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PREEMPTIVE DICLOFENAC FOR POST OPERATIVE ANALGESIA IN PATIENTS WITH MAJOR GYNECOLOGIC ABDOMINAL SURGERY UNDER GENERAL ANESTHESIA IN ADAMA HOSPITAL, ETHIOPIA,2020.

PRINCIPAL INVESTIGATORS: YOHANNES MEBRATU (B.Sc.)

ADVISORS: GERESU GEBEYEHU (B.Sc. M.Sc.)

SELAMAWIT SHIFERAW (B.Sc. M.Sc.)

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Principal Investigator: Yohannes Mebratu

Contact: Email: yohannesm5@gmail.com

Telephone: +251924903877 / +251967727415

Advisors: Geresu Gebeyehu (BSC, MSC in Clinical Anesthesia, Lecturer)

Selamawit Shiferaw (BSC, MSC in Clinical Anesthesia, Lecturer)

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Declaration

I, the undersigned, declare that this thesis is my original work in partial fulfillment of the requirements for the Master of Science degree in Anesthesia. I understand that plagiarism will not be tolerated and all directly quoted material has been appropriately referenced.

Name: **Yohannes Mebratu**

Signature: _____

Submission to MSc Tutor, Department of Anesthesia, Addis Ababa University

Date of Submission: _____

This thesis work has been submitted for examination with my/our approval as Advisors and Tutors on the MSc in Advanced Clinical Anesthesia course

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Abstract

Introduction: Preemptive analgesia has become one of the most promising strategies of pain management. A significant proportion of patients suffer moderate to severe intensity of pain after surgery. If not managed timely this can lead to prolonged hospital stay, return to the hospital after discharge, reduction of the quality of life of the patients, development of chronic pain and organ system complications.

Objective: The aim of this study was to assess the effectiveness of preemptive diclofenac (75mg, IM) for postoperative pain management in patients that undergone gynecologic abdominal surgery in Adama hospital.

Methods: This prospective cohort study recruits 90 ASA I and II, age>18 patients. Study participants were selected by systematic random sampling technique. Study participants were grouped as group D (who received preemptive diclofenac) and group N (who doesn't receive preemptive diclofenac). The outcome variables of the study were pain intensity, total analgesia consumption, first analgesia request time and incidence of nausea and vomiting within 24 hrs. postoperatively. Two samples z-test and Mann Whitney U test was used for analyzing numeric data. Categorical variable between two groups were analyzed using chi-square test. p -value <0.05 is considered statistically significant.

Results: Median pain score in the first 24 hrs. post operatively in group D and group N respectively was:- 2^{nd} hr:1(0-2) vs 2(1-3), 4^{th} hr:2(1-3) vs 3(2-4),8^{th} hr:2(1-3) vs 4(3-5),12^{th} hr:3(2-4) vs 3(2-4) and 24^{th} hr:3(2-4) vs 3(2-4) with a p value of 0.007,0.004, 0.001,0.261 and 0.796 respectively. Mean first analgesia request time in group D and group N respectively was 186.60±35.19 and 174.45±24.88 with a p value of 0.087. Post-operative 24 hr. mean total analgesic consumption in group D and group N respectively was: - diclofenac consumption: 146.25±50.81 vs 187.50±50.95 and Tramadol consumption: 153.75±44.41 vs 177.50±50.57 with a p value of 0.0006 and 0.035 respectively.

Conclusion and Recommendation: Preemptive intramuscular administration of diclofenac significantly decreases postoperative pain score and analgesic consumption in patients with gynecologic abdominal surgery. Based on this we recommend intramuscular administration of 75mg of diclofenac 30 min to 1 hr. before surgery.

Key words: Analgesic consumption, first analgesia request, gynecologic abdominal surgery, post-operative pain, postoperative pain score, preemptive diclofenac.

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Abbreviations

ASA – American Society of Anesthesiologists

CI-Confidence Interval

GA- General Anesthesia

IASP-International Association for the Study of Pain

IM-Intramuscular

IV- Intravenous

NRS – Numeric Rating Scale

NSAIDS-Non-Steroidal Anti-Inflammatory Drugs

PCA -Patient Controlled Analgesia

PACU – Post Anesthesia Care Unit

PI -Principal Investigator

PONV – Post Operative Nausea and Vomiting

PR –Pulse Rate

PUD-Peptic ulcer disease

SD – Standard Deviation

SPSS-Statistical Package for Social Sciences

VAS – Visual Analogue Scale

WHO-World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 Background

Pain is defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". Postoperative pain is the acute pain that is induced by surgical trauma and gradually decreases when the tissue starts healing (1).

Several degrees of postsurgical pain are expected after most surgical procedures with variable extent among individuals undergoing similar surgery. Generally, more extensive surgical procedures are associated with greater acute pain. Postsurgical pain is Inflammatory by nature which is consequence of peripheral tissue damage due to surgery and it is temporary, subsiding rapidly or persisting only until the healing process is complete(2).

Pain after gynecological abdominal surgery has both visceral and somatic origins. The visceral component is from autonomic innervation of the parametrium, the upper vagina and the visceral peritoneum, while the somatic component is from lower thoracic and upper lumbar somatic nerves innervating the muscle, skin, fascia and other subcutaneous soft tissue (3).

A Prospective cross-sectional study done in Ethiopia which asses practice and outcomes of Postoperative Pain Management among Surgically Patients show abdominal surgery (35.7%) as the largest surgical procedure. The pain incidence was 91.4% and 80% of patient undertreated among surgical patients. Reported mean pain intensity was 6.72±1.44 on 10-point NRS with mean total tramadol dose of 122.56±21.3 mg and 101.46±19.3 mg diclofenac(4).

Preemptive analgesia has become one of the most promising strategies of pain management. The precise definition of preemptive analgesia remains controversial. However, the explanatory concept behind it indicates that an analgesic intervention begins before the noxious stimulus arises which has beneficial effects reducing postoperative pain and the occurrence of postoperative pain(5).Crile proposed that blocking noxious signals prior to a surgical incision may lead to some degree of CNS protection against postoperative pain, though at that time, the mechanism remained unclear. It is now recognized that nociceptor function is dynamic and may be altered after tissue injury, that leads to pronounced and prolonged postoperative pain(6).

Preemptive analgesia, also called preoperative analgesia, has been studied ever since the beginning of the 20th century as a way of reducing or preventing the production of mediators responsible for nervous stimulation. It is characterized as an anti-nociceptive treatment for the prevention of central changes induced by afferent sensitization due to tissue injury caused by surgical procedures (7).Damage to tissues has been shown to provoke a magnified reaction to noxious stimuli, peripherally by diminishing the threshold of nociceptive afferent nerve terminals and centrally by augmenting the excitability of second-order sensory neurons in the spinal cord, later resulting in an amplification and extension of postoperative pain after surgery(8).

Preemptive analgesia believed to reduce pathologic pain. Pathologic pain is different from physiologic pain in several aspects: It is excessive in intensity and can be activated by low-intensity stimuli (6).

1.2. Statement of the problem

In a survey in the US dating back to 1995, 57% of patients reported postsurgical pain as a concern prior to surgery and 80% reported moderate-to-severe pain after surgery. In a 2003 survey of 250 patients undergoing surgery, 33% were concerned about pain during surgery and 59% (the largest group) were concerned about pain following surgery (9, 10).

Postoperative pain remains one of the major challenges of surgery in the history of surgery and anesthesia. Postoperative pain is experienced by nearly all patients undergoing surgical procedures. While pain is a predictable part of the surgical recovery process, it is imperative that clinicians attempt to prevent and mitigate postoperative pain as it poses significant clinical, psychological and economic implications. Such complications include but are not limited to: increased risk of deep vein thrombosis and pulmonary embolism secondary to pain-induced immobilization, insomnia, demoralization, extended length of stay, readmission, and patient dissatisfaction with medical care(11).

More than 80% of patients who undergo surgical procedures experience acute postoperative pain. Evidence suggests that more than 50% of patients who undergo surgery report inadequate postoperative pain relief. Inadequate pain relief negatively affects quality of life, function, and functional recovery. It also causes increased risk of post-surgical complications and persistent postsurgical pain (11, 12).

Suboptimal acute pain management following abdominal surgery carries a wide range of complications. These effects occur in diverse organ systems, the pulmonary(hypoventilation, decreased vital capacity, pulmonary infection), cardiovascular (coronary ischemia, myocardial infarction), gastrointestinal (reduced motility, ileus, nausea and vomiting) and renal (increases urinary retention and sphincter tone, oliguria)(13, 14).Inadequate management of postoperative pain might also lead to thromboembolic complications, prolonged hospital stays, return to the hospital after discharge, reduction of the quality of life of the patients and development of the chronic pain(15).

Progress in acute pain management over the last 30 years has demonstrated that effective pain relief can be achieved with a range of inexpensive drugs and treatments (NSAIDs, Opioids, nerve blocks). Yet the vast majority of patients in less developed areas of the world have little or no access to even the most limited of therapies that could alleviate their suffering from acute or chronic pain(16).Although many therapeutic agents effectively eliminate postoperative pain, their adverse effects may be detrimental to patient recovery. For example, opioids used for postoperative analgesia may provoke nausea, debilitating bowel dysfunction, sedation, respiratory depression and long-term physical dependence. These adverse effects contribute to increased hospital cost, polypharmacy, and patient dissatisfaction. As such, goals of acute postoperative pain management include reduction of pain incidence and severity as well as the prevention of adverse effects of some analgesics(11, 17).

1.3. Justification

Even with our current knowledge and an armamentarium of analgesic agents, postoperative pain management has not changed much in the past two decades and is not optimally treated(18).

Although some anesthetists/clinicians used to practice preemptive analgesia as part of their post-operative management in our country, others fail to practice it routinely. The probable reason for this, in addition to knowledge gap, may be their ambiguity about its effectiveness. So, this study will add on to clear such ambiguities.

Preoperative analgesia that can prevent postoperative pain is of great interest. Analgesics given before surgical trauma are thought to have a pre-emptive effect; implying that analgesia will start before the surgical stimulus, leading to a reduction of CNS input and, hence, reducing pain. Studies using different NSAIDs pre-emptively have had mixed results; some studies showing a benefit other showing no benefit(19, 20).

Although preemptive analgesia with different agents has been successful in experimental animal models, conclusions from human studies remain controversial. Sporadic studies have established some considerable preemptive benefits of NSAIDs. As a result, the objective of this study was to ascertain the impact of a NSAID, diclofenac, on pain severity and analgesic requirement in the early postoperative period(8).

The reason why diclofenac is preferred from NSAIDs is since it is widely available in our country and it is the most commonly employed analgesic to treat post-operative pain in our country.

In this study major abdominal surgery was also chosen since it is the most commonly performed procedure in our country and one of the types of operations in which postoperative pain and post-operative pain related complications are significant.

Systematic reviews suggest that current preemptive analgesic therapy, e.g. systemic non-steroidal anti-inflammatory drugs (NSAIDs), decreased analgesic consumption but not post-operative pain scores. Although there is a widespread belief of the efficacy of preemptive analgesia among clinicians, large scale randomized controlled trials will be necessary to prove the current concepts(5).

In this study, an effort would be made to find out analgesic efficacy of preemptive diclofenac for management of post-operative pain after Major Abdominal operation. The results of this study will be an important input for deciding to the controversy regarding the effectiveness of preemptive analgesia. If preoperative administration of a single dose of diclofenac reduces post-operative pain intensity, analgesic consumption and extends the time of first analgesic request post-operatively and if it can significantly decrease the incidence of postoperative complications, this will be important contribution to the challenge of post-operative pain management in our country.

CHAPTER TWO: LITERATURE REVIEW

A double blinded, randomized, placebo-controlled study done in India in 2013 which assesses the analgesic efficacy of a Preoperative dose of diclofenac sodium IM in treating postoperative pain associated with Laparoscopic Sterilization shows patients who had received diclofenac sodium 2 hrs. prior had significantly lower incidence of pain during the immediate as well as the early postoperative period (1st and 3rd hour($p<0.05$)) compared to placebo group(21).

In 2015, A single center, randomized, blinded trial was done in Hungary to test the hypothesis that a single 100-mg preoperative dose of diclofenac reduces the intensity of post craniotomy headache, and reduces analgesic requirements. The result shows that visual analogue pain scores (mean (95% CI)) were slightly, but significantly lower with diclofenac group than control group at all times. The study also shows reduced systemic analgesic requirements in diclofenac group, over the initial five postoperative days, compared to control group.($P <0.05$)(22).

A randomized clinical trial done in India in 2012 demonstrates Effect of preemptive rectal diclofenac on post-operative analgesic consumption for repair of cleft palate. The study founds preemptive rectal diclofenac results in effective analgesia in the immediate post-operative period, as shown by decreased pain scores and reduced opioid consumption (P=0.00002)(23).

Study done in Sweden which assesses the effect of preemptive diclofenac in the treatment of post-laparoscopy pain. Preemptive diclofenac group gets better analgesia at 24 hr. compared to control group ($P < 0.05$) and decreased the number of patients who needed additional postoperative analgesia in diclofenac group compared to placebo group ($P <0.05$). (24).

In 2016, a study was done in India that assesses preemptive analgesic efficacy of diclofenac sodium for surgical removal of third molars. Statistically significant difference was found in pain experience during 1st postoperative day(p=0.0153). Patients after receiving preoperative diclofenac sodium 100mg experienced less pain compared to the placebo side. There was no difference in pain experience was found between the study and control group on subsequent postoperative days(7)

RCT was done in Iran in 2014 that compares the effects of preemptive administration of diclofenac suppository and intravenous pethidine in spinal anesthesia. They underwent the study with three groups of patients including a placebo group as a control. The result of comparison between diclofenac and placebo groups shows largest Pain free period in diclofenac group compared to placebo. (P = 0.038)(25).

In 2002 a study done in Turkey investigated the effect of preincisional rectal diclofenac on pain scores and postoperative morphine requirements of children undergoing tonsillectomy after in a randomized clinical trial. The mean VAS score of the diclofenac group was significantly lower than the control group on arrival in the PACU (P < 0.01) and it remained significantly lower in the PACU stay of the children. The mean total morphine consumption of the diclofenac group was less than the control group in the PACU (P =0.012) and in the ward (P =0.021)(26).

Randomized Controlled Trial was done in India, in 2015to assess the efficacy of diclofenac Suppository as a Preemptive Analgesia in Ultrasound-guided Biopsy of Prostate. The study compares preprocedural Diclofenac suppository and Xylocaine gel with Xylocaine gel only in patients undergoing trans rectal ultrasound (TRUS)-guided biopsy of prostate for pain. They concluded that the mean pain score at the time of TRUS probe insertion, immediately after taking biopsy cores, and 2Â hours after biopsy is statistically significantly higher in placebo group than in diclofenac group(27).

A study done in Pakistan in 2009 that evaluates the effectiveness of intramuscular diclofenac sodium for postoperative analgesia when started as preemptive analgesic agent in orthopedic surgery shows significant reduction in postoperative pain in a group for whom preemptive diclofenac was given (p value approx. 0). Preemptive diclofenac also reduced the requirement of rescue analgesics in this group(28).

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CHAPTER THREE: OBJECTIVES

3.1. General Objective

The aim of this study is to assess the effectiveness of preemptive intramuscular diclofenac (75 mg) for postoperative pain management in patients that undergone major gynecologic abdominal surgery in Adama hospital from March to August 2020.

3.2. Specific Objectives

- ✓ To compare difference in pain scores between the treatment and non-treatment groups
- ✓ To compare the time of first analgesic request between the two groups
- ✓ To compare the total analgesic consumption between the two groups
- ✓ To compare the incidence of nausea and vomiting between the two groups

CHAPTER FOUR: STUDY METHODOLOGY

4.1. Study area

This study was conducted in Adama Hospital Medical College. Adama Hospital Medical College was founded in 1938. It is Located in Adama that is around 99 km to the southeast of Addis Ababa. The hospital, which is previously clinical setting start to function as teaching since 2011. It is One of the highest rank government hospitals in Ethiopia regarding patient flow, availability of specialist professionals and wide area of service coverage. The specialty services provided by the hospital nowadays has broadened by providing specialty services like neurosurgery in addition to general and gynecologic surgery. It has eight functional major operation rooms.

4.2. Study design and period

A hospital based prospective cohort study was conducted from March to August, 2020.

4.3. Population

4.3.1. Source population

All patients who were scheduled for elective gynecologic abdominal surgery in Adama Hospital

4.3.2. Study Population

Patients who underwent elective gynecologic abdominal surgery under general anesthesia in the course of study period who fulfilled the inclusion criteria.

4.4. Inclusion and Exclusion criteria

4.4.1. Inclusion Criteria

ASA class I and II patients with gynecologic abdominal surgery were included in the study

4.4.2. Exclusion Criteria

History of chronic pain, Age<18, Use of anti-pains within 6 hrs. preoperatively, Patients with nerve blocks perioperatively and Patients with cognitive impairment were excluded from the study.

4.5. Study Variables

4.5.1. Dependent Variable

- Postoperative pain intensity (NRS score (0-10))
- Time to first analgesic request (in minutes)
- Total analgesic consumption (morphine, tramadol or other analgesics) in the first 24 hrs. after surgery
- Incidence of nausea and vomiting in the first 24 hrs. after surgery

4.5.2. Independent Variables

- ASA Class
- Age
- Weight
- Preoperative diagnosis
- Surgery duration
- Anesthesia duration
- Intra operative analgesic type
- Intra operative analgesic dose
- Exposure variable(diclofenac)
- Induction agent
- Baseline MAP
- Baseline HR

4.6. Operational Definitions

- **Acute postoperative pain** is a pain experienced immediately after surgery usually lasting not more than few days.
- **Anesthesia duration: the** time from anesthesia induction drug administration to extubation.
- **ASA Classification:** is the anesthesia and surgery risk ranking validated by American society of anesthesiologists.
- **ASA I:** a normal healthy patient.
- **ASA II:** a patient with mild systemic diseases without restricted function.
- **Chronic Pain:** a pain that lasts at least 12 weeks.
- **Gynecologic Abdominal surgery:** Any gynecologic surgical procedure that involves opening the abdominal wall through the rectus sheath for gynecological procedures.
- **NRS:** Is one of pain assessment tools that involves asking a patient to rank his or her pain from 0-10 with the understanding that 0 is equal to no pain and 10 the worst pain.
- **Preemptive analgesia** is anti-pain treatment that starts before the time of painful/surgical stimuli.
- **Surgery duration:** the time from skin incision to skin closure
- **Time to first analgesic request:** The time in minutes that is measured from the end of surgery to the first time when the patient requests analgesic postoperatively.

4.7. Sample size and sampling procedure

4.7.1. Sample size

The sample size was calculated based on mean comparison of pain score with equal sample size for two independent cohort. There is no previous study on the effectiveness of preemptive diclofenac for postoperative pain in the study area and we take the results of a similar study done in India in 2016, that shows the mean pain score was 1.80 (±1.19) and 2.53 (±1.11) in the preemptive diclofenac and placebo group respectively in the first 24 postoperative hours(7).

The required sample size shows that 95% likelihood of the mean pain score difference between two groups was calculated as:

$$n_1 = \frac{(\delta 1^2 + \delta 2^2)\,(Z\alpha/2 + Z\beta)^2}{(\mu 1 - \mu 2)^2}$$

Where n_1 = the sample size in each of the groups ($n_1 = n_2$).

μ1 = Sample mean in exposure group.

μ2= Sample mean in non-exposure group.

μ1 - μ2 = the difference the investigator wishes to detect

(σ1)2 = Sample variance in exposure group

(σ2)2= Sample variance in non-exposure group.

Alpha(α) =0.05, Zα/2= 1.96.

Power = 0.80, Zβ= 0.84.

$$n_1 = \frac{(1.19^2 + 1.1^2)\,(1.96 + 0.84)^2}{(1.8 - 2.53)^{\ 2}}$$

n_1=39

Additional 6 patients in each group were included (around 10%) to account for possible attrition rate. Then the sample size for each group is $n_1 = n_2$= 45.

4.7.2. Sampling method

Patients, aged>18, who underwent major gynecologic abdominal operation during the study period that satisfies the criteria were recruited in the study until the desired sample size reaches. Study participant patients were grouped subsequently as Anesthetists giving either preemptive 75 mg diclofenac for post-operative analgesic supplementation, in addition to the usual postoperative analgesic administration for post-operative pain, as Group D or only given post-operative analgesic administration for post-operative pain without the supplementation of preemptive diclofenac as Group N. Systematic random sampling method was used. From Situational analysis on the log book, 200 patients estimated to undergo major gynecologic abdominal surgery during the study period. Ninety participants were recruited with the probability of about 50%. Using the skip interval (k=N/n, 200/90 ~2), N= number of patients during the study period, n = sample size, k = interval. From the two patients, one patient was taken and then the first patient was selected through lottery method in both groups. It takes three extra weeks to reach the number of exposed group equal to unexposed group.

4.7.3. Data collection Procedures

Data was collected by two BSc anesthetists with minimum of two years' experience. Another Senior BSc anesthetist was assigned to assist and supervise the data collectors. Before data collection, training was given for data collectors about NRS scoring system. On the morning of the surgery data collector instructed the patient about self-reporting pain using eleven-point NRS score 0 to 10.

The pain management practice of the hospital was as per WHO post-operative pain management guideline i.e. mild pain (NSAIDs, mainly Diclofenac), moderate pain (NSAIDs (Diclofenac) +week opioid (tramadol)) and severe pain ((NSAIDs (Diclofenac) +week opioids mainly tramadol + any available strong opioids).

There is variation in post-operative pain management practice among anesthetists/clinicians in the study area. In addition to the widely practiced post-operative pain management at the post-operative time, some anesthetists used to practice diclofenac 75 mg intramuscularly 30 min upto1hr before incision (start of surgical procedure) preoperatively for postoperative analgesic supplementation. Some others (the majority) orders post-operative analgesic intervention in the

postoperative time alone. Accordingly; I used this opportunity to assign the study participants in either of the two groups. Patients who received Preemptive,75 mg diclofenac for postoperative analgesic supplementation, in addition to the usual analgesic administration at the post-operative time, were grouped as Group= D, while patients who only receives post-operative analgesic administration at the post-operative time were grouped as Group N. Anesthesia management for the surgery in the study hospital is performed by B.Sc. and M.Sc. anesthesia professionals.

In the postoperative time, patients transferred to recovery room and then to the ward when they recover from anesthesia. In ward follow up of patients is usually by ward nurses and pain management is usually with tramadol and diclofenac based on patient complain and sometimes on Anesthetist/physician order.

During Postoperative period pain intensity, diclofenac and tramadol consumption, time for the first analgesic request as well as incidence of nausea and vomiting were assessed using systematically structured questionnaire by the data collectors in both groups. At ward/PACU, the data collector ask the patient to report their pain based on 11-point NRS score starting from 2^{nd} hour post operatively. NRS score and other variables were documented at the 2^{nd} hour, 4^{th} hour, 8^{th} hour, 12^{th} hour and 24^{th} hour at PACU/wards after end of surgery in both groups. A time in minutes from end of procedure to first request of analgesics were documented. Total analgesia consumption in the first 24 hours also documented. In addition, incidence of postoperative nausea and vomiting is documented in the first 24 hours after surgery.

4.7.4. Data quality management

The data collectors were Trained about the objectives and relevance of the study The data collectors and supervisors also oriented about each item included in the study tools and the whole process of data collection. During data collection, regular supervision and follow up were undertaken. Clean up and cross-checking of data was done before analysis.

4.8. Data analysis and Interpretation

SPSS V-22 and MS-Excel V-16 were used for data analysis. Numeric data were described in terms of mean ± SD or median, Interquartile range. Comparison of numerical variables between study groups were done using two samples z-test and Manny Whitney U test based on whether the data can be presented with mean ± SD or median, Interquartile range respectively. Categorical variables were described as frequency and percentage. Chi-square test was used to test Statistical difference between groups for categorical variables. A p value <0.05 considered statistically significant.

4.9 Ethics committee approval

Before the start of the study, ethical clearance was obtained from Addis Ababa university ethical clearance committee. Official support letter was written to Adama hospital to get permission to data collection. The relevance of the study was explained to each participant. Informed consent was also obtained from each participant by the data collector. Participants who were not willing to participate in the study & those who wish to quit their participation at any stage was allowed to do so without any restriction.

4.10 Dissemination

The final results of the study will be presented to Addis Ababa university department of anesthesia as part of MSc thesis, copies of final results will be disseminated and presented at national conferences and will be sent to national and international journals for publishing.

CHAPTER FIVE: RESULTS

5.1 Sociodemographic and perioperative data

Age, ASA, Weight, Induction agent, Intra operative analgesic type and dose, operation duration and Anesthesia duration, preoperative diagnosis, baseline MAP and baseline HR were compared between the two groups as depicted in Table 1.

Table 1: Socio demographic and operative characteristics data computed by z-test (numeric data) and chi-square test (categorical data)

	Group D(n=45)	Group N(n=45)	P-Value
Age (year) *	32.55±7.82	31.45±8.45	0.448
ASA I / II #	29/16	27/18	0.664
Weight (Kg)*	54.733±5.77	55.800±6.46	0.408
Induction agent#			
Ketofol	28 (62.2%)	27 (60%)	0.996
Ketamine	11 (24.4%)	12(26.6%)	
Propofol	5(11.1%)	5(11.1%)	
Thiopentone	1 (2.2%)	1(2.2%)	
Intraoperative analgesic type#			
Morphine	14 (31.1%)	16(35.6%)	0.655
Pethidine	31(68.9%)	29(64.4%)	
Intraoperative analgesic dose*			
Morphine(mg)	1.24±2.11	1.74±2.47	0.302
Pethidine(mg)	37.78±26.43	33.22±26.93	0.418
Surgery duration (min)*	81.60±25.19	80.70±22.89	0.868
Anesthesia duration(min) *	95.85±26.68	94.20±23.97	0.772
Preoperative diagnosis#			
Benign	41(88.9%)	40(87.5%)	0.725
Neoplastic	4(11.1%)	5(12.5%)	
Base line MAP*	90.10±10.95	89.42±10.79	0.778
Baseline HR*	88.46±10.65	88.35±10.43	0.969

Hint: *Mean±SD ; # Case number

5.2 Comparison of Postoperative Pain Severity by Numeric Pain Rating scale

The median, IQR NRS score between groups at different time were presented as shown below.

Table 2: Comparison of postoperative pain severity using 11-point NRS score (0-10) (Man Whitney U test)

Variables expressed as median, IQR	Group D (n=45)	Group N (n=45)	P value
2nd post-operative time NRS score	1(0-2)	2(1-3)	.007
4thpost-operative time NRS score	2(1-3)	3(2-4)	.004
8thpost-operative time NRS score	2(1-3)	4(3-5)	.001
12thpost-operative time NRS score	3(2-4)	3(2-4)	.261
24thpost-operative time NRS score	3(2-4)	3(2-4)	.796

Hint: IQR-Inter quartile range

The median NRS score were lower in the exposed group (group D) in the2nd 4th and 8th hour with a p value of 0.007, 0.004 and 0.001 respectively as shown in figure below.

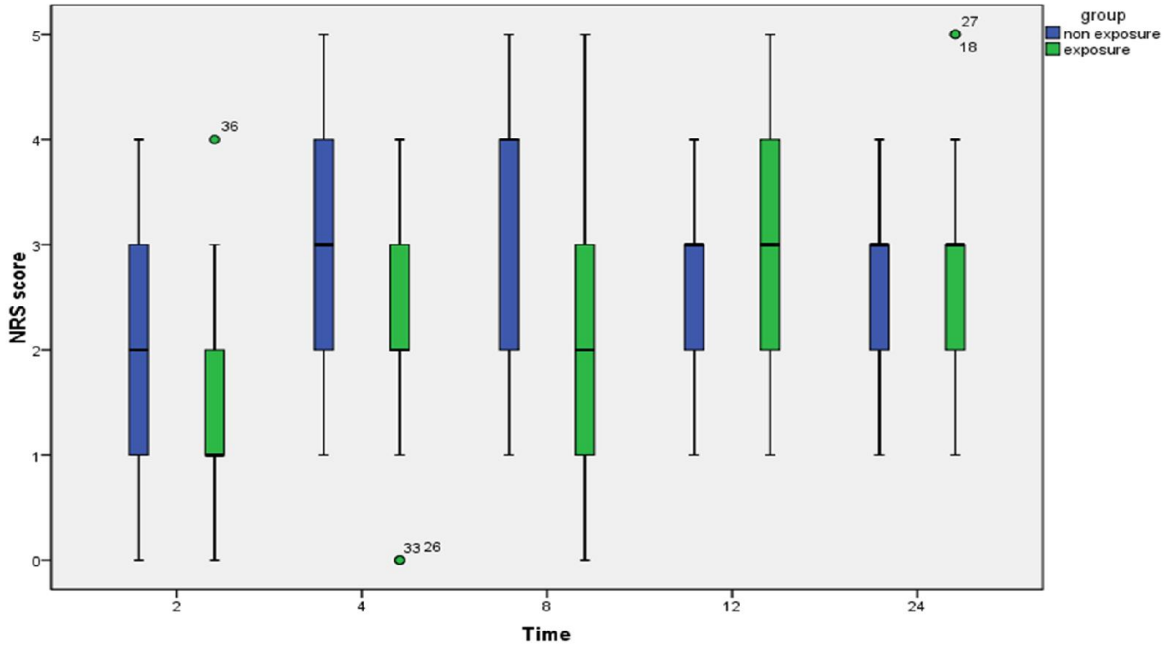

Figure 1: Comparison of postoperative pain using 11-point NRS score (0-10)

5.3 Comparison of time to first analgesia request

The mean time taken for first analgesia request in both groups is presented in the table below. (Table 3).

5.4 Comparison of cumulative analgesia consumption between groups

Mean total 24 hours diclofenac and tramadol consumption for both groups are presented in the table below. (Table 3).

Table 3:Comparison of time to first analgesia request and 24 hours total diclofenac and tramadol consumption(z-test)

	Exposed group(n=45)	Non-exposed group(n=45)	P-value
Time to first analgesia request(minutes)	186.60±35.19	174.45±24.88	.087
Total analgesia consumption within 24hr.			
Diclofenac (IM)	146.25±50.81	187.50±50.95	.0006
Tramadol (IV)	153.75±44.41	174.44±50.57	.0350

5.5 Incidence of Nausea and Vomiting

The incidence of nausea over 24 hours was 37.5%. The proportions of patients with nausea was higher (42.5%) in non-exposed than exposed group (32.5%) (p=0.536). The incidence of vomiting over 24 hours was 15%. The proportions of patients with vomiting was higher (17.5%) in non-exposed than exposed group (12.5%) (p=0.531) as shown in the figure below. (Chi-Square Test).

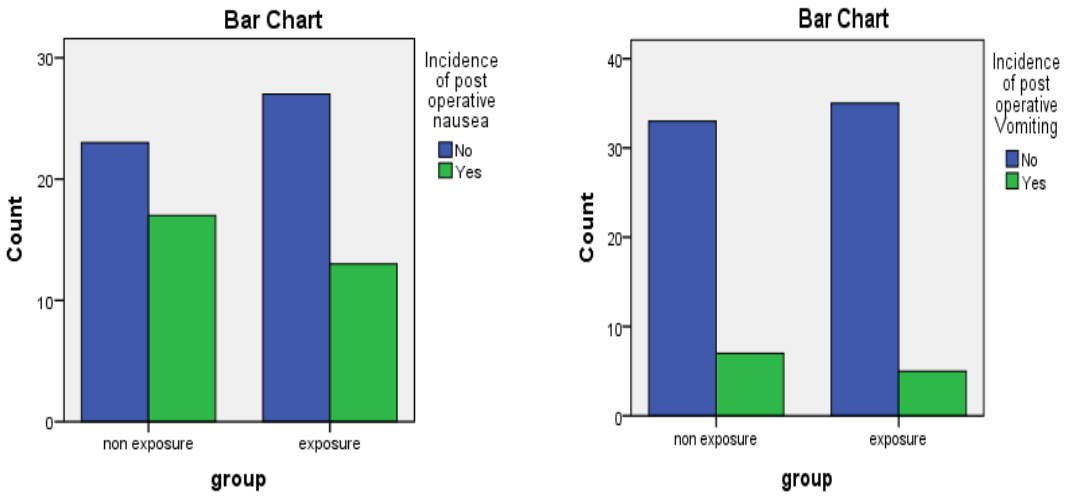

Figure 2:Incidence of nausea and vomiting

CHAPTER SIX: DISCUSSION

This study shows a single preoperative dose of Diclofenac sodium reduced the post-operative pain intensity in the early postoperative hours and significantly reduces analgesic demand for 24hrs. post operatively in patients undergoing elective gynecologic abdominal surgery.

Our study demonstrated that the median (IQR) NRS pain score was significantly lower in exposed group compared to non-exposed group at the 2^{nd},4^{th} and 8^{th}hr. postop: -1(0-2) vs 2 (1-3),2(1-3) vs 3(2-4) and 2(1-3) vs 4(3-5) with a p value of 0.007,0.004 and 0.001 respectively. Statistically significant difference was not observed in the 12^{th} and 24^{th} postoperative hours. The result of this study is comparable with RCT done in Ethiopia showing statistically significant lower median pain score in preemptive diclofenac group compared to placebo group in the 4^{th},6^{th} and 8^{th}post-operativehours. ($p<0.05$). The difference observed between the two studies in the 2^{nd} hour is probably due to the difference in study design(29).Our study has also comparable result with a similar randomized controlled trial done in India which shows significantly lower pain score in the 1^{st},2^{nd} and 3^{rd}postoperative hours($p<0.05$).The likely explanation for the comparability may be the similarity of route of administration and the dose of diclofenac sodium given preemptively(21).The result of this study is in contrary to the result of RCT done in India which shows no significant difference of preoperative administration of diclofenac in the early postoperative hours(2^{nd} and 4^{th}hrs) between treatment and placebo groups($p>0.05$).The likely explanation for this difference may be the route of administration of preoperative diclofenac(rectal route in this case).In addition, the study population in this RCT is pediatrics and this might also takes part in the difference because of the physiologic difference of pediatrics to adults(23).

According to our study, the total post-operative Diclofenac and Tramadol consumption were lower in exposed group. The mean (SD) diclofenac consumption in mg were 146.25±50.81 mg in exposed group compared to 187.50±50.95mg in non-exposed group, p=0. 0006.The mean (SD) tramadol consumption in mg were 153.75±44.41 mg in exposed group compared to 174.44±50.57mg in non-exposed group, p=0. 035.Our result is in line with the RCT done in Ethiopia regarding tramadol consumption. This RCT demonstrates significantly reduced tramadol consumption in preemptive diclofenac group when compared to placebo group, p=0. 001.The likely explanation for this similarity may be both of the studies are done in Ethiopia and the pain management practice and the skill and experience of health professionals tends to be similar (29). The result of our study is also comparable with RCT done in Hungary which demonstrates a single preoperative dose of diclofenac significantly reduced morphine consumption in the five consecutive postoperative days in the treatment group when compared to placebo group($p<0.05$)(22). Similar findings that used diclofenac as post-operative analgesic were not obtained, as most studies uses strong opioids like morphine and pethidine for postoperative pain management.

With regard to time to first analgesia request our study showed non- significant difference between exposed and non-exposed group. The mean (SD) in minute is 186.60±35.19 and 174.45±24.88 between exposed group and non-exposed group respectively ($p = 0.087$). This is in contrary to the RCT done in Ethiopia that demonstrates significant increase in the mean first analgesic request time in preemptive diclofenac group compared to placebo group. The probable difference in the result between the two studies, in addition to the difference in study design, may be the nurse's response to patient's analgesic request(29).

Our result shows the overall incidence of nausea and vomiting in the first 24 hours is 37.5% and 15% respectively. The proportions of patients who experiences nausea is 32.5% and 42.5% in exposed and non-exposed group respectively (p=0.536). The proportions of patients who experiences vomiting is 12.5% and 17.5% in exposed and non-exposed group respectively(p=0.531). Though there is numerically higher proportion in incidence of nausea and vomiting in non-exposure group compared to exposure group, statistically significant difference was not observed. This finding is in line with a randomized controlled trial done in Ethiopia that shows only numerically lower (but not statistically significant) incidence of nausea and vomiting

in the group that takes preemptive diclofenac compared to the group that doesn't take preemptive diclofenac(29).

Multiple studies have demonstrated the effect of preemptive analgesic administration of diclofenac for postoperative pain reduction but some with different route of administration from our study. Our study uses IM route of administration which has a faster onset next to IV route of administration. Other routes of administration like rectal route has prolonged onset compared to IV and IM routes. The effect of IV and IM routes is also more predictable than other routes(30).

Strength and Limitation

Limitation of the Study

- Lack of randomization and control
- Pain severity were not assessed at movement
- Almost all studies we used for comparison were randomized control trial.
- Discussion is limited by the unavailability of adequate studies.

Strength of the study

The study area was selected based on adequacy of patient flow that takes part to take larger sample size.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

Conclusion

We concluded that preemptive intramuscular diclofenac (75mg) reduces NRS pain score and analgesia consumption compared to non-exposure group in patients undergo gynecologic abdominal surgery.

Recommendation

We recommend for anesthetists and other health professionals to consider preemptive intramuscular diclofenac as component of postoperative pain management option for patients that undergo gynecologic abdominal surgery.

We also recommend for researchers randomized controlled study on this area.

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ANNEX

Annex I: Information sheet to get permission for the research

Introduction

This information sheet is prepared with the aim of assessing the effectiveness of preemptive diclofenac for post-operative pain management in patients with gynecologic abdominal surgery. The research team includes Principal investigator, two senior advisors from AAU, two BSc anesthetists for data collection and MSc anesthetist for supervision from Adama Hospital.

Name of Principal investigator: - Yohannes Mebratu (2nd year MSc Student)

Name of advisers: - Mr.Geresu Gebeyehu and Mrs. Selamawit Shiferaw

Name of sponsor: - AAU

Name of organization: - AAU, College of health sciences, Anesthesia department.

Risk

There is no risk or harm you will face as a result of participation in this research.

Benefits

There is no incentive to be gained by taking part in this project. The information collected from this research project will be kept confidential. You can contact the committee by the address below.

Tel: - +251924903877

E-mail:yohannesm5@gmail.com

Annex II: Consent form

English version

Dear participant:

This is a research designed to assess effectiveness of Preemptive diclofenac as part of analgesia for postoperative time for patients with gynecologic abdominal surgery under General anesthesia. As a chance you were included in the study. So, we kindly request your involvement in the study to achieve the objective of the study. However, your honest response to those questions will help us to asses and understand the effect.

Would you willing to participate in the study please? YES/NO

Tel: - +251924903877

E-mail:yohannesm5@gmail.com

Amharic version

የተከበራችሁ የጥናቱ ተካፋዮች

የዚህ ጥናት ዋና አላማ በኦሮሚያ ጤና ቢሮ ስር በሚገኝዉ አዳማ ሆስፒታል ኦፕራሲዮን ክፍል የማህፅን የሆድ እቃ ቀዶ ህክምና የሚደረግላቸው ህሙማን ከጠቅላላ አነስቴዝያ በፊት የሚሰጠው የህመም ማስታገሻ (ዳይክሎፌናክ) ከቀዶ ህክምና በኋላ ህመም በምን ያህል እንደሚቀንስ ለማወቅ ነዉ።በአጋጣሚ እርስዎም በዚህ ጥናት እንዲሳተፉ ተመርጠዋል።የዚህ ጥናት ጥቅም እርስዎ በሚሰጡት ምላሽ መሰረት መረጃዎችን በማጠናቀር በሚገኝዉ ዉጤት መሰረት እየተሰራበት ካለው ጋር ለማገናዘብ እንዲቻል ነዉ።ጥናቱ በትክክል አላማውን እንዲመታ የእርሶዎን ድጋፍ እንጠይቃለን።የማንኛውም ግለሰብ ስም አይመዘገብም እንዲሁም ሀሳቡ ብቻውን ይፋ እንዲወጣ አይደረግም::ሙሉ በሙሉ በምስጥር የተጠበቀ ነው።በጥናቱ መሳተፍ አለመሳተፍ የራስዎ መብት ብቻ ነዉ።ግልፅ የሆነ ምላሽንና ከልብ የመነጨ ተሳትፎዎን እንዲሰጡን በአክብሮት እንጠይቃለን።

ለመሳተፍ ፈቃደኛ ነዎት ?

ሀ/ አዎ ፊርማ …….. (ቃለ መጠይቁን መቀጠል ይችላሉ)

ለ/ አይደለሁም……..(ቃለ መጠይቁን ያቁሙ)

የጥያቄው መለያ ቁጥር ……መጠይቁ የሚካሄድበት ቀን ..... የተጀመረበት ሰአት…. …..

የጠያቂው ስምና ፊርማ---------- ----------

የሱፐርቫይዘር ስምና ፊርማ---------- ----------

ለመሳተፍ ፈቃደኛ ስለሆኑ እናመሰግናለን።

Annex III- Questionnaire

Patient serial Code		
Bed no:		Response
1	Age	
2	Weight	
3	BMI	
4	ASA	
5	Sex	
6	Education status	

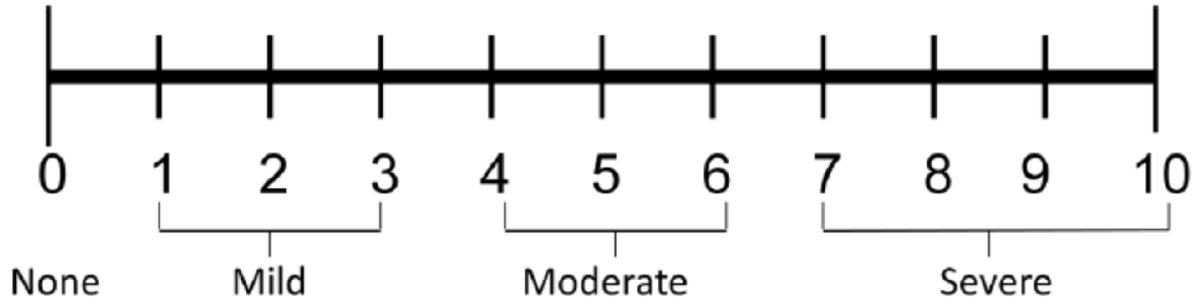
Data during preoperative period(chart review and interview)			
SN	Question	Response	
	Vital sign		
	Base line Heart rate		
	Base line Blood pressure(MAP)		
	Base line RR & spo2		
	Preoperative Numeric rating score		
21	Preoperative Diagnosis	Benign……. Neoplastic……	
22	Performed Procedure:		
23	Surgeon experience(in yrs)		
24	Coexisting medical disease	DM HTN Arthritis	
25	Does the patient take premedication?	▪ Diazepam ----------mg	

		▪ Tramadol ----------mg ▪ Pethidine ----------mg ▪ Morphine ----------mg ▪ Fentanyl ----------mg	
Question related to anesthetic and surgical interventions			
	Question	Response	
30	Type of Induction agent	1. IV 2. Inhalational	
31	Type and dose of medications given at the time of induction	Ketamine----------mg Ketofol----------mg Thiopental ----------mg Propofol ----------mg Suxamethonium--------mg Vecuronium ----------mg Pancuronium----------mg Pethidine----------mg Morphine----------mg Fentanyl----------mg	
32	Vital sign before skin incision	BP:_____mmhg PR:_____bpm Sao2_____%	
33	Vital sign after skin incision	BP:_____mmhg PR:_____bpm Sao2_____%	
34	Additional Intraoperative analgesia given?	1. YES 2. NO Drug/ dose_____	
	Maintenance of Anesthesia MAC/Dose	Halothane _____ Isoflurane _____ Pancronium _____ Suxamethonium _____	

		Vecoronium_____	
35	Duration of surgery		
36	Duration of anesthesia		

	Hemodynamic parameters and analgesia requirement at point of time post-operatively					
	Follow up time	HR	BP mmHg	NRS	Analgesic dose	Analgesic time
40	2^{nd}hr.post op					
	4^{th} hr. post op					
	8^{th} hr. post op					
	12^{th} hr. post op					
	24^{th} hr. post					
41	Total analgesic consumption and type of analgesics					
	Arrival Time @ Recovery Room		Local Time			
42	First analgesia required time		Local Time			
43	Nausea and Vomiting(24hrs post op)					
	Nausea		Present ------ Absent-------			
	Vomiting		Present ------- Absent-------			

English version: numeric Rating scale (NRS)



The scale will be taken 5 times within the first 24 hours. Patients will be asked to rate their pain and recorded at 2^{nd},4^{th},8^{th},12^{th} and 24^{th} hr. post-operatively.

The patient will be asked one of the following questions:

a. What number on a 0 to 10 scale would you give your pain right now?
b. When the explanation suggested above is not sufficient for the patient, further explanation or conceptualization of the scale will be done:

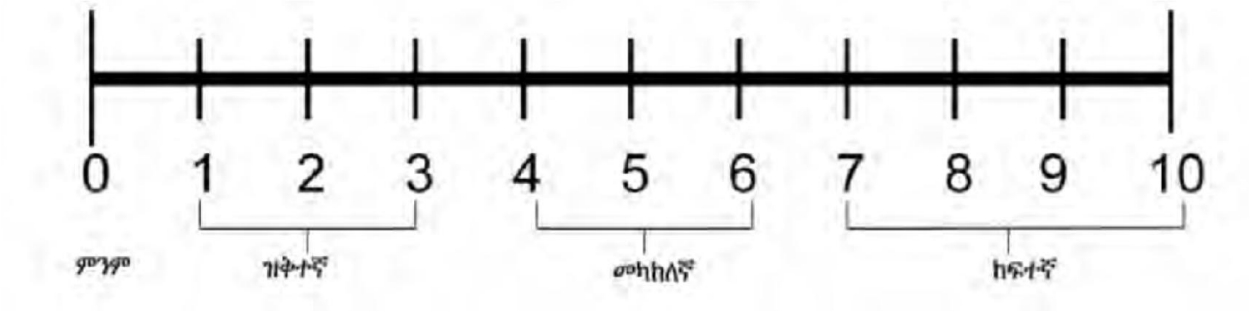
   0 = No Pain

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

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

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

አማርኛ ትርጉም: በቁጥር አምሳያ መለኪያ(VNRS)



ይህ መለኪያ በመጀመሪያዉ 24 ሰአት5 ጊዜ የሚወሰድ ሲሆን.

በሽተኛዉ የሚጠየቃቸዉ ጥያቄዎች

ሀ. አሁን የሚሰማዎትን ህመም በየትኛዉ ቁጥር ይወክሉታል;

ለ. ከዜሮ እስከ አስር ካሉት ቁጥሮች አሁን የሚሰማዎትን ህመም የትኛዉ ቁጥር ይገልፀዋል

ከላይ የተሰጠዉ ማብራሪያ በቂ ሳይሆን ሲቀር ለበሽተኛዉ የበለጠ መረጃ መስጠት አስፈላጊ ሆኖ ይገኛል

0- ምንም ህመም የለም

1-3 - ትንሽ ህመም አለ

4-6 - መካከለኛ ህመም አለ

7-10 - ከባድ ህመም አለ