College of Medicine and Health Science

Department of Anesthesiology

The Effectiveness of Low-Dose Ketamine and Intravenous Lidocaine versus Fentanyl for Postoperative Pain for Patients Undergoing Elective Gynecologic Surgery under General Anesthesia at Dilla University General and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10, 2023, to June 10, 2023: A Multi-Centered Randomized Controlled Trial

The issuance of ethical approval was received with a protocol unique number "duirb/037/23-05" from the College of Medicine and Health Sciences at Dilla University following the submission of the study plan to the institutional review board

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II. Acronyms and Abbreviations

ACA	Advanced Clinical Anesthesia
DBP	Diastolic Blood Pressure
GA	General Anesthesia
ICU	Intensive care Unit
MAP	Mean Arterial Pressure
MSC	Masters in Science
NMDA	N-methyl D-aspartate
NRS	Numerical Rating Scale
NSAID	Non-steroidal Ant-inflammatory Drug
OBA	Opoid Based Anesthesia
OFA	Opoid Free Anesthesia
PACU	Post-anesthesia Care Unit
PCM	Paracetamol
PI	Principal Investigator
POI	Post-Operative Ileus
PONV	Post-Operative Nausea and Vomiting
SBP	Systolic Blood Pressure
SNNPR	Southern Nations Nationalities and Peoples Region.

III. Executive Summary

Background: Long-term use of opioids has been linked to various side effects and decreased patient satisfaction after anesthesia. A combination of drugs with opoid was used for intraoperative analgesia. Multiple drugs, by avoiding opioids, was a new opinion suggested. Opioid-free anesthesia with a combination of drugs is a new idea to avoid opoid from postoperative analgesia.

Objective: To determine the effectiveness of low-dose ketamine and intravenous lidocaine versus fentanyl for postoperative pain in patients undergoing elective gynecologic surgery under general anesthesia at Dilla University Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10 to October 10, 2023.

Methodology: A multicenter, randomized, controlled, single-blinded superiority trial will be conducted with 70 adult patients undergoing elective gynecologic surgery under general anesthesia. Randomization will be done by a computer-generated random allocation sequence in equal ratios to the treatment group (T = 35) and the control group (C = 35). The primary dependent variable is the pain severity measured by a visual analog scale postoperatively at discharge from the post-anesthesia care unit, 6th hour, 12th hour, and 24th hour, and the secondary outcomes are postoperative nausea and vomiting, postoperative analgesia request, and intraoperative cardiac adverse events. Student's t-test, analysis of variance, and chi-square test will be used for data analysis. A p-value of less than 0.05 was determined as statistically significant.

Work plan and budgeting: - study will be conducted from April 10, 2023, to October 10, 2023, with a cost of 41625 ETB.

1. Introduction

1.1. Background

Surgical procedures that are performed based on the underlying cause and the specific needs of the patient result in nociception, which is mediated by pathways through the nervous system with the interplay of various factors involved in the experience of pain. Two-thirds of patients who underwent surgery reported moderate to severe postoperative pain. To reduce the effects and promote a speedy recovery, surgical pain management techniques were urged to cover both non-pharmacological and medication-based therapies(1-4).

According to evidence, fewer than half of people who undergo surgery report satisfactory pain alleviation. Inadequate pain control and the use of unmodified techniques harm the quality of life, function, and functional recovery of patients who underwent surgery. The perioperative anesthesia handling and thorough consideration of medications administered to a surgical patient have been applied(3).

Opioids are commonly used medications to treat perioperative pain for a long period. They have been used as anti-nociceptive, decreasing alertness, and reducing the amount of centrally acting anesthetics(5). They had also been administered to decrease blood pressure during laryngoscopy and intubation and suppress airway reflexes during airway manipulation. However, opoid usage has been linked to a variety of adverse effects such as postoperative ileus, constipation, postoperative nausea and vomiting (PONV), and opposite effects including opioid-induced pain modulation and tolerance(6, 7)

A shift of pain management strategies with the implementation of less invasive surgical techniques and the advancement of anesthesia management has been implemented. Drugs that aim at different nociceptive receptors have been discovered and applied in perioperative patient care. Multimodal analgesia, which combines both opioids and opioid-free analgesics to avoid the negative consequences of using opioids alone, has been employed (1, 8). However, the issue of pain enhancement and opioid-related adverse events has not been fully resolved and has been reported with the technique of multimodal anesthesia (9, 10).

Opioid-free anesthesia (OFA) involving a combination of drugs and techniques was suggested to avoid opioids from intraoperative analgesia. It was intended to avoid opoid from the postoperative analgesia regimen but was later taken as a viable and optional method for perioperative anesthesia management(11, 12). Individual medications such as N-methyl-D-aspartate (NMDA) antagonists, sodium channel blockers, anti-inflammatory drugs, and alpha-2 agonists are being administered for analgesia. They aimed to reduce the reduction of MAC of volatile anesthetics, avoiding negative effects associated with opiates, and providing greater patient satisfaction after surgery when used in combination (13-18).

Intravenous lidocaine in doses less than 2mg/kg is reported to relieve pain by blocking sodium channels in both the peripheral and central nervous systems. It was also thought to reduce central and deafferentation pain and aid in wound healing. At lower doses up to 1 mg/kg, ketamine can provide significant pain relief without negative effects by eliminating opioid tolerance and having anti-hyperalgesic effects. A combination of intravenous (IV) lidocaine and low-dose ketamine can be used for intraoperative analgesia without adverse effects, even though it has not been routinely used for intraoperative anesthesia.

1.1. Problem statement

The increased utilization of opioids has raised worries and disapproval about the customary practice of opioid administration for anesthesia. A study by Chan et al(19) in Canada reported that about 73% of patients undergoing major surgery and 66.7% of patients undergoing intermediate procedures were using perioperative opoid. It is reported that approximately 11% of patients who undergo surgery with opioid anesthesia experience moderate to severe adverse effects related to opioids(20). Patients given perioperative opioids were associated with risks including a doubled likelihood of inpatient mortality, a 30% rate of readmission within a month, 55% longer hospital stays, and tripled hospitalization costs, which highlight the urgent need for effective solutions to the problem (20-23).

Both OFA and OBA acknowledge the pain-relieving abilities of opioids but also note that opoid can lead to increased pain sensation after surgery and an increased need for analgesics(24, 25). According to the nationwide survey in the US(26), the occurrence of pain was 84% postoperatively in general surgical patients, and 74% of patients who underwent major surgery reported debilitating pain at immediate postoperatively hours. A study in Europe by Buvanendran et al(27) reported that greater than 50% of gynecologic surgical patients experience substantial to extreme postoperative pain up to discharge from the hospital, which was mainly associated with the intraoperative use of opioids.

A study by R. Park et al(28) in Europe reported the occurrence of severe pain after gynecologic surgery was 32% within 24 hours postoperatively, which was mainly associated with poor pain management at immediate discharge. A study by Anberbir et al(29) at Addis Ababa reported that about 73% of gynecologic surgical patients experience moderate to severe pain more than once within 24 hours postoperatively. Preoperative anxiety, urban dwellings, and being uneducated were the reported reasons for pain severity.

Though the literature on OFA technique in procedures such as laparoscopic cholecystectomy, gynecologic, and bariatric surgery has shown its advantages(4, 25, 30), certain scholars have reported inconclusive and contesting results (31-33). The postoperative opioid-free anesthesia (POFA) trial, which was the most comprehensive and current multicenter trial, was stopped due to safety concerns after a few patients developed severe bradycardia(24).

The majority of the research is constrained to certain surgical procedures and is carried out in settings with modern facilities; however, a paucity of literature on the subject. Additionally, most of the studies done on OFA are carried out in Europe and Asia, and there are the fewest studies in Africa (19(4)).

Despite the reported surgeries under OFA techniques were being reported with better profiles, the effectiveness of the technique has not been well established. Contrasting research results and lack of relevant literature in resource-constrained environments made the implementation of the OFA idea challenging and indeterminate. Nevertheless, more research is required to address the issue in the resource desiccated settings like our country. The purpose of this trial is to compare the effectiveness of low-dose ketamine and intravenous lidocaine for postoperative pain compared with fentanyl for patients undergoing gynecologic surgery under general anesthesia.

1.2. Significance of the study

Even though the OFA concept remained doubtful of its validity and feasibility, reducing opioid-related harm in surgical patients improves the patient's postoperative recovery. The calamities associated with opioid-based anesthesia are obvious and need to be solved. Some works of literature on the OFA principle have reported improved postoperative recovery, and others reported comparable results and drug-related side effects. Additional studies will narrow these gaps within the findings.

Gynecologic surgery carrying a risk of postoperative nausea and vomiting, as well as moderate to severe discomfort, can benefit from avoiding the use of opioid-based anesthesia techniques. This can decrease unwanted opoid effects, higher costs, longer hospital stays, higher postoperative pain scores, and can increase postoperative patient satisfaction.

Two recent RCTs conducted in Cameroon and Egypt have shown promising results using the OFA protocol without dexmedetomidine, which could lead to the adoption of the OFA technique in resource-limited settings. In works of literature on OFA in resourceful settings, drugs like ketamine, lidocaine, NSAIDs, and others, can open the eyes of investigators covered in dexmedetomidine's fancy, especially for resource-depleted settings.

This single-blinded prospective randomized controlled trial aimed to determine the effectiveness of OFA with low-dose ketamine and intravenous lidocaine vs. general anesthesia with fentanyl for postoperative pain in patients undergoing elective gynecologic surgery under general anesthesia. Due to the lack of comparable studies on the subject, the outcome of the study can lead to a quick pace for patient management and is acceptable in the scientific environment preferred by scientific literature.

2. Literature review

A growing body of knowledge has described the potential adverse effects of opioid analgesics, and the latest calamity, the "opioid crisis," needs keen emphasis. To overcome the associated calamity, works of literature urged the practice of giving up on opioids and the use of other modalities for pain pharmacotherapy(8, 20). OFA is one of the modalities, and the most recent and toothsome works of literature are in developed countries, so the idea quickly improved, but the lack of the saint drug held back the idea in the developing world(5, 34).

2.1. Perspectives on OFA and opoid-based anesthesia

Helene Beloeil, in the narrative review, described OFA as a rationale that aimed to avoid the intraoperative use of opioid analgesics. He urged that the intraoperative use of opioids is associated with an increase in postoperative pain scores by worsening the sensitization of injured tissue during surgery. OFA using a combination of modalities and drugs, including NMDA receptor inhibitors, anti-inflammatory drugs, Na+ channel blockers, and 2-agonists, was documented at decreasing doses of individual drugs by avoiding the side effects associated with specific drugs (35).

The American Society for Enhanced Recovery and Perioperative Quality's joint consensus statement in 2020 proposed the suitability of OFA techniques and praised the findings of existing works in the literature, but questioned the availability of significant data on the benefits and harms of the strategy. They advocated the feasibility of the OFA technique in terms of reduced recovery room time, decreased PONV, reduced analgesic requirements, and a decreased postoperative pain scale(36). An article from the American Anesthesiology described OFA as a “fashion” that they termed a campaign aimed at eradicating opoid from use as a pain medication (37).

2.2. Opioid-related adverse events between OFA and OBA

In the systematic review and meta-analysis of five RCTs on the intraoperative use of OFA vs. conventional GA on adult patients undergoing non-cardiac surgery, Frauenknecht et al. reported a 20% reduction in PONV with a CI of 0.77 (0.61–0.9) and a P value of 0.03 in the OFA group. They documented the association of delayed recuperation, a higher hospital stay, and increased medical costs with patients given opioid anesthesia(25).

An RCT by Feng et al(38) on 120 adult patients undergoing thoracoscopic lung resection compared the incidence of PONV with patients undergoing anesthesia under OFA with ketamine and dexmedetomidine and OBA with sufentanil. They reported the occurrence of PONV in the OBA group, which was twice as much as the PONV in the OFA group (15% vs. 31.7%), OR = 0.38, at 95% CI (0.16-0.91), and a p-value of 0.031 at 24 hours postoperatively.

Massoth et al(32) conducted an RCT comparing the occurrence of PONV in 152 women undergoing gynecological surgery by OFA using dexmedetomidine and ketamine with conventional GA with sufentanil. They reported no significant difference in the occurrence of PONV (71.4% in the opioid-based anesthesia group vs. 70.5% in the OFA group, with a p-value of 0.91), vomiting or antiemetic requirements (8.1% vs. 10.5%) with a p-value of 0.57, and the occurrence of adverse effects at 24 hours postoperative.

The large-scale retrospective cohort study on data of 521 patients who underwent laparoscopic hysterectomy by Forget et al(39) reported comparable outcomes in the occurrence of nausea (10% vs. 7%) and vomiting (2% vs. 1%) with p-values of 0.21 and 0.3, respectively, in the patient groups receiving OBA and OFA. The study was conducted on the data of 118 patients who received OFA with clonidine and ketamine, and 403 patients given OBA with sufentanyl.

2.3. Severity of postoperative pain

In a systematic review and meta-analysis of 11 RCTs comparing OFA and standard GA with opoid on laparoscopic, gynecological, and abdominal surgeries, Olausson et al. reported significantly lower postoperative analgesic consumption in the OFA group (-6.0 mg with a p-value of 0.00001). They also documented decreased adverse effects of opioids (0.32, I2 = 56%, and p-value of 0.00001), while no significant difference in GI symptoms, shivering, and postoperative hypoxemia between the two groups (40).

Unlike Olausson et al.'s, Frauenknecht et al.'s meta-analysis of 5 RCTs on OFA vs. conventional GA with opioids found a non-significant difference in postoperative pain scores; a p = 0.38 difference between the two groups. They noted that the short duration of action of remifentanil, which most works of literature they reviewed used, may have affected the outcome of the postoperative pain score (25).

A randomized placebo-controlled trial done by Kang et al. on 168 female patients undergoing breast surgery in Japan with the OFA group given ketamine 0.5 mg/kg vs. the placebo group has documented a lower postoperative pain scale in patients receiving ketamine (69.0% vs. 86.9% with P = 0.005 at 3 months) (15) in the patients received OFA.

An RCT on OFA vs. OBA by Torchier et al(30) on 36 patients without dexmedetomidine for gynecologic surgeries, including breast surgery, documented a higher postoperative pain scale (reported by the NRS) in patients receiving opioids at 24 hr. and 48 hr. They also reported a 100% success rate of intraoperative opioid-free anesthesia with ketamine 0.5 kg/mg followed by infusion, and lidocaine 1.5 mg/kg bolus, followed by infusion.

2.4. The effectiveness of drugs used in OFA

Wang et al., in the review of 12 randomized controlled studies comprising about 900 patients undergoing different surgical procedures under GA, compared s-ketamine in bolus doses of 0.075 to 0.5 mg/kg and infusions from 1.25 to 10 μg/kg/min with placebo. They recorded better pain scores at rest up to 24 hours in patients given ketamine and similar pain scores at 48 hours postoperatively (p = 0.53) in both ketamine and placebo(41).

In another meta-analysis of nine randomized controlled trials comparing IV ketamine with placebo for adult surgical patients on opioid use, Forget et al also documented a significant decrease in postoperative pain scale at 24 hours in patients taking ketamine, with a mean difference of -0.79. About a 97 mg and 186 mg decrease in opiate consumption at 24 and 48 hours, respectively, were documented in patients taking ketamine (16).

In the review of recent works of literature on subanesthetic doses of ketamine for intraoperative pain and up to 48-hour postoperative administration, Jouguelet et al. reported a reduction of postoperative pain score and up to 40% reduction of postoperative analgesic consumption by bolus then continuous infusions given of up to 1.2 mg/kg/h or 1.3 mg/kg ketamine doses, respectively. On subanesthetic ketamine use, and reported that ketamine, when used in a subanesthetic dose, has no documented associated adverse events (42).

Touchier et al. performed an RCT by using lidocaine with ketamine on 36 gynecologic patients without dexmedetomidine and reported better hemodynamic stability in the OFA group (p = 0.0026) compared to opioid-based anesthesia with remifentanil (30).

Foo et al., in the statement on the efficacy and safety of lidocaine, described the analgesic, anti-hyperalgesic, and anti-inflammatory effects of lidocaine from its actions on muscarinic and NMDA receptors. They recommended 1–2 mg/kg as an initial bolus followed by a continuous infusion of 0.5–3 mg/kg/hr. Avoiding a dose greater than or equal to 3 mg/kg/hr, and avoiding lidocaine in patients with hepatic or renal impairment. Lidocaine should not be used on patients whose weight is less than 40 kg(12).

Weibel et al. performed a systematic review and meta-analysis of an RCT with 280 patients who used 1–5 mg/kg boluses and infusions of 1–3 mg/kg/h IV lidocaine found a significant reduction in pain score up to four hours after surgery, with a mean difference of 0.84, 95% CI 1.10 to 0.59, and at 24 hours, with a mean difference of 0.34, 95% CI 0.57 to 0.11. The pain score at 48 hr. was similar in both groups, the occurrence of ileus was lower in patients given lidocaine (4.8% vs. 13.9%), and the time of the first poop was comparable in both groups. The time it took for the first flatus and intestinal movement, as well as the time it took for bowel sounds to return, were all shorter in the lidocaine group (43).

OFA has been reported as a better option to general anesthesia with opioids, with a few literary masterpieces excluded. According to the findings of works of research, OFA can offer a superior perioperative anesthetic substitute, a better quality immediate post-operative recovery, and can avoid the usual opioid-related adverse events. Other drugs, as dexmedetomidine, which sprouts OFA, and seems to bring bad luck, can be used as fixings for opioid-related issues in settings that cannot access this drug. IV lidocaine, low-dose ketamine, dexamethasone, and some more drugs

Hypothesis Testing

Null hypothesis (H0)

Opoid-free anesthesia with low-dose ketamine and intravenous lidocaine is not more effective than general anesthesia with fentanyl for postoperative pain in adult patients undergoing elective gynecologic surgery under general anesthesia.

$\mu 1 \leq \mu 2$; $\mu 1$ is the mean pain severity at the GA with fentanyl group, and $\mu 2$ is the mean pain severity at the OFA (low dose ketamine and IV lidocaine) group

Alternative hypothesis (HA)

Opioid-free anesthesia with low-dose ketamine and intravenous lidocaine is effective for postoperative pain compared with general anesthesia with fentanyl for patients undergoing elective gynecologic surgery under general anesthesia.

$\mu 1 > \mu 2$; $\mu 1$ is the mean pain severity at the GA with fentanyl group, and $\mu 2$ is the mean pain severity at the OFA (low dose ketamine and IV lidocaine) group.

3. Objectives

3.1. General objective

To determine the effectiveness of low-dose ketamine and intravenous lidocaine vs. Fentanyl for postoperative pain in adult patients who underwent elective gynecologic surgery under general anesthesia at Dilla University Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10, 2023, to October 10, 2023

3.2. Specific objectives

To compare the postoperative pain severity between groups of adult patients who underwent elective gynecologic surgery under general anesthesia at Dilla University Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10 to October 10, 2023

To compare postoperative analgesic requests between groups of adult patients who underwent elective gynecologic surgery under general anesthesia at Dilla University General and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10 to October 10, 2023

To compare the occurrence of PONV between groups of adult patients undergoing elective gynecologic surgery under general anesthesia at Dilla University Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10 to October 10, 2023

To compare the occurrence of intraoperative cardiac adverse events for adult patients undergoing elective gynecologic surgery under general anesthesia at Dilla University Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10 to October 10, 2023

4. Methodology and materials

4.1. Study area and period

The research will be carried out at Dilla University General and Teaching Hospital in Gedio Zone, and Hawassa University Comprehensive and Specialized Hospital in Hawassa, SNNPR Ethiopia, from April 10, 2023, to October 10, 2023.

Dilla University General and Teaching Hospital is located in the administrative center of the Gedeo Zone, SNNPR, on the main road, 372 km from Addis Ababa to Nairobi. Dilla University General and Teaching Hospital is in the southern part of town, on the main road to Moyale. The hospital has about eight specialty departments, such as anesthesiology, surgery, obstetrics and gynecology, internal medicine, and pediatrics.

The general and teaching hospital has one OT with four fully functioning ORs, a post-anesthesia care unit (PACU) with four beds, and an intensive care unit (ICU) with eight beds. There are elective procedures scheduled five days a week; surgical procedures two days a week, gynecological and obstetrics, including elective C/S, two days a week, and orthopedic and trauma operations two days a week. The Gedio zone and neighboring areas of SNNPR, Sidama region, and Oromia region have millions of residents who use the referral and teaching hospital.

Hawassa University Comprehensive and Specialized Hospital in Hawassa, situated in southwestern part of Hawassa city, the capital of Sidama, is situated 275 kilometers (km) south of Addis Ababa. In the Southern Nations, Nationalities, and People Region (SNNPR) and the nearby Oromia area, the tertiary Hawassa University Referral Hospital (HURTH) provides medical care for almost 12 million people. An operating room, intensive care unit (ICU), 16 wards with 400 beds, and 11 floors make up this hospital.

4.2. Study design

A multi-centered, randomized, controlled, single-blinded trial will be conducted at Dilla University General and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital.

4.3. Population

4.3.1. Source population

All patients undergoing elective gynecologic surgery under general anesthesia at Dilla University General and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital.

4.3.2. Study population

Adult patients between the ages of 18 and 65 undergoing elective gynecologic surgery under general anesthesia at Dilla University General and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital during the study period.

4.4. Inclusion and exclusion criteria

4.4.1. Inclusion criteria

ASA I and II patients between the ages of 18 and 65 undergoing elective gynecologic surgery at Hawassa University Comprehensive and Specialized Hospital and Dilla University Teaching Hospital under general anesthesia between April 10, 2023, and October 10, 2023, and gave informed consent.

4.4.2. Exclusion criteria

Patients with allergies to any of the drugs used in the trial

Patients with chronic pain

Patients who are diagnosed with CNS diseases, like psychiatric diseases or epilepsy(46)

Patients who are hypertensive and taking beta-blockers, as well as those who have preoperative bradycardia, hypotension, or any type of heart block(47)

Patients weighing less than 40 kg or obese patients (BMI > 35 kg/m2)(12)

Patients with a history of smoking

Patients who are scheduled for postoperative mechanical ventilation

4.5. Sampling procedure and sample size

The sample size (N) was calculated by the formula for a continuous outcome variable with equal sample sizes in both groups, $n = 2[(Z\acute{\alpha}/2 + Z(1-ß))^2 * \sigma^2]/(d^2)$ by G-power calculator. We assumed: significance level ($Z\alpha/2$) = 0.05, taken 1.96, and power of study $Z(1-ß)$ = 0.80, taken 0.84; σ^2 is the standard deviation taken from a previous study in South Korea([48]), which is 1.9. Assuming a medium effect size in the OFA group compared to those receiving fentanyl is clinically significant, the calculated sample size for each group is 31, resulting in 62 participants in both groups. To account for potential contingencies, an additional 10% is added to the final sample size, resulting in 70 participants.

4.6. Random sequence generation

The eligible participants presenting for gynecologic surgery at both study areas during the study period will be selected. Participants will be allocated to study groups by a computer-generated random allocation sequence number created by an independent anesthetist with a 1:1 allocation to the treatment group (T) and control group (C) the night before surgery.

4.7. Allocation concealment and blinding

Participants will be given a sealed envelope with the letter of the study group name in it and will be allowed to present it to the OR. Anesthesia providers involved in patient management wii be allowed to know the drugs given and groups due to differences in anesthesia techniques, ethical issues, and patient diversity. Apart from patient management, the anesthetist will not be involved in any other study processes. Only participants assigned to groups will not know which group they will be selected for.

4.8. Study variables

4.8.1. Dependent (outcome) variables

4.8.1.1. Primary outcome variable

- The postoperative pain severity

4.8.1.2. Secondary outcome variables

- Postoperative analgesic requests between groups
- The occurrence of postoperative nausea and vomiting (PONV)between the groups
- The occurrence of intraoperative cardiac adverse events between groups

4.8.2. Independent variables

- Age
- Height
- Weight
- ASA physical status
- BMI
- Educational background
- Marital status
- Anesthetic experience
- Type of diagnosis and procedure
- Participants' hemoglobin and hematocrit
- Preoperative hemodynamic variables

4.9. Operational definitions

Nausea: The experience associated with the pressure to vomit

Opoid-free analgesia: A combination of various opioid-sparing techniques with absolute avoidance of opioids for pain relief in the pre-and postoperative periods.

Opoid-free anesthesia: It is a combination of various opioid-sparing techniques with absolute avoidance of opioids from induction of anesthesia until the extubation time

Postoperative nausea and vomiting: Any nausea, retching, or vomiting occurring in the first 24 hours after surgery

The Postoperative pain: pain felt up to 24 hours after an operation by the patient's expression

NRS: Valid and reliable tool for assessing pain intensity in all populations, regardless of literacy level(1, 50). It employs a 0-to-10 rating scale, with zero representing no pain and 10 representing the worst possible pain.

VAS: This is a pain rating scale; the scores are derived from patient-reported valuations of symptoms that are recorded at 1 point along a 10 cm line that shows a continuum between the 2 edges of the scale, which are "no pain" and "worst pain(51)

Vomiting: Projection of contents of the stomach out through the mouth.

4.10. Data collection procedures

After getting ethical clearance from the Dilla University College of Health Sciences and Medicine ethical review board, a structured questionnaire will be formed and translated into the respective languages by the principal investigator (PI). Two BSC anesthetists involved in patient management will be selected at both study areas and trained in the overall process of participant handling and data collection.

During the preoperative period

Patients undergoing gynecologic operations during the study period will be assessed and told about the study process and anesthetic the day before the surgery. The patient will receive maintenance fluid, had bilateral peripheral IV lines secured, and was NPO the night before surgery. On the morning of the procedure, both a standard informed consent form for the procedure and a separate consent form for the study will be checked and available.

The availability and functionality of the bilateral IV line, and NPO status will be checked, and prophylactic drugs will be given. Standard preoperative questionnaires will be used, and data will be collected through patient responses and medical records, such as patient monitoring and charts.

At intraoperative period

Routine ASA monitoring will be checked and applied for patients in both groups when the patient presented to the OR. The functionality and availability of the bilateral IV line and urinary catheter will be rechecked. Propofol (3 mg/kg) will be given to induce anesthesia after the patient had been pre-oxygenated for both groups. An intravenous bolus of 0.5 mg/kg of ketamine during the induction phase for patients in the treatment group, then a continuous infusion of 0.2 mg/kg/hr. 0f ketamine. A bolus of 1.5 mg/kg will be given before induction, and the same dose of lidocaine will be administered every 15 to 20 minutes after induction of anesthesia until the start of skin closure.

Patients in the control group will be induced with fentanyl 2 µg/kg given during induction of anesthesia with propofol 3mg/kg. 0.5 µg /kg of fentanyl will be given every 20-30 minutes up to the start of skin closure.

Intubation will be performed after administering 1.5–2 mg/kg IV suxamethonium. Inhalational anesthetics as availabilities (Isoflurane 0.75–2% and Halothane 1%_ 2%) were opened after the position of the ETT was confirmed, and Dexamethasone 0.15mg/kg IV bolus will be given after securing the ETT.

Anesthesia will be maintained with inhalational agents according to the patient's tidal volume of 6–8 ml/kg adjusted to maintain oxygen saturation >95% with 3- 4 ml 100% oxygen flow, and end-tidal CO2 between 32 and 45 mmHg. Muscle relaxation will be maintained with vecuronium 0.8 mg/kg. Intraoperative anesthesia depth will be assessed by clinical signs as well as by patient monitoring. Estimated intraoperative blood loss will be supplied with ringer lactate or normal saline.

The intraoperative participants' data will be collected from the anesthesia record chart and patient monitoring. Intraoperative hemodynamic variables will be collected every 10 minutes. Intraoperative cardiac adverse events such as intraoperative bradycardia (pulse rate less than 50 bpm), tachycardia (PR greater than 100 bpm), hypertension, and hypotension we diagnosed and managed as per institutional protocol. Intraoperative nausea or vomiting in both groups will also be managed as an institutional protocol.

When the surgeon begins skin closure, the inhalational agent will be turned off. A pre-prepared reversal agent bolus (neostigmine 0.05 mg/kg with atropine 0.02 mg/kg IV) was administered for patients given long-acting muscle relaxants after checking the adequacy of spontaneous ventilation, adequate movement of the respiratory bag, oxygen saturation >95percentage and ETCO2 between 32 and 45 mmHg after the skin is closed.

During the postoperative period

The postoperative pain severity will be assessed by the validated VAS starting from the patient's discharge from PACU to 24 hours postoperatively. Data will be collected at discharge from PACU, at 6 hours, 12 hours, and 24 hours postoperatively. Analgesia request at postoperative times will be recorded as the patient's request for analgesia according to the VAS score. PONV data will be collected from the time of arrival at PACU at 6 hours, 12 hours, and 24 hours postoperatively according to the patient's signs and symptoms.

4.11. Data quality assurance

The questionnaire will be pretested on 5% of the study population who will not participate in the main study in two study areas. Training on the verification and orientation of the study, the data collection tools, and the data collection process will be provided to data collectors a week prior to the start of data collection

During data collection, regular supervision and follow-up will be undertaken; the principal investigator (PI) will follow the collection process and will collect the filled questionnaire daily. The completeness and consistency of the daily data of individual participants will be checked. Missing data will be crosschecked and corrected before entered into a computer for analysis. The daily collected data was inserted into the locked patient data file on the computer accessed only by the PI

4.12. Data Processing and Analysis Procedure

After every data collection night, inconsistencies in data collection will be examined and fixed. Epi. Info version 7.2 will used for data entry and Statistical Package for the Social Sciences (SPSS) version 27will be used for data analysis.

The normality of data distributions for quantitative variables will be assessed using the Kolmogorov-Smirnov test and Levene's test will be used to check the homogeneity of variance. The plot of the Box will be used to check outliers. Histograms and visual inspection of individual data will be used to verify the data distribution.

Independent t-tests and ANOVA tests will be used to assess continuous data on pain severity at different postoperative times, and results will be presented as mean plus standard deviation. The categorical data of PONV at different postoperative times will be analyzed by chi-square or Fisher exact test and presented as frequencies, percentages, and a bar chart graphically. P-values of less than 0.05 will be determined as statistically significant.

4.13. Ethical Considerations

Ethical clearance will be obtained from the College of Medicine and Health Sciences of Dilla University after the submission of the study protocol to the institutional review board. The support letter will be written to Hawassa University Comprehensive and Specialized Hospital. The risks, benefits, and objectives will be clearly explained, and written informed consent will be obtained from each participant. Throughout the trial period, a data monitoring committee comprised of three personnel from the Dilla University anesthesiology department will check on participant concerns, process of intervention, and modification of study process as needed.

After the approval of the IRB at Dilla University College of Health Medicine and Health Sciences, the study protocol will be registered on clinicaltrial.gov, and the findings of the study will be reported in compliance with the CONSORT statement guidelines for randomized controlled trials. Individuals who wish to withdraw from the research will be permitted to depart the premises, and any information collected during the administration of anesthesia will be analyzed.

4.14. Dissemination of the Results

The results of the result of this study will be presented to the Dilla University College of Medicine and Health Sciences Department of Anesthesiology staff. It will also be presented at the annual research conference. This research will be submitted to reputable journals for publication.

4.15. Work plan

Time frame or proposal and thesis development

Activities	Time in Months																					
	Dec./2022			Jan./2023			Feb./2023			March/2023			Apr./2023			May/2023			June/2023		
Research title defense																						
Development of research proposal																						
Acceptance of research proposal																						
Development of research tools																						
Sample selection																						
Training of data collectors																						
Data collection																						
Data entry																						
Data analysis																						
First draft submissions																						
Final thesis defense																						

Table 1.1 Time frame for proposal development and thesis

Budget breakdown for proposal and thesis development

Budget category	Unit cost	Multiplying factor	Total cost(birr)
For training			
Supervisor	400	1	400
Data collectors	200	3	600
For data collection			
Supervisor	200	30*1	6000
Data collectors	200	30*3	18000
Study Drugs			
Lidocaine IV 2% #40 vials			2500
Fentanyl IV 1mg #35 ampules'			2500
Stationary			
Writing pad	30	20	600
Pen	20	20	400
Pencil	10	30	300
Coffee/tea	10	5*30	1500
Eraser	15	5	75
Printing and binding	500	4	2000
Sharpener	35	10	350
Flash disk	400	2	800
CD (RW)	200	3	600
Duplicating Questionnaire	50	40	2000
Total			38625 ETB
10% added			41625ETB

Table1.2. budgeting breakdown for proposal development and thesis development

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Annexes

4.16. Annex One

Informed consent form English Language version

This informed consent form is for patients undergoing elective gynecologic surgery under general anesthesia at Dilla University Referral and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital inviting them to participate in a study on Low-Dose Ketamine and Intravenous Lidocaine vs. Fentanyl for intraoperative pain management. The topic of our study is The Effectiveness and Safety of Opioid-Free Anesthesia with Low-Dose Ketamine and Intravenous Lidocaine vs. Fentanyl for intraoperative pain Patients Undergoing Elective Gynecologic Surgery under General Anesthesia at Dilla University General and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10, 2023 to June10, 2023- A Multi-Centered Randomized Controlled Trial

Purpose of the study

Surgical pain is the worst and most severe type of pain that requires analgesics to alleviate. Opioids have been the cornerstone of intraoperative analgesia for decades. Despite opiate-related side effects like shivering, nausea, and vomiting; an increased postoperative pain scale; decreased post-operative patient satisfaction; and more, some are disfavoring opiate use intraoperatively. Opoid-free anesthesia is a recent idea aimed at averting opioid-related adverse effects. The purpose of this research is to determine the Effectiveness of intraoperative use of Low-Dose Ketamine and Intravenous Lidocaine vs. with Fentanyl for Patients Undergoing Elective Gynecologic Surgery under General Anesthesia at Dilla University General and Teaching Hospital and Hawassa University Comprehensive and Specialized Hospital from April 10, 2023 to June10, 2023.

Interventions: The study will involve two groups of patients, with the study group undergoing surgery under intraoperative opiate-free anesthesia with low-dose ketamine and IV lidocaine and the control group receiving standard general anesthesia with opiate (fentanyl 1-3µg/kg).

At doses of up to 3-5 mg/kg intramuscularly and 2 mg/kg intravenously, ketamine is a general anesthetic that has been used for many years as a non-barbiturate dissociative anesthetic. It was linked to sympathetic stimulation and hallucination at doses greater than or equal to 2 mg/kg. Ketamine at low doses of up to 1 mg/kg induces analgesia and only mild sedation. The medications have been utilized within this dose as a management tool for intraoperative shivering and as additional analgesics in multimodal analgesia. When administered intravenously at the recommended low dose, it has been reported to have no known side effects.

Lidocaine is a local anesthetic and anti-arrhythmic drug that has been used intramuscularly to block neuromuscular transmission by reversibly inhibiting the generation and propagation of action potentials acting on the sodium channel. Intravenous lidocaine is a recent advancement in drug preparation that is additive-free. It is documented as having analgesic, anti-inflammatory, and decreasing postoperative pain score at IV doses up to 2 mg/kg. Additionally, when used with multimodal analgesia, the drug was documented to avoid opioid-related adverse events.

Lidocaine with additives like adrenaline and sodium carbonate is contraindicated for intravenous use. In addition, doses greater than 3 mg/kg are related to adverse effects like tinnitus, vertigo, and respiratory compromise, and a much higher dose can result in cardiac arrest. Mostly, IV lidocaine is given as a 1.5 mg/kg bolus or infusion, and this dose, when used up to 24 hours, has no reported adverse effects.

Procedure: We call all interested individuals to participate in the study aimed to determine the safety and efficacy of opioid-free anesthesia compared with standard general anesthesia with opioids in improving the quality of postoperative patient recovery and avoiding opioid-related adverse effects such as increased postoperative pain scale, PONV, shivering, and others. You will be asked for some information about your situation and health status. With your permission, some data will be recorded from your chart, and you will be asked to be monitored for about two days after your operation.

You will be asked to sign the consent form that explains your willingness to participate in the study before the start of the study. You do not have to take part in this research if you do not wish to, and refusing to participate will not affect your treatment at this hospital in any way. You will still have all the benefits that you would otherwise have at this hospital. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. None of your information will be exposed, and all of your data will be coded, including your name.

Inducement and privateness

There will be nothing gained by taking part in this study. The information collected from the study will be kept confidential and only accessible by the main researcher and the data monitoring committee. The data will be coded and locked, with no labeling identifying you or anyone else participating in the study, which will only be accessed by the main investigator. The proposal for the study will be reviewed and approved by the IRB of the DURTH, and ethical clearance will be obtained.

Withdrawal from study

You will have complete freedom to refuse at any time during the research. You will not be harmed or injured in any way by refusing to participate in the research. If you do not want to participate in this study, it will not have a positive or negative impact on you during your stay here in our hospital.

You are being asked to take part in a research study. Before you decide to participate in this study, it is important that you understand why the research is being done and what it will involve. Please read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information.

Contacts when anything happened

You can contact the following personnel from the data monitoring committee anytime you need

Voluntary participation

Your participation in this study is voluntary. It is up to you to decide whether to take part in this study. If you decide to take part in this study, you will be asked to sign a consent form. After you sign the consent form, you are still free to withdraw at any time and without giving a reason. Withdrawing from this study will not affect the relationship you have, if any, with the researcher. If you withdraw from the study before data collection is completed, your data will be returned to you or destroyed.

Informed consent

This consent form is aimed at inviting participants who are going to have an operation to participate in the study, which is collecting information for research on the safety and efficacy of opioid-free anesthesia compared with conventional anesthesia with opioids at Dilla University Referral and Teaching Hospital, Ethiopia 2023.

I am _____, a member of the research team. We are performing a study on the safety of opioid-free anesthesia. I am going to give you information and invite you to be part of this research. Before you decide, you can talk to anyone you feel comfortable with about the research. If there are any words that, you do not understand. Please ask me to stop as we go through the information, and I will take the time to explain. You can ask me any more questions about any part of the research study if you wish to. Do you have any questions?

CONSENT

I have read and understand the provided information and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without cost. I understand that I will be given a copy of this consent form. I voluntarily agree to take part in this study.

Participant's signature _____ Date _____

Investigator's signature _____ Date _____

Informed consent Amharic Language Version

በመረጃ የተደገፈ የስምምነት ቅጽ

ይህ በመረጃ የተደገፈ የስምምነት ፎርም በዲላ ዩኒቨርሲቲ አጠቃላይ እና ማስተማሪያ ሆስፒታል እና በሀዋሳ ዩኒቨርሲቲ ኮምፕረሄንሲቭ እና ስፔሻላይዝድ ሆስፒታል በአጠቃላይ ሰመመን ውስጥ የማህፀን ቀዶ ጥገና ለሚደረግላቸው ታካሚዎች ነው። የጥናታችን ርዕስ "hopoid **ነፃ አጠቃላይ ማደንዘዣ እና የተለመደ አጠቃላይ ማደንዘዣ ከኦፒዮይድ ጋር ያለዉን ውጤታማነት እና ደህንነት በምርጫ ላይ የተመሰረተ የማህፀን ቀዶ ጥገና ለሚደረግላቸው ለአዋቂ ታካሚዎች፡ በዘፈቀደ፣በቁጥጥር የሚደረግ እና ብዙ ማእከል ያለው ሙከራ፤ በዲላ ዩኒቨርሲቲ አጠቃላይ እና ማስተማሪያ ሆስፒታል እና በሀዋሳ ዩኒቨርሲቲ ኮምፕረሄንሲቭ እና ስፔሻላይዝድ ሆስፒታል በኢትዮጵያ፣ በ**2015 **ዓ.ም**

የዋናው ተመራማሪ ስም፡- አማኑኤል አሰፋ አኔቴዥያ ት/ት ክፍል የሁለተኛ ድግሪ ተማሪ

የድርጅቱ ስም፡- ዲላ ዩኒቨርሲቲ ሪፈራል ሆስፒታል፣ የህክምና እና ጤና ሳይንስ ኮሌጅ የአንስቴዚዮሎጂ ት/ት ክፍል

ስፖንሰር ያደረገዉ ተቋም፡- ዲላ ዩኒቨርሲቲ

የተመራማሪ ኢሜል አድራሻ dawona1@gmal.com

የተመራማሪ ስልክ ቁጥር +251925230585/+251979721905

በዚህ ምርምር ጥናት ላይ እንድሳተፉ እየተጠየቅን ነው። በዚህ ጥናት ውስጥ ለመሳተፍ ከመወሰንዎ በፊት ጥናቱ ለምን እንደሚደረግ እና ምን እንደሚያጠቃልል *መረዳትዎ* አስፈላጊ ነው። እባክዎ የሚከተለውን *መረጃ* በጥንቃቄ ያንብቡ። ግልጽ ያልሆነ ነገር ካለ ወይም ተጨማሪ መረጃ ከፈለጉ ተመራማሪውን ይጠይቁ።

<u>የጥናቱ ዓላማ</u>: **የቀዶ ጥገና ህመም የህመም ማስታገሻ *መድሃኒቶችን* የሚፈልግ በጣም የከፋ እና በጣም ከባድ ህመም *መሆኑ* ይታወቃል። እንደ *መንቀጥቀጥ*፣ ማቅለሽለሽ እና ማስታወክ ካሉ የተዛመዱ የጎንዮሽ ጉዳቶች ቢኖሩምኦፖይዶች ለብዙ ኦፕሬተ ዓመታት በቀዶ ሕክምና ውስጥ የህመም ማስታገሻዎች የማዕዘን ድንጋይ ሆነዉ የቀዩ ናቸዉ። ከቀዶ ጥገና በኋላ የሕመም *መጠን* መጨመር; ከቀዶ ጥገና በኋላ የታካሚ እርካታ መቀነስ; እና በሌሎችም የጎንዮሽ ጉዳቶች አንዳንድ ሀኪሞች በቀዶ ሕክምና ውስጥ ኦፖይድን *መጠቀምን* አይወዱም። ኦፖይድ-ነጻ ማደንዘዣ ከላይ የተጠቀሱ ከኦፒዮይድ ጋር የተዛመዱ አሉታዊ ተጽእኖዎችን ለማስወገድ የታለመ የቅርብ ጊዜ የሀሳብ ትግበራ ነው። የዚህ ጥናት ዓላማ በዲላ ዩኒቨርሲቲ ሪፈራል እና ማስተማሪያ ሆስፒታል ከመጋቢት** 22 2015 **ዓ.ም እስከ ሰኔ** 22 2015 **ዓ.ም ባለው ጊዜ ውስጥ በአጠቃላይ ማደንዘዣ ውስጥ በምርጫ ቀዶ ጥገና ለሚደረግ አዋቂ ታካሚዎች ከኦፒዮይድ-ነጻ ማደንዘዣ እና *መደበኛ* አጠቃላይ ሰመመን ያለውን ውጤታማነት እና ደህንነት ለመወሰን ነው።**

ጣልቃ-ገብነት፡ ጥናቱ ሁለት ቡድኖችን ያካተተ ሲሆን የጥናት ቡድኑ (ከኦፖይድ ነፃ ማደንዘዣ) በዝቅተኛ መጠን በደም ሥር ዉስጥ የሚሰጥ “ketamine ኢና lidocaine” የሚባሉ መዲሃኒቶችን ስወስድ የቁጥጥር ቡድኑ መደበኛ አጠቃላይ ሰመመን ከኦፒዮይድ መድኃኒቶችን ይቀበላል።

እስከ 3-5 mg/kg በጡንቻ ውስጥ እና 2mg/kg በደም ውስጥ የሚሰጥ “ketamine” ለአጠቃላይ ማደንዘዣ የሚሰጥ መድሃኒት ሲሆን ለብዙ አመታት እንደ “barbiturate dissociative” ማደንዘዣ ሆኖ ሲያገለግል ቆይቷል። ከ 2 mg/kg በላይ ወይም እኩል በሆነ መጠን ከርህራሄ ማነቃቂያ እና ቅዠት ጋር ተያይዟል። እስከ 1 mg/kg ባለው ዝቅተኛ መጠን ያለው “ketamine” ደግሞ ህመምን በማስታገስ እና ቀለል ያለ ዕንቅልፍ በማስተኛት ይታወቃል። መድሃኒቱ በዚህ መጠን በቀዶ ሕክምና ወቅት ለሚፈጠር መንቀጥቀጥ እና እንደ መልቲሞዳል የህመም ማስታገሻ መድሃኒት ተጨማሪ የህመም ማስታገሻዎች ጥቅም ላይ ውለዋል። በተመከረው መከራዎችም ዝቅተኛ መጠን በደም ውስጥ በሚሰጥበት ጊዜ ምንም አይነት የጎንዮሽ ጉዳት እንደሌለው ተዘግቧል።

“Lidocaine” ደግሞ በሴላችን ዉስጥ ባለዉ “sodium channel” በሚባል መረጃ ተቀባይ ላይ በመስራት የነርቭ ጡንቻ ስርጭትን ለመግታት በመጀመሪያ በጡንቻ ውስጥ ጥቅም ላይ የዋለ ማደንዘዣ ነው። በደም ውስጥ የሚሰጥ lidocaine ከተጨማሪ ነገር ነፃ የሆነ የመድኃኒት ዝግጅት እና የቅርብ ጊዜ ግኝት ነው። የህመም ማስታገሻ እና ፀረ-ብግነት ውጤቶች እንዳሉት ሆኖ እስከ 1 mg/kg ስንጠቀም ከቀዶ ጥገና በኋላ የህመም ደረጃዉን እንደሚቀንስ ተመዝግቧል። በተጨማሪም፣ ከመልቲ ሞዳል የህመም ማስታገሻ ጋር ጥቅም ላይ ሲውል፣ መድሃኒቱ ከኦፕዮይድ ጋር የተገናኙ አሉታዊ ክስተቶችን ለማስወገድ እንደሚጠቅም ተመዝግቧል።

Lidocaine እንደ አድሬናሊን እና ሶዲየም ካርቦኔት ካሉ ከተጭማሪ ነገሮች ጋር ከተዘጋጀ ለደም ሥር ጥቅም የተከለከለ ነው። እንዲሁም ከ 3 mg/kg በላይ እንደ ጆሮ ዉስጥ እንደመጮህ፣ ማዞር እና የመተንፈሻ አካላት ችግር ካሉ አሉታዊ ውጤቶች ጋር የተገናኙ ናቸው፣ በጣም ከፍ ያለ መጠን የልብ ድካም ሊያስከትል ይችላል። በአብዛኛው, በደም ውስጥ የሚሰጥ lidocaine የሚሰጠው እስከ 2 mg/kg በአንዴ ወይም በማስከተል, እና ይህ መጠን እስከ 24 ሰዓታት ድረስ ጥቅም ላይ ሲውል, ምንም የጎንዮሽ ጉዳት አልተመዘገበበትም።

የአሰራር ሂደት፡- ከኦፒዮይድ ነፃ የሆነ ሰመመን ከመደበኛ ኦፖይድ ጋር የሚሰጥ ሰመመን ጋር በማነፃፀር ከቀዶ ጥገና በኋላ የማገገሚያ ጥራት የማሻሻል እና ከኦፖይድ ጋር የተዛመዱ የጎንዮሽ ጉዳቶችን ለማስቀረት በሚደረገዉ ጥናት ላይ ሁሉም ፍላጎት ያላቸው ግለሰቦች እንዲሳተፉ ጥሪ እናስተላልፋለን ። በተጨማሪም ጥናቱ የህመም ደረጃ መጨመር፣ ከቀዶ ጥገና በኋላ የሚከሰት ማቅለሽለሽ እና ማስታወክ፣ መንቀጥቀጥ እና ሌሎች የመሳሰሉ የመድሃኒቱን ጉዳቶችን ለማስቀረት ያለመ ነዉ። በእርስዎ ፈቃድ ስለ አጠቃላይ ሁኔታዎ እና የጤና ሁኔታዎ የተወሰነ መረጃ ይጠየቃሉ፤ የተቀረዉ ደግሞ ከህክምና መረጃ ገበታዎ ይመዘገባል። ከቀዶ ጥገናዎ በኋላም ለሁለት ቀናት ያህል ክትትል ይደረግልዎታል።

<u>ተነሳሽነት እና ግላዊነት:-</u> በዚህ ጥናት ውስጥ በመሳተፍ ምንም የሚገኝ ጥቅም አይኖርም። ከጥናቱ የሚሰበሰበው መረጃ ሚስጥራዊ ሆኖ በዋና ተመራማሪው እና በመረጃ ተቀጣጣሪው ኮሚቴ ብቻ ተደራሽ ይሆናል። ውሂቡ ኮድ ተደርጎ ይቀለፋል፣ እርስዎን እና ሌሎች በጥናቱ ውስጥ የሚሳተፉትን የሚለይ መለያ ይኖራል፤ ይህንም የሚያዉቀዉ ዋና መርማሪ ብቻ ነው። ጥናቱ ከመጀመሩ በፊትየጥናቱ ሙሉ የጥናት ሀሳብ በዩኒቨርሲቲዉ ተቋማዊ ግምገማ ቦርድ ተገምግሞ እና ጸድቆ የስነምግባር ማረጋገጫ ያገኛል።

<u>ከጥናት መውጣት:-</u> በማንኛውም ጊዜ ትናቱን አቋርጠዉ የመዉጣትሙሉ ነፃነት ይኖርዎታል። በጥናቱ ውስጥ ለመሳተፍ ፈቃደኛ ባለመሆኑዎ እዚህ በሆስፒታል በሚቆዩበት ጊዜ በምንም መልኩ አይጎዱም፤ በዚህ ሆስፒታል ውስጥ ሊኖሯቸው የሚችሏቸው ሁሉንም ጥቅሞች ይኖሩዎታል። ጥናቱ ከመጀመሩ በፊት በጥናቱ ለመሳተፍ ፈቃደኛ መሆንዎን የሚገልጽ የስምምነት ቅጽ ላይ እንዲፈርሙ ይጠየቃሉ። ካልፈለጉ በዚህ ጥናት ውስጥ መሳተፍ የለብዎትም። እዚህ እንደ ታካሚ ምንም አይነት መብትዎን ሳያጡ በፈለጉት ጊዜ በምርምር መሳተፍን ማቆም ይችላሉ። የትኛውም መረጃዎ አይጋለጥም እና ሁሉም ውሂብዎ ስምዎን ጨምሮ ኮድ ይደረጋሉ።

እርዳታ በሚያስፈልግበት ጊዜ የሚገናኙበት

መረጃ በሚፈልጉበት ጊዜ ከቁጥጥር ኮሚቴ የሚከተሉትን ማግኘት ይችላሉ።

1) **ስለሺ ሃይሉ ረዳት ፕሮፌሰር ኢና የዲላ ዩኒቨርሲቲ የአኔስትዮሎጂ ት/ት ክፍል መምህር**

   ስልክ ቁጥር፡- +251 91 378 5100

2) **መስፍን ጉርሙ የዲላ ዩኒቨርሲቲ የአኔስትዮሎጂ ት/ት ክፍል መምህር**

   ስልክ ቁጥር፡- +251 92 408 1119

3) **በላይ በቀለ የዲላ ዩኒቨርሲቲ የአኔስትዮሎጂ ት/ት ክፍል መምህር**

   ስልክ፡ +251938511104

<u>በፈቃደኝነት ተሳትፎ:-</u> በዚህ ጥናት ውስጥ ያለዎት ተሳትፎ በፈቃደኝነት ነው። በዚህ ጥናት ውስጥ ለመሳተፍ ወይም ላለመሳተፍ መወሰን የእርስዎ ውሳኔ ነው። በዚህ ጥናት ለመሳተፍ ከወሰኑ፣ የስምምነት ፎርም እንዲፈርሙ ይጠየቃሉ። የስምምነት ቅጹን ከፈረሙ በኋላ በማንኛውም ጊዜ ምክንያትዎን በመናገር ከጥናቱ ለመውጣት ነፃ ነዎት። ከዚህ ጥናት መውጣት ከተመራማሪው ጋር ወይም ከሆስፒታሉ ጋር ያለዎትን ግንኙነት አይጎዳውም:: መረጃ መሰብሰብ ከመጠናቀቁ በፊት ከጥናቱ ከወጡ፣ የእርስዎ ውሂብ ባለዉ መረጃ በጥናቱ ውጤት ውስጥ ይካተታል።

በመረጃ የተደገፈ ስምምነት

ይህ የስምምነት ፎርም ኦፕራሲዮን የሚደርጉ ተሳታፊዎችን በጥናቱ ላይ እንዲሳተፉ ለመጋበዝ ሲሆን ይህም በዲላ ዩኒቨርሲቲ ሪፈራል እና ማስተማሪያ ሆስፒታል የተለመደውን የኦፖይድ ሰመመን ከኦፒዮይድ-ነጻ ሰመመን ደህንነት እና ውጤታማነት ጋር በማነጻጸር ለምርምር መረጃን በማሰባሰብ ላይ ነው።

እኔ _____ የምርምር ቡድን አባል ነኝ። ከኦፒዮይድ-ነጻ ማደንዘዣ ደህንነት ላይ ጥናት እያደረግን ነው። መረጃ እንድጸጥ እና የዚህ ጥናት አካል እንድሆኑ እጋብዛለሁ። ከመወሰንዎ በፊት, ስለ ጥናቱ ምኞት የሚሰማዎትን ማንኛውንም ጥያቄ ማንኛዉንም ሰው ማነጋገር ይችላሉ. ከፈለጉ ስለ የትኛውም የዳግም ፍለጋ ጥናት ክፍል ተጨማሪ ጥያቄዎችን መጠየቅ ይችላሉ።

ስምምነት

የቀረበውን መረጃ አንብቤ ወይም ተነቦልኝ ተረድቻለሁ፤ ጥያቄዎችንም ለመጠየቅ እድሉን አግኝቻለሁ። የእኔ ተሳትፎ በፈቃደኝነት እንደሆነ ተረድቻለሁ፤ ቦማንኛውም ጊዜ ምክንያቴን ገልጬ ያለምንም ከልካይ ለመልቀቅ ነፃ መሆኔን ተረድቻለሁ። ጥናቱ ከመጀመሩ በፊት የዚህ የስምምነት ቅጽ ቅጂ እንደሚሰጠኝ ተረድቻለሁ። በዚህ ጥናት ለመሳተፍ በፈቃዴ ተስማምቻለሁ።

የተሳታፊ ሰም እና ፊርማ _____ ***ቀን*** _____

የመርማሪው ሰም እና ፊርማ _____ ***ቀን*** _____