ በዚህ ጥናት ላይ አይፃፍም፡፡ ስለዚህም የእርሶ ምላሽ ሚስጥራዊነቱ የተጠበቀ ነው::በዚህ መጠይቅ ላይ ለመሳተፍ መስማማትም ሆነ አለመስማማት ይችላሉ፡፡ ባለመስማማቶ ምንም የሚጎዱት ነገር የለም፡፡

ምንም አይነት ጥያቄ ካለዎት ቀጥሎ በተፃፈው አድራሻ ተመራማሪውን ማግኘት ይችላሉ፡፡

1. ጀማል ቱኒ (ዋና ተመራማሪ): ስልክ _____

2. ሂርቦ ሳሙኤል (አዲስ አበባ ዩኒቨርሲቲ መምህር እና የጥናቱ አማካሪ)

3. ሰናይት አወቀ (አዲስ አበባ ዩኒቨርሲቲ መምህር እና የጥናቱ አማካሪ)

የመረጃ ሰብሳቢ ስምና ፊርማ

ስም _____ፊርማ _____ ቀን_____

መለኪያዉ በ 24 ሰአት ዉስጥ 6ጊዜ የሚለካ ሲሆን ታካሚዎች የሚሰማቸዉ የህመም መጠን እንዲያሳዩን እንጠይቃለን

ታካሚዎች የሚከተሉትን ጥያቄዎች ይጠየቃሉ፤-

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

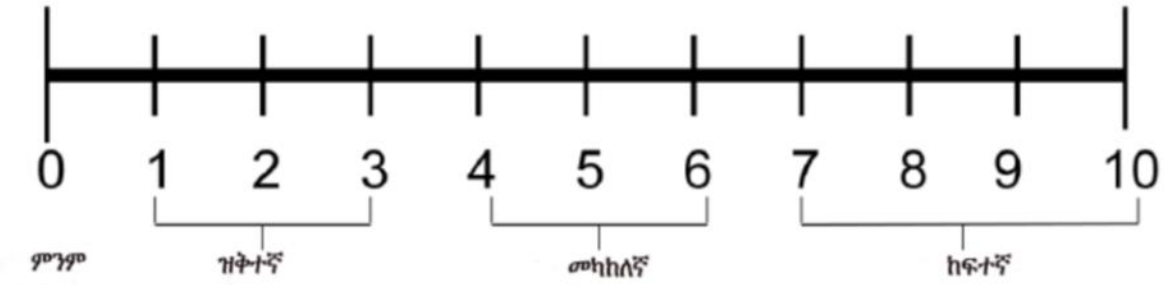
ለ. ከላይ የተገለጸዉ በቂ ካልሆነ ተጨማሪ ማብራሪያ ይሰጦታል ፡

1 No pain _ ህመም የለም (0)

2 Mild pain _ መካከለኛ ህመም ይሰመኛል (1-3)

3 Moderate pain _ ከፍተኛ ህመም (4-6)

4 Severe pain _ በጣም ከፍተኛ ህመም (7-10)



Annex III. Questionnaires

Section I: Socio-demogragrafic characteristics				
Sr no	Questions	Response		code
	card no			
201	Age	_____Yr		
202	Weight	_____ kg		
203	height	_____cm		
204	BMI	_____ kg/m2		
205	parity	Primi, multigravida(_____)		
206	ASA	II		
207	educational status	1 can't read & write 2 read and write 3 diploma 4 degree and above		
208	No. of previous C/S	No, 1, 2, 3, 4		
Section II: preoperative period				

Sr no	Questions	Response
301	Base line HR	_____bpm
302	Base line BP with MAP	_____mmhg and _____
303	Base line SPo2	_____%
304	Any premedication?	Yes no
305	If yes drug name and dose?	1 plasil.....mg 2 dexamethasone.....mg 3 cimetidine.....mg 4 others (specify).....mg

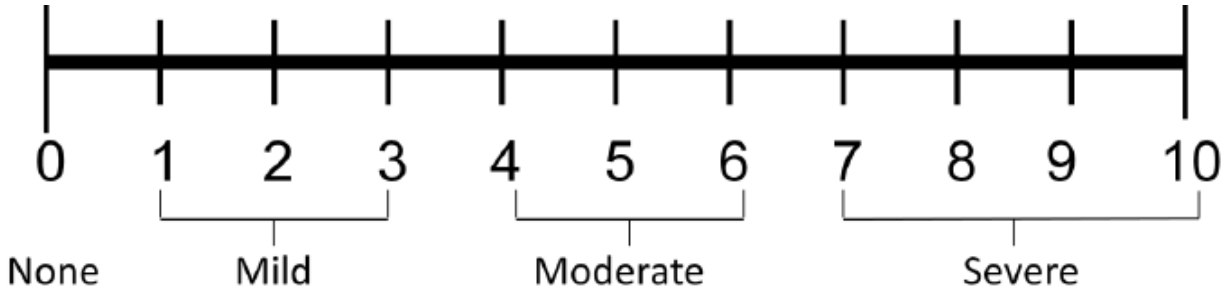
Section III: Questions related to anesthesia and surgery			
Sr.no	Questions	Response	
401	Preload fluid	_____ml	
402	Spinal needle gauge	23,24,25 or ------	
403	Lumbar puncture site	b/n L2/3, L3/4, L4/5	
404	SA given at what time?	_____ local time	
405	Concentration of bupivacaine used for SA?	A 0.5% plain bupivacaine B 0.5% heavy bupivacaine	
406	Volume used for block?	_____ml	
407	Time taken to block success	_____ minutes	

408	Pre incision ketamine	Yes/ _____mg No	
409	Fluid given intraop.	Type NS, RL, Other _____ Volume _____ ml/L	
410	Intraoperative blood loss	_____ml	
411	Duration of surgery	_____minutes	

Section IV: hemodynamic parameters intraoperative			
Sr no	Parameter	Time (in minute)	Value
501	Pulse and BP		HR NIBP MAP
		5′	____, _____mmhg ____
		10′	____, _____ mmhg ____
		15′	____, ___ __mmhg ____
		20′	____, _____mmhg ____
		25′	____, _____mmhg ____
		30′	____, ____ __mmhg ____
		35′	____, _____mmhg ____
		40′	____, _____mmhg ____
		45′	____, _____mmhg ____
		50′	____, _____mmhg ____
		55′	___, ____ ___mmhg ____

601. Parturient arrived recovery room at _____local time

Numerical pain rating score.



Section v: question on postoperative pain severity at rest.			
Sr no	Questions	Responses (/)	Score
701	Numerical pain rating scale at 1st hour	No, Mild, Moderate Severe	
702	Numerical pain rating scale at 2st hour	No , Mild, Moderate Severe	
703	Numerical pain rating scale at 6st hour	No, Mild, Moderate Severe	
704	Numerical pain rating scale at 12st hour	No, Mild Moderate Severe	
705	Numerical pain rating scale at 18st hour	No, Mild Moderate Severe	
706	Numerical pain rating scale at 24st hour	No, Mild Moderate Severe	

Section VI: time to request 1st analgesia			
Sr no	Question	Response	
801	Time to request 1st analgesia (from time of block to first request)	_____mins/hr	

Section VII: Total analgesia consumption for 24hr			
Sr no.	Question	Response in (mg)	
901	Morphine		
902	Pethidine		
903	Fentanyl		
904	Tramadol		
905	Diclofenac		
906	Others (specify) ……..		

Section IX: Postoperative vital sign

No	time	Response hr, sbp/dbp, map respectively
101	At 1hr postop.	___bpm, _____mmhg, _____
102	At 2hr postop.	___bpm, _____mmhg, _____
103	At 6hr postop.	___bpm, _____mmhg, _____
104	At 12hr postop.	___bpm, _____mmhg, _____
105	At 18hr postop.	___bpm, _____mmhg, _____
106	At 24hr postop.	___bpm, _____mmhg, _____

Annex IV: Data completeness check sheet

No.	Variables	yes	no
1	Are patient selection right?		
2	Are patients sociodemographic completed?		
3	Are intra operative data completed?		
4	Postoperative variable full filed?		
5	Postoperative medication documented?		

Annex V: ASA Physical Status Classification System

ASA PS classification	Definition	Adult examples	Obstetrics examples
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use	
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease	Normal pregnancy*, well controlled gestational HTN, controlled preeclampsia without severe features, diet-controlled gestational DM.
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents.	Preeclampsia with severe features, gestational DM with complications or high insulin requirements, a thrombophilic disease requiring anticoagulation.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis	Preeclampsia with severe features complicated by HELLP or other adverse event, peripartum cardiomyopathy with EF<40, uncorrected/ decompensated heart disease.
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction	Uterine rupture.
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes		

NB: we omit pediatrics ASA physical classification in above table so refer from ASA PS classification.

Adopted from ASA House of Delegates on October 15, 2014, and last amended on December 13, 2020