ADDIS ABABA UNIVERISTY

COLLEGE OF MEDICINE AND OTHER HEALTH SCIENCE

DEPARTMENT OF ANESTHESIA

EFFECTIVENESS OF IV FENTANYL ALONE VS COMBINED WITH PARACETAMOL IN ATTENUATING HEMODYNAMIC RESPONSE TO LARYNGOSCOPIC INTUBATION AND POST OPERATIVE PAIN IN LAPAROSCOPIC CHOLECYSTECTOMY PATIENTS AT GOVERNMENTAL HOSPITALS, ADDIS ABABA, ETHIOPIA, 2025.

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June, 2025

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Declaration

I, the undersigned, declare that this study, “effectiveness of iv fentanyl vs a combination fentanyl with paracetamol in attenuation of hemodynamic responses to laryngoscopic intubation and post-operative pain in patient underwent laparoscopic cholecystectomy at governmental hospital, Addis Ababa, Ethiopia,2025’’ is my original work, fulfilling part of the requirements for my Master of Science degree in Anesthesia. I understand that plagiarism is strictly prohibited, and I affirm that all direct quotations and sources have been properly referenced.

Declared by:

Name: Demisu Dejene

Signature: _____

Date: _____

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Approval sheet

This is to certify that the thesis prepared by Demisu Dejene entitled “effectiveness of iv fentanyl vs a combination fentanyl with paracetamol in attenuation of hemodynamic responses to laryngoscopic intubation and post-operative pain in patient underwent laparoscopic cholecystectomy at governmental hospital, Addis Ababa, Ethiopia,2025’’ is submitted in partial fulfillment of the requirements for the master of science degree in anesthesia with the regulation of Addis Ababa University and meets the standard with respect to originality and quality

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June, 2025.

Addis Ababa, Ethiopia.

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Abbreviations/Acronyms

ASA	The American Society of Anesthesiologists physical state classification
BSc	Bachelor of Science
CI	confidence interval
DBP	Diastolic blood pressure
ETT	Endotracheal tube
EC	Ethiopian calendar
GA	General anesthesia
GC	Gregorian calendar
Group F	Fentanyl group
Group FP	Fentanyl with paracetamol group
IV	Intravenous
HR	Heart rate
LETI	Laryngoscopic and endotracheal intubation
LI	Laryngoscopic intubation
M	Mean difference
MSc	Master of science

MAP	Mean arterial pressure
OR	Operation room
PCM	Paracetamol
SBP	Systolic blood pressure
SPSS	Statistical Package for Social Sciences

ABSTRACT

Background: Laryngoscopy and endotracheal intubation can cause significant increases in heart rate and blood pressure, posing risks for patients with cardiovascular disease. Similarly, inadequate postoperative pain control, such as after laparoscopic cholecystectomy, can lead to serious complications. Minimizing these effects is essential for safe anesthesia and better patient outcomes. Therefore, evaluating iv fentanyl alone vs its combination with paracetamol is essential to enhance anesthesia care and patient outcome in resource limited settings.

Objectives: To compare the effectiveness of iv fentanyl alone vs a combination of fentanyl with paracetamol in attenuating hemodynamic response to laryngoscopic intubation and post operative pain in patient undergoing laparascopic cholecystectomy at governmental hospital, Addis Ababa, Ethiopia,2025.

Method: An institutional based multicenter observational prospective cohort study was conducted on 116 adult patient who underwent laparoscopic cholecystectomy. The hemodynamic parameters like HR, SBP, DBP, and MAP at various time points up to 10^{th} minutes post-intubation were recorded and postoperative pain severity was assessed using NRS. Student's t-test and Mann-Whitney U test for parametric and non-parametric data were used respectively.

Result: The mean heart rate was lower significantly in a combination of fentanyl with paracetamol group compared to fentanyl alone at 1st and 3rd minutes after intubation with p = 0.024, p=0.013 respectively. The MAP was lower significantly in fentanyl with paracetamol group compared to fentanyl alone at 1^{st} and 3^{rd} minutes after intubation with p = 0.009, p=0.01 respectively. No difference in heart rate and blood pressure among the group at 5^{th} and 10^{th} minutes after intubation (p>0.05). Total analgesia consumption was lower in fentanyl with paracetamol group than fentanyl group with $p < 0.05$ and pain severity score was comparable across the group with p-value >0.05.

Conclusion: A combination of fentanyl with paracetamol is more effective in attenuating hemodynamic pressor response to laryngoscopic intubation and post-operative pain severity when compared to fentanyl in patient undergoing laparoscopic cholecystectomy.

Keywords: Hemodynamic response, post-operative response, fentanyl, paracetamol

CHAPTER ONE. INTRODUCTION

1.1. Background

Laparoscopic cholecystectomy is the preferred surgical method for treating gallbladder disease due to its minimally invasive nature. This approach leads to less postoperative pain, faster recovery times, and shorter hospital stays compared to traditional open surgery(1,2). However, despite these benefits, patients undergoing laparoscopic cholecystectomy still experience significant changes in heart rate and blood pressure during laryngoscopy and intubation, and they also experience postoperative pain (3).

Hemodynamic response to laryngoscopic intubation is a critical consideration during anesthesia(4).Endotracheal intubation is a procedure involving tube placement into the trachea through the mouth or nose of a patient to provide needed oxygen and anesthesia (5). Maintaining a patent airway is the primary duty of anesthesiologists toward their patients., which is the most crucial element in preserving healthy, productive breathing. The fact that the gold standard for airway care is tracheal intubation. Laryngoscopy is performed prior to intubation in order to visualize the larynx and surrounding structures(6)

However, during general anesthesia, direct laryngoscopy and tracheal intubation cause sympathetic activation and the release of plasma catecholamines, which clinically appear as tachycardia and hypertension in addition to increased intracranial and intraocular pressure (7).This hemodynamic response is a result of activating α and β adrenergic receptors and mechanically stimulating the laryngopharynx and epipharynx (8).

Evidence from studies suggests that laryngoscopy and intubation are associated with an average increase of approximately 20% in heart rate and 40–50% in blood pressure(9), if preventive measures are not taken, it may lead to serious complications such as myocardial ischemia, ventricular arrhythmias, and cerebral hemorrhage (10),but these may vary depending on a number of variables, including the anesthetic agent used, the level of anesthesia, the anesthetist's experience, the length of the laryngoscopy and intubation, and the precautions taken before airway manipulation(11).

A typical side effect of surgery, especially laparoscopic cholecystectomy, is postoperative pain. It can significantly impact patient recovery, leading to delayed movement, prolonged hospital stays, and lower quality of life(12). Inadequate pain management can also increase the risk of complication, such as pneumonia, blood clots, infection and delayed wound healing, as well as the development of chronic pain(13).

To reduce adverse effects during laryngoscopy and intubation, various techniques have been employed, including increasing anesthesia depth and administering medications (6,8).Therefore, effective management of hemodynamic responses is essential for maintaining patient's health and minimizing discomfort during surgery(14).

To address postoperative pain, various analgesic strategies have been explored, including the use of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjunctive medications such as paracetamol(15). Paracetamol is under the aniline analgesic drug class. Its chemical name is para-acetylaminophenol, and it is the active metabolite of phenacetine. The primary mode of action involves the suppression of the cyclooxygenase enzyme, which triggers the release of prostaglandins, a crucial mediator of pain, fever, and inflammation. Its effects begin within five to ten minutes(11). It has been found to enhance analgesia when used in combination with opioid (16).

Fentanyl is frequently administered to reduce the hemodynamic response associated with laryngoscopy and intubation (5,10,17).It is a powerful synthetic narcotic analgesic with a quick onset and short duration of action; It possesses an analgesic potency that is 75 to 125 times greater than that of morphine (5,6). However, it can have side effects, including respiratory depression and delayed recovery(2).

Therefore, a combining of fentanyl with paracetamol may offer a synergistic analgesic effect and potentially reduce the required dose of fentanyl, thereby minimizing its side effects. Additionally, hemodynamic responses during laryngoscopy and intubation may still require additional interventions, so a combination may also provide additional benefits in attenuating the hemodynamic response to laryngoscopic intubation. By investigating the comparative effects of fentanyl alone and the combination of fentanyl and paracetamol, this study aims to determine the

optimal strategy for managing hemodynamic response and postoperative pain relief in patients undergoing laparoscopic cholecystectomy, thereby improving patient safety and comfort.

1.2. Statement of problem

Postoperative pain management remains a critical aspect of patient care following surgical procedures, particularly laparascopic cholecystectomy, where pain is a common complaint(3).Despite advancements in analgesic techniques, many patients experience significant pain postoperatively, which may result in higher opioid requirements, extended hospitalization, and slower recovery (18).

Manipulation of the airway and discomfort associated with laryngoscopy and intubation can cause a rise in heart rate and blood pressure(19,20). These responses can result the development of arrhythmia, myocardial ischemia, infarction, surgical bleeding, and cerebral hemorrhage in those who are vulnerable, particularly those with cardiovascular comorbidities(5). These may complicate anesthesia. It can also increase the risk of complications and mortality in patients with prior myocardial infarction, coronary artery disease, hypertension, pre-eclampsia, intracranial tumors, elevated intracranial pressure, or elevated intraorbital pressure (21,22).

It is difficult to achieve a deep enough level of anesthesia using only IV or inhaled medications to prevent significant physiological responses to intubation. Therefore, various combinations of anesthetic drugs and adjuvants have been used to enhance the effects of anesthesia while reducing adverse cardiovascular effects to some extent, though with varying effectiveness (23). In addition to this, various analgesic agents have also been used to alleviate postoperative pain perception.

Among these, fentanyl is widely utilized to manage hemodynamic responses during laryngoscopic intubation and to control postoperative pain. However, its effectiveness compared to the combined use of fentanyl and paracetamol is still uncertain. There is a need to explore whether combining intravenous fentanyl with paracetamol can provide better control of the hemodynamic responses and postoperative pain perception compared to fentanyl alone. This study aims to investigate the comparative efficacy of intravenous fentanyl versus a combination of intravenous fentanyl and paracetamol in attenuating hemodynamic responses to laryngoscopic intubation and post operative pain in patients undergoing laparascopic cholestectomy at institutional based, governmental hospital, Addis Ababa, Ethiopia.

1.3. Justification of the study

Although advancements in anesthesia and the broad use of minimally invasive techniques such as laparoscopic cholecystectomy have been achieved, controlling hemodynamic responses particularly heart rate and blood pressure during laryngoscopic intubation remains particularly challenging in patients with cardiovascular comorbidities, as well as managing pain after surgery, remain significant challenges. Those problems can result the patient to develop sudden death due to myocardial ischemia, delayed recover, prolonged hospital stay and increase post operative analgesic consumption which is one of the major cost drivers in the postoperative period. Therefore, effective management of hemodynamic responses and post operative pain is crucial to ensure patient safety and optimal health results.

Intravenous fentanyl is commonly used in our setup to mitigate hemodynamic fluctuations as well as post operative pain. However, there is still different opinions and recommendations among researchers on the effectiveness of paracetamol in terms of hemodynamic stability during intubation and providing post operative pain relief. Some authors suggest that IV paracetamol administration before induction does not attenuate hemodynamic response as significant as inj. Fentanyl and they recommend that it's better to use paracetamol in combination with other drugs to effectively attenuate the hemodynamic response to laryngoscopic intubation. Another author showed that intravenous paracetamol (1g) significantly improved pain relief quality, but it did not lead to a significant reduction in total morphine consumption postoperatively and they recommend that a combination of intravenous paracetamol with opioid medications are better for optimal pain management. This recommendation justifies the need for further investigation. As far as my knowledge and search, there is no local research investigating the potential benefits of combining fentanyl with paracetamol in improving the attenuation of hemodynamic responses and post operative pain relief. This combination may offer a more effective and safer approach to managing hemodynamic instability during laryngoscopic intubation and post operative pain.

This study aims to address this knowledge gap by evaluating the comparative effectiveness of intravenous fentanyl alone versus a combination of fentanyl and paracetamol in mitigating hemodynamic responses and post operative pain. By conducting this research, we seek to provide evidence-based guidelines tailored to the specific demographic and clinical context of Ethiopia. The findings of this study could potentially lead to improved anesthetic protocols,

minimizing adverse hemodynamic effects and enhancing patient safety during laryngoscopic intubation.

Furthermore, this research contributes to the broader field of anesthesiology by potentially introducing a more effective pain management approach that enhances patient outcomes, especially within resource-constrained settings.

CHAPTER TWO LITERATURE REVIEW

2.1. Hemodynamic response to laryngoscopy and Tracheal intubation.

Laryngoscopy and intubation often provoke significant cardiovascular effects, including hypertension, tachycardia, and elevated catecholamine levels (24) and so, it is essential to manage these responses effectively.

A prospective randomized double-blind controlled study done in Egypt (2022) on 60 adult patients, between 20 and 60 years, American society of anesthesiologists grade I and II patient scheduled to underwent surgery under general anesthesia with endotracheal intubation often experience a hemodynamic stress response during laryngoscopy and intubation, characterized by tachycardia, hypertension, and various cardiac arrhythmias(9).

A prospective, randomized control study done in India (2016) on 60 adult patients undergoing elective coronary artery bypass grafting (CABG) were randomly allocated to three groups of 20 each: MC(Macintosh),McGrath(MG)(video laryngoscope), and Truview(TV)(video laryngoscope). Hemodynamic parameters were recorded at multiple time points before and after intubation. In all three groups, heart rate and diastolic blood pressure significantly increased at 0 and 1minute following intubation ($P < 0.05$). Mean arterial pressure rose at 0 minute in the MG and TV groups, and at 1 minute in all three groups ($P < 0.05$). An increase in systolic arterial pressure reached statistical significance only in the TV group at the 1-minute mark ($P < 0.05$) (25).

A systematic review in Indian (2016) found that even though laryngoscope design, duration, and the forces applied to the laryngoscope contribute to hemodynamic fluctuations, the pressor response produced by Macintosh laryngoscopy is superior to others(26).

2.2. Efficacy of fentanyl on hemodynamic response to laryngoscopic intubation and post operative pain relief

Numerous studies have looked at various doses and timings to administer fentanyl and its effect on the intubation response and post operative pain relief. In normotensive ASA I/II patients,

various authors indicate that a dose of 2micg/kg given between 3-5 min prior to LETI suppresses the pressor response and relief post operative pain.

A randomized control trial (RCT) study in Pakistan (2022) was conducted on 92 patients' ASA status I and II, Mallampati class I and II, and patients undergoing elective surgery of both male and female participants aged between 18 and 60 years. Group A patients received lidocaine treatment, while 46 patients in group B were administered fentanyl. Heart rate and MAP were recorded preinduction, postinduction, and postintubation. 1, 2-, 3-, 4-, and 10-minutes showed that attenuating the hemodynamic response was most successfully accomplished by administering IV fentanyl 3 mcg/kg 5 minutes prior to induction (5).

A randomized control trial study done in India (2019) on 90 patients between the age group of 15 to 60 years belonging to ASA classes I and II for various elective surgeries under general anesthesia of both sexes was randomly allocated into three groups: Group A—Inj. Fentanyl 2µg/kg IV, Group B—Inj. Nalbuphine 0.2 mg/kg IV, and Group C—Inj. Normal saline (10 cc) shows that fentanyl is more effective than nalbuphine and normal saline in attenuating hemodynamic stress responses to laryngoscopy and endotracheal intubation and There was no difference in demographic characteristics (age, weight, male-female ratio, height, BMI, and ASA-PS) between the two groups with p-value>0.05 (27).

In contrast, a randomized control trial (RCT) study in India (2018) on 60 ASA grade I and II patients of either sex undergoing general anesthesia for elective surgery. Patients were randomly divided into two groups of 30 patients each. Dexmedetomidine in a dose of 1micg/kg was given to Group A patients and Fentanyl 2 micg/kg was given to Group B patients. Both drugs were administered slowly intravenous 10 min before induction. They conclude that fentanyl 2micg/kg i.v. administered ten minutes before airway instrumentation, it exhibits a variable response to laryngoscopy and intubation. However, dexmedetomidine 1micg/kg i.v. is satisfactory and produces a more favorable hemodynamic profile than fentanyl 2mic/kg, and but they recommend that larger studies are required to strengthen these conclusions (6).

A prospective randomized controlled trial in Asians (2023) on 102 patients of either sex, aged between 18 and 65 years, of the ASA I/II under general anesthesia were divided into two groups of 51 patients each: Group Labetalol-Fentanyl and Group Fentanyl. Group Labetalol-Fentanyl

received 0.25 mg/kg intravenous labetalol diluted in 10 mL saline 5 minutes before intubation, followed by 2 µg/kg fentanyl administered 3 minutes prior to intubation. Meanwhile, Group Fentanyl was given 10 mL intravenous normal saline 5 minutes before intubation and 2 µg/kg fentanyl 3 minutes before intubation. HR, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure were noted down as before intubation, after intubation, at intubation, and immediately after 1, 3, 5, 10 as well as 15 minutes for patients in each group. The findings indicated that, from intubation up to 15 minutes, Group F showed elevated parameters compared to Group LF, likely as a result of the stress response with the differences being statistically significant in both groups ($P < 0.05$). However, there was no any statistically significant between the two groups in terms of demographic characteristics with p-value>0.05 (17).

A randomized, prospective, double-blind study was conducted in India (2016) on 100 patients, ASA-I or II, aged 18-60 years, who presented for elective, non-cardiovascular surgeries and were divided into 2 groups: group C to receive IV Clonidine and group F to receive IV Fentanyl, respectively, administered 5 min. prior to intubation. Each group included 50 patients, and results at 10 minutes post-intubation showed that heart rate reduction was more pronounced with Clonidine compared to Fentanyl, with mean values of 61.84/min and 84.64/min, respectively and this difference was statistically significant ($p < 0.001$).The systolic and diastolic blood pressure also showed a significant suppression ($P <0.001$), with Clonidine showing better results, but there was no significant group difference in the distribution of the age; sex, and BMI with p-value >0.05 (19).

Another randomized control trial (RTC) study done in India (2021) on 60 adult patients of both sexes (ages between 20 and 33), labeled as ASA I and ASA II, undergoing elective surgery were randomly assigned into two groups of 30 each: Group E received 0.5 mg/kg intravenous esmolol, while Group F received 1 µg/kg intravenous fentanyl. Vital signs, including heart rate and blood pressure, were recorded at three stages: prior to induction, following induction, and after intubation. They conclude that esmolol in a dose of 0.5 mg/kg is more effective than fentanyl in a dose of 1 micg/kg in attenuating the hemodynamic response after endotracheal intubation. However, there was no difference between the two groups according to body weight, gender and age with p-value >0.05 (10).

A randomized controlled trial conducted in Korea in 2008 on 56 patients scheduled for elective total abdominal hysterectomy. For postoperative pain, participants were randomly assigned to one of two groups: Group F (28 participants) received fentanyl, and Group R (28 participants) received remifentanil. Pain intensity was assessed using a visual analogue scale (VAS; 0–10), and both the time of the first request for analgesics and the amount of additional analgesia required were recorded. Result show that there were no significant differences in VAS, time to first postoperative analgesics, and additional analgesics between the 2 groups and they conclude that fentanyl is safer for postoperative analgesia than continuous infusion of remifentanil(28)

Another RCT study conducted in Korea (2015), ASA class I/II, age 20-60year undergo either elective total laparoscopic hysterectomy (TLH) or laparoscopic myomectomy under general anesthesia. Patients were randomly divided into two groups for postoperative IV-PCA: one received oxycodone (group O), and the other received fentanyl (group F), indicated that patients on oxycodone consumed significantly less opioid through patient-controlled administration, with an average of 10.1 ± 8.5 mL compared to 16.6 ± 12.0 mL in the control group (P = 0.013)and concluded that oxycodone is a viable alternative to fentanyl for postoperative pain management, as both demonstrated comparable effect (29)

2.3. Efficacy of paracetamol on hemodynamic response to laryngoscopic intubation and post operative pain relief

The effectiveness of paracetamol in minimizing the hemodynamic response to laryngoscopy and intubation is a subject of ongoing debate. Different dosages, timings, and administration routes have been examined in numerous research and the complex nature of pain after laparoscopic cholecystectomy suggests that effective analgesic treatment should be multimodal(30)

A prospective randomized study in India in 2019 on 60 patients of ASA classes I and II undergoing elective surgery under general anesthesia was selected and divided into two groups, each comprising 30 patients. Group P received 20 mg/kg of paracetamol 30 minutes before induction, while Group F received an injection of 1 mcg/kg of fentanyl before induction and recorded hemodynamic response at intubation and 1, 3, 5, and 10 min after intubation and showed that Intravenous paracetamol given 30 minutes before induction helps to reduce the hemodynamic response. but is not as significant as with inj. Fentanyl. They recommend that it's

better to use paracetamol in combination with other drugs to effectively attenuate the hemodynamic response to laryngoscope and intubation.(8)

A double-blinded randomized placebo-control trial study done in Iran (2014) on the effects of paracetamol on cardiovascular responses to tracheal intubation and postoperative pain in the mother and on neonatal Apgar score compared to control (placebo group), which was undertaken on 60 women in ASA I, found that the SBP, DBP, MAP, and HR were controlled significantly better in the paracetamol group than in the placebo group ($P < 0.05$) (31)

A randomized clinical trial study done in Iran 2014 on 62 patients with ASA class I/II who required laryngoscopy and tracheal intubation for elective surgery were assigned to receive propacetamol 2 g/I.V./infusion (group P) or lidocaine 1.5 mg/kg (group L) prior to laryngoscopy. Show that in both groups P and L, MAP increased after laryngoscopy and the changes were statistically significant ($P < 0.001$). Both groups experienced significant changes in heart rate (HR) following intubation ($P < 0.02$). However, the pattern of these heart rate changes differed significantly between the two groups ($P < 0.001$). In Group L, heart rate (HR) increased significantly for up to 9 minutes after intubation ($P < 0.001$), whereas in Group P, HR stayed stable during the same period ($P = 0.8$). Taking propacetamol 2 grams an hour before intubation helps reduce heart rate increases after laryngoscopy, but it doesn't effectively prevent sudden blood pressure changes after intubation (32)**.**

Another prospective randomized control trial study in India (2019) on 160 patients of ASA classes I and II undergoing elective surgery under general anesthesia was selected and divided into two groups. Group A received 1 gram of paracetamol in a 100-ml volume of saline, whereas Group B received 0.9% normal saline infusion in a 100-ml volume. Intravenously (I.V.) thirty minutes prior to induction over fifteen minutes. Conclude that administration of paracetamol (1g) 30 minutes prior to induction of anesthesia could not totally blunt all the cardiovascular responses to laryngoscopy and intubation, but it did show better control of heart rate after intubation.(33).

In contrast, a randomized clinical trial study in 2016 was done in India on 110 patients of ASA I/II, mallampati grades I and II, undergoing elective C/S under general anesthesia. Random allocation of patients in two groups was done (Group A: placebo and Group B: paracetamol).

The placebo group (n = 55) received normal saline, and the paracetamol group (n = 55) received 1 g intravenous paracetamol. The drug was infused an hour before the surgery. Two baseline readings of heart rate, systolic blood pressure (BP), diastolic BP, and mean BP were recorded before induction, and these readings were repeated during intubation, showing that administration of IV paracetamol 1hr before cesarean section has no significant effect in preventing hemodynamic changes at the time of endotracheal intubation(11).

Another randomized, double-blind clinical trial study done India (2020) on 60 patients of ASA physical status I and II, aged 30 to 55 years, undergoing the abdominal surgical procedure of 1 to 3-hour duration were randomly divided into two groups. Patients in group N received nalbuphine hydrochloride 0.15 mg/kg body weight intravenously, 30 minutes before induction. Patients in group P received acetaminophen infusion (paracetamol) 15 mg/kg intravenously, 30 minutes before induction; BP and HR were recorded pre-induction, post-induction, and post-intubation of 1,5, 10, and 15 minutes, showing that there was a significant rise in heart rate and blood pressure after laryngoscopy and endotracheal intubation with acetaminophen (P group) as compared to the N group, in which nalbuphine effectively reduced the tachycardia and hypertension (34).

A single-blind, randomized, prospective, case-control trial conducted in Bangladesh (2019) on 60 adult patients, classified as ASA class I and II, undergoing laparoscopic cholecystectomy were randomly allocated into two groups: Group A received intravenous Paracetamol (10 mg/kg) prior to skin incision, while Group B received a placebo (normal saline). The results demonstrated that patients in Group A required significantly less postoperative opioid analgesia compared to those in Group B ($p=0.012$). Additionally, pain scores were consistently lower in Group A throughout the 24-hour evaluation period ($p=0.027$) and conclude that administration of intravenous Paracetamol as a pre-emptive analgesic effectively reduced postoperative pain and opioid consumption. However, there was no significance difference in demographic data and duration of surgery among groups (35)

A randomized, double-blind clinical trial was conducted in Iran, in 2018, on 240 pregnant women aged 18 to 40 years who were referred for elective cesarean sections. Participants were randomly assigned to either a paracetamol group or a control group, with each group containing 120 individuals. The results indicated that the mean pain scores at 6hr and 24hr post-surgery were significantly lower in the paracetamol group compared to the control group (36)

In contrast, a randomized controlled trial conducted by Rajoria et al. in 2023, which compared the analgesic efficacy of preoperative intravenous paracetamol and ketorolac for patients undergoing laparoscopic cholecystectomy, found that the preemptive administration of 30 mg of intravenous ketorolac is more effective than intravenous paracetamol 1 g for postoperative pain relief, reduction in total analgesia consumption and prolong time for need of first rescue analgesic throughout 24 hours postoperative evaluation with p-value <0.05 (37).

Another randomized controlled trial conducted in 2013 involved 30 patients undergoing laparoscopic cholecystectomy who were randomly assigned to receive either IV paracetamol or standard opioid analgesia. There were no significant differences in age, weight, or surgery duration ($P > 0.05$). However, they found that IV paracetamol (1 g) significantly improved pain relief, as shown by lower Visual Analog Scale (VAS) scores ($P = 0.01$), though it did not significantly reduce total morphine consumption during the first six hours postoperatively ($P = 0.24$). The authors recommended combining IV paracetamol with opioids for better pain control (38), which supports the inclusion of paracetamol in our study.

Furthermore, Aweke et al.'s 2020 randomized controlled trial indicated that, for laparotomy patients, using paracetamol in combination with tramadol or diclofenac preemptively offered better results than using paracetamol alone. These combinations reduced postoperative pain severity, lowered total tramadol consumption, and extended the time until the first analgesic was requested (all with $P < 0.05$)(39). This showed that the possibility that combinations with other agents may yield even better outcomes than paracetamol alone.

Research hypothesis

Effectiveness of iv fentanyl alone versus a combination of iv fentanyl with paracetamol in attenuating hemodynamic response to laryngoscopic intubation and postoperative pain in patient undergoing elective laparoscopic cholecystectomy.

HO: There is no a significant difference in terms of hemodynamic responses (heart rate, blood pressure) between patients receiving intravenous fentanyl alone and those receiving a combination of intravenous fentanyl and paracetamol during laryngoscopic intubation.

HA: There is a significant difference in terms of hemodynamic responses (heart rate, blood pressure) between patients receiving intravenous fentanyl alone and those receiving a combination of intravenous fentanyl and paracetamol during laryngoscopic intubation

HO: There is no difference in terms of 1st analgesia request time between two groups during post-operative period.

HA. There is a difference in terms of 1st analgesia request time between two groups during post-operative period

HO: There is no a significant difference in postoperative pain severity score between the two groups.

HA: There is a significant difference in postoperative pain severity score between the two groups.

HO: There is no significant difference on post operative total analgesic consumption between the two groups.

HA: There is significant difference on post operative total analgesic consumption between the two groups.

CHAPTER THREE. OBJECTIVE OF THE STUDY

3.1. General objective

To compare the effectiveness of iv fentanyl alone versus a combined with paracetamol in attenuating hemodynamic response to laryngoscopic intubation and post operative pain in patient undergoing laparascopic cholecystectomy at governmental hospitals, Addis Ababa, Ethiopia, 2025.

3.2. Specific objectives

- To compare hemodynamic responses (HR, MAP) during laryngoscopic intubation between patient receiving fentanyl alone and those receiving fentanyl with paracetamol.
- To compare the 1st postoperative analgesic request time between two groups.
- To assess the severity of postoperative pain in both groups using a numerical rating scale at 1, 2, 4, 6, 12 and 24 hours.
- To determine total analgesic consumption within the first 24hours post-operatively in both groups.

3.3. Conceptual framework

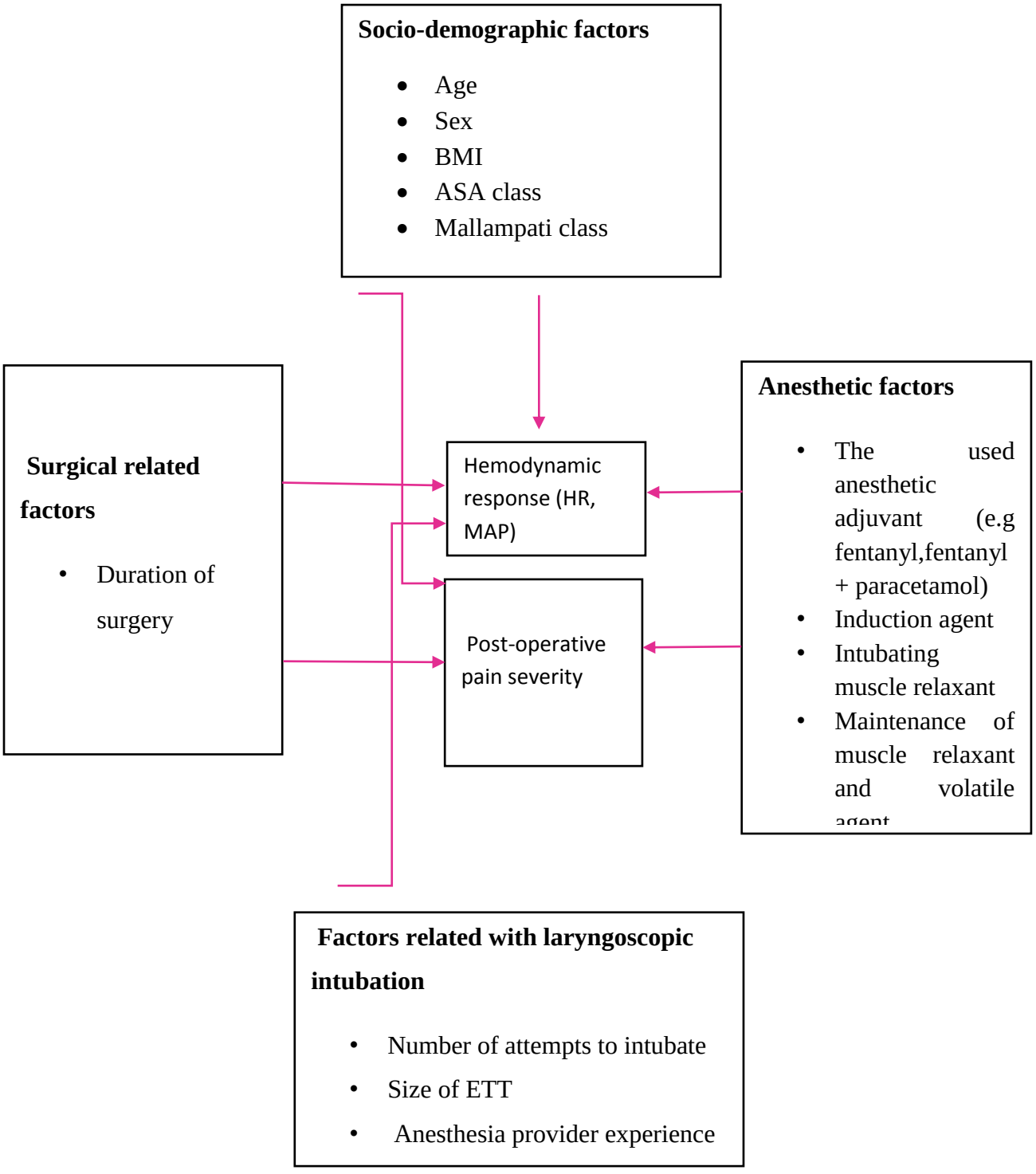


Figure 1.Conceptual frame work for major factors affecting hemodynamic response and post operative pain

CHAPTER FOUR. METHODOLOGY

4.1. Study area and period

Addis Ababa is the capital city of Ethiopia, covering an area of approximately 527 square kilometers. It had an estimated population of almost 4 million in 2023 and it is growing very rapidly like many African cities. The study was conducted at 3 randomly selected Governmental Hospitals, Addis Ababa, Ethiopia from February 01, 2025 to April 30, 2025. Addis Ababa is an important center of diplomacy, and despite being a relatively young city, it offers a good introduction to Ethiopia and its culture. Addis Ababa is home to over 52 hospitals, including 12 public and more than 40 private facilities. While most private hospitals have been established within the last 21 years, all public hospitals date back more than three decades. For the city's estimated four million residents, public hospitals serve as the primary healthcare option, especially for those from middle- and low-income groups. Out of the 12 hospitals, the Federal Ministry of Health (FMoH) administers four, two are under the Army and Police, five are under the city government of the Addis Ababa health bureau and one (Black Lion Hospital) is under the Addis Ababa University, which was given to it in 1998 from the FMoH to be used as teaching hospital.

Zewditu Memorial Hospital, established in 1976 during the Derg regime, is located in Kirkos Sub-City, District 08, Addis Ababa. The hospital is named after Empress Zewditu, a cousin and predecessor of Emperor Haile Selassie. Currently, it is administered by the Addis Ababa Health Bureau. The hospital provides services to an estimated 167,400 people annually across various departments, receiving patients referred from within the city and across the country. It has five major operating rooms, two Post-Anesthesia Care Units (PACUs), and performs an average of 100 laparoscopic surgeries per year.

Menelik II Referral Hospital, established in 1910 E.C. (Ethiopian Calendar), is located in Yeka Sub-City. It provides healthcare services with a surgical bed capacity of 135. The Surgery Department is one of its major departments, equipped with three major operating tables and performing an average of 240 laparoscopic surgeries annually.

Yekatit 12 Hospital Medical College (Y12HMC), located in Addis Ababa, is one of the governmental hospitals in the city, established in 1923. The hospital offers services in various units, including medical, surgical, and pediatric wards, ICU, operating rooms, and recovery rooms. Y12HMC has one obstetric, two burn, one ENT, one maxillofacial, and four general surgery operating theaters. On average, it performs 300 laparoscopic surgeries per year. The hospital also has two Post-Anesthesia Care Units.

4.2. Study design

Hospital based multi-centered observational prospective cohort study was conducted.

4.3. Source and study population

4.3.1. Source of population

All adult patients who had laparoscopic cholecystectomy under general anesthesia with endotracheal intubation at the study hospitals were included

4.3.2. Study population

All adult patients who underwent elective laparoscopic cholecystectomy under general anesthesia with endotracheal intubation and those who fulfill inclusion criteria during the study period.

4.4. Study variable

4.4.1. Dependent Variable

- Hemodynamic response (HR, MAP).
- First analgesia request time.
- Postoperative pain severity (NRS score (0-10).
- Total analgesic consumption (diclofenac, morphine, tramadol or other analgesics) in the first 24 hrs. after surgery.

4.4.2. Independent variable

- Age, sex, weight, BMI
- ASA physical status, mallampati class
- IV induction agent, maintenance of muscle relaxant and volatile agent

- Exposure variable; fentanyl or fentanyl combined with paracetamol
- Surgery duration
- Number of attempts to intubate, size of ETT, anesthesia provider experience.

4.5. Operational definition

Baseline value: Hemodynamic parameters were measured after the patient was brought in to operation room, was defined as baseline value.

Pressor response: It is defined as an increase in hemodynamic parameter (Heart rate, Systolic blood pressure, Diastolic blood pressure and mean arterial blood pressure) by 20% and above from base line(40).

Hemodynamic parameters: heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure which was measured before induction, immediately 1,3,5and 10minutes after intubation.

Fentanyl 2mcg/kg: The usual dose most commonly used for attenuation pressor response during intubation and post operative pain relief.

Paracetamol 15mg/kg: intravenous infusion preparation was 1g in 100ml and 500mg in 50ml for attenuation of pressor response during laryngoscopic intubation and as post operative pain management.

Intubation: insertion of flexible tube or airway device in the trachea or supra glottis.

Laryngoscopy: A device for direct visualization of the trachea during ETT insertion

Endotracheal tube: A plastic tube which are placed in the trachea

Laryngoscopic intubation (LI): Insertion of an airway device or endotracheal tube into the trachea guided by laryngoscopy

ASA status: A surgical risk classification system validated by the American Society of Anesthesiologists, defined as follows:

ASA I: An individual without any organic, functional, or mental health issues

ASA II: controlled medical conditions with mild systemic effect and no limitation of functional ability

ASA III: A severe systemic illness that limits physical activity

ASA IV: Uncontrolled medical conditions that severely impair functional capacity and pose a potential life threat

ASA V: A life-threatening condition with minimal chance of survival without surgical intervention

ASA VI: A patient in a state of brain death undergoing the organ donation process

Mallampati: A method used to assess the difficulty of endotracheal intubation

Mallampati class I- When the soft palate is fully visible

Mallampati class II: When the uvula is fully visible

NRS: A pain assessment tool where patients rate their pain on a scale from 0 to 10, with 0 indicating no pain and 10 representing the worst pain (41).

Post-operative pain: Pain persists up to 24hour after surgery(42)

Preemptive analgesia: An analgesic treatment administered prior to the painful or surgical event (35)

Surgery duration: The period between skin incision and skin closure

Time to first analgesic request: The interval measured in minutes between surgery completion and the patient's initial request for pain relief.

Hypotension: Decreased in SBP by 20% from the baseline(40)

Bradycardia. Decrease in HR by 15% from baseline (40)

4.6. Inclusion and Exclusion criteria

4.6.1. Inclusion criteria

- Elective laparascopic cholecystectomy patient under general anesthesia during the study period.
- Patients age between 18 and 60 years

- American society anesthesiology physical status I and II
- Mallampati class I and II

4.6.2. Exclusion criteria

- Patients with history of cardiac disease.
- Patients with severe respiratory diseases, such as chronic obstructive pulmonary disease (COPD) or asthma,
- Patients with hypertension and on anti-hypertensive medication
- Patients on beta blocker,
- History of allergy to the study drugs
- Patients with predicted difficult intubation such as short neck, BMI>35kg/m^2
- Patient with unanticipated difficult intubation
- Laryngoscopy duration beyond 15second
- Patient who induced with ketamine
- Surgical incision started within 10min of intubation
- Patients who received any other agents to reduce pressor response (lidocaine, magnesium sulfate alpha-2 agonist and opioids other than study drug) before laryngoscopic intubation
- Patients with diagnostic laparoscopy
- Patients unable to communicate or have a psychological disorder

4.7. Sampling Technique and Sample Size Determination

4.7.1. Sample Size Determination

Sample size was calculated using the following two independent sample size formula (comparison of two means) for continuous outcomes based on a previous study done in India.(43), by taking the mean HR and MAP at different times, and the largest sample size was taken using the comparison of two means with an equal sample size formula, which shows a HR mean and standard deviation of 83.53±7.20 mmHg and 80.13±4.84 mmHg among the fentanyl and fentanyl with paracetamol groups, respectively, at 6 minutes after intubation. With the level of significance being 5%, Z = confidence level at 95% (standard value of 1.96) and power of 80%.

$n=[(S1^2+S2^2)\ (Z\alpha/2 +Z\beta)^2]/\ (\mu1- \mu2)^2$

Where

μ1 and S1 are the mean and standard deviation of fentanyl group respectively

μ2 and S2 are the mean and standard deviation of fentanyl with paracetamol group respectively

α = type I error (level of significance)

β = type II error (1-β = power of the study)

Power = the probability of getting a significant result

f (α,β) =7.84, when the power = 80% and the level of significance = 5%

Hence $n= [(7.20)^2 + (4.84)^2\ (1.96+0.84)^2]/\ (83.53-80.13)^2= 51.04516$

$n=51.04516 \approx 52$ patients in each group

Hence, after accounting for a 10% non-response rate in each group, we included 58 patients per group, resulting in a total of 116 adult elective surgical patients in this study.

4.7.2. Sampling Technique

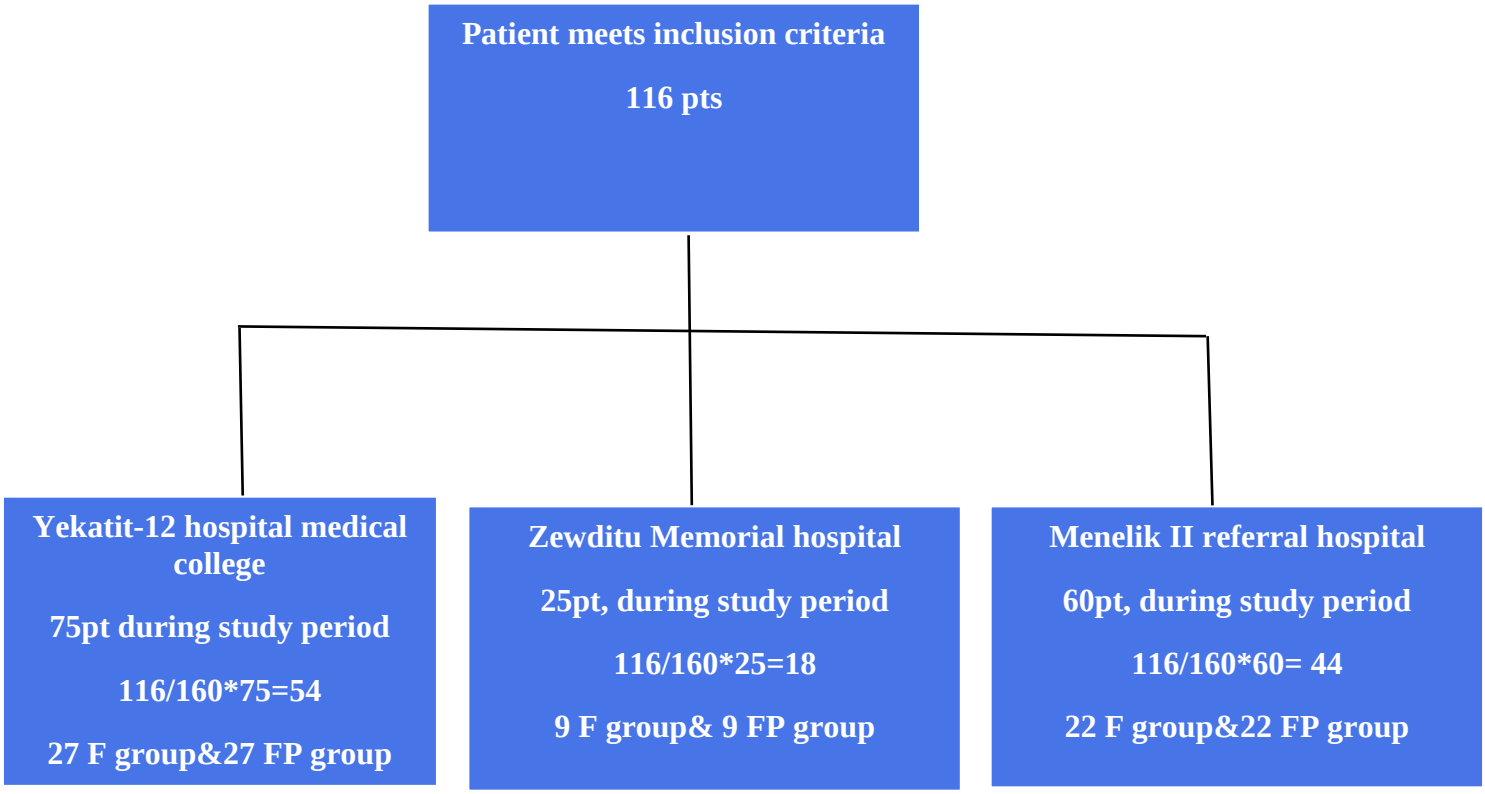
Zewditu Memorial Hospital, Menelik II Referral Hospital, and Yekatit 12 Hospital Medical College were randomly selected as the study area. A situational analysis indicated that, on average, 53 patients meeting the inclusion criteria undergo laparoscopic cholecystectomy per month across these hospitals. Therefore, an estimated total of 160 eligible patients were expected during the three-month study period (N = 160).

Based on the required sample size (n = 116), a systematic random sampling method was employed. The sampling interval (K) was calculated as:

$K = N / n = 160 / 116 \approx 1.37$, which was approximated to 1.

This means that all eligible patients listed in the daily surgical schedule were consecutively included until the desired sample size was achieved.

To know total number patient included in the study period within each study area as follows.



4.8. Data collection technique

Questionnaires were prepared in both English and Amharic, which include demographic data, clinical characteristics, hemodynamic parameters, NRS scoring system, time of first analgesia requires and total analgesic consumption. Before data collection, training was given for data collectors about NRS scoring system. On the morning of the surgery data collector instruct the patient about self-reporting pain using eleven-point NRS score 0 to 10.

Data was collected by one MSc and two BSc anesthetists. Both observations and chart reviews were used to collect the appropriate data. A reviewing patient chart was employed for demographic, anesthesia, and surgery-related factors, whereas the observation includes recording of hemodynamic parameters (HR, SBP, DBP, and MAP) after the patient was brought in to operation room (baseline), before intubation and immediately at the 1^{st} min, 3^{rd} min, 5^{th} min, and 10^{th} minute after intubation from anesthesia monitoring. Patients who received fentanyl 2 mcg/kg three minutes before intubation were categorized as Group F, while those who received both fentanyl 2 mcg/kg (three minutes prior) and paracetamol 15 mg/kg (ten minutes prior to intubation) were classified as Group FP. Procedures including catheter insertion, nasogastric tube placement, and surgical incision were delayed for 10 minutes after intubation to ensure accurate data collection. An additional dose of fentanyl (1 mcg/kg) was administered intraoperatively if both heart rate and blood pressure rose more than 20% above baseline, despite adequate anesthetic depth.

In the postoperative period, pain severity, total analgesic consumption, and time to first analgesic request was evaluated in both groups using a systematically structured questionnaire by data collectors. In the ward or PACU, the data collector asked patients to rate their pain using the 11-point NRS starting from the first postoperative hour. NRS scores and other variables were recorded at the 1st, 2nd, 4th, 6th, 12th, and 24th hours after surgery in both groups. The time (in minutes) of the first analgesic request was recorded, and total analgesic consumption (in mg) over the first 24 postoperative hours was documented for both groups.

During the first 24 hours postoperatively, analgesic treatment was administered when patients either reported pain or had a numeric rating scale (NRS) score of ≥2. The analgesics used—

diclofenac, tramadol, and morphine—were selected based on hospital protocol and availability at the study site.

4.9. Data Quality Control

To ensure quality of data, pre-test of the checklist was performed with 5% of total sample size on patients who fulfill the inclusion criteria at study area before actual data collection and thus data collected for the pretest was not be included in actual sample data. Training and orientation about the objectives and relevance of the study were provided for data collectors and supervisors. Completed questionnaires were submitted and reviewed daily during data collection to prevent data loss. Consistency and completeness were ensured throughout data collection, entry, and analysis.

4.10. Data Analysis and Interpretation

Data was checked manually for completeness and entered into Epi-data version 4.7. Data was cleaned and analyzed with the SPSS version 20 computer program. Normality of the distribution of data was tested by the Shapiro-Wilk test, while homogeneity of variance was assessed using Levene's test for equality of variance. Mann Whitney Test was used to analyze asymmetric numeric data. Comparison of numerical variables study groups were analyzed using student t-test. Normally distributed data was expressed in terms of mean ± SD and while non- normally distributed data was by median and IQR. Categorical data was analyzed by using Chi-square tests and was expressed in percentage. P value<0.05 was considered statistically significant for all analyses. Descriptive statistics were used to summarize data, tables, and figures for display results.

Assumptions which our data fulfilled to be carried out on independent sample t-test:

- ✓ Our outcome variables were measured on a continues scale (HR and MAP)
- ✓ Our independent variable (anesthetics adjuvant) was contained two categorical (independent group), group F and group FP.
- ✓ Independence of the observations were assumed
- ✓ There were no significant outliers in both groups for all data that we ran independent t test.

- ✓ Normality of the data were checked by Shapiro wilk W-test for each and every data that we ran independent t-test and approximately normality was assumed ($p > 0.05$)
- ✓ Homogeneity of the variances were approximately assumed for each and every data that we ran independent t-test by Levene's test of equality of variance ($p > 0.05$)

Assumptions which our data fulfilled to be carried out on Mann-Whitney U-test.

- ✓ Our outcome variables were measured on a continues scale (NRS:0-10)
- ✓ Independence of the observation were assumed
- ✓ Non-normal distribution was assumed
- ✓ The test assumed the shapes of the distributions were similar
- ✓ Different patients in each group were assumed.

4.11. Ethical Consideration

The study was conducted after obtaining ethical approval from Addis Ababa city health bureau, Addis Ababa University's department of anesthesia ethical committee. After the permission from Addis Ababa city health bureau and department of anesthesia ethical committee, an official support letter was written to Zewditu Memorial Hospital, Menelik II Referral Hospital and Yekatit 12 Hospital Medical College and permission for data collection was sought from the hospital authorities. The purposes and importance of the study were explained, and verbal informed consent was obtained from each participant. Confidentiality was maintained at all levels of the study by using an anonymous questionnaire. In addition, all the responses were kept confidential and anonymous.

4.12. Result dissemination plan

This paper will be shared with Addis Ababa University College of Health Sciences, the Ethiopian Association of Anesthetists, and the Addis Ababa City Health Bureau. Following presentations at workshops and seminars, strong efforts will be made to publish the findings in a reputable international journal.

CHAPTER FIVE.RESULT

5.1. Demographic and clinical characteristics of the patients

The analysis and interpretation of the study involved 116 patients, 58 from each group. There were no significant differences between the two groups in terms of age, gender, BMI, ASA physical status, Mallampati classification, induction agent, type and maintenance of muscle relaxant, type and MAC% of inhalational agents, surgery duration, endotracheal tube (ETT) size, number of intubation attempts, and anesthesia provider experience ($p > 0.05$), as shown in Table 1.

Table 1.Demographic and clinical characteristics of the study participants who underwent laparascopic cholestectomy under general anesthesia at governmental hospitals, from February 1- April 30, 2025.

Characteristics		F group(n=58)	FP group (n=58)	P-value
		Frequency (%)	Frequency (%)	
Sex	Male	11(47.8)	12(52.2)	0.816
	Female	47(50.5)	46 (49.5)	
Age(years) (mean ± SD)		39.8±5.95	40.4±7.79	0.612
BMI(kg/m2)(mean ± SD)		22.9±0.9	22.8±1.034	0.563
ASA class	I	39 (50.6)	38 (49.4)	0.844
	II	19 (48.7)	20(51.3)	
Mallampati class	Class I	41 (51.9)	38 (48.1)	0.550
	Class II	17 (45.9)	20(54.1)	
Induction agent	Propofol	41(49.4)	42 (50.6)	0.837
	Thiopental	17(51.5)	16 (48.5)	

Maintenance of muscle relaxant given within 10 minutes	Vecuronium	39 (49.5)	40(50.6)	0.842
	No relaxant within ten minutes	19 (51.4)	18 (48.6)	
Maintenance inhalational agents	Halothane	45(51.1)	43 (48.9)	0.786
	Isoflurane	13(48.1)	14(51.9)	
MAC of inhalational agents	MAC 1%	21 (46.7)	24 (53.3)	0.848
	MAC 1.5%	22(52.4)	20 (47.6)	
	MAC 2%	15 (51.7)	14(48.3)	
	NO	41 (53.2)	36 (46.8)	
No of attempts for intubation	One	44 (51.8)	41 (48.2)	0.529
	Two	14(45.2)	17(54.8)	
Diameter of ETT	6mm	9(56.3)	7(43.8)	0.858
	6.5mm	38(49.4)	39(50.6)	
	7mm	11(47.8)	12(52.2)	
Anesthesia provider experience	BSc student	22(48.9)	23(51.1)	0.695
	MSc student	4(66.9)	2(33.3)	
	One year	16(55.2)	13(44.8)	
	Above one year	16(44.4)	20(55.6)	
Duration of surgery(min)(mean ± SD)		110.14±5.273	109.47±4.227	0.449

Intraoperative Fentanyl (micg)	60.43 ± 8.444	60.34± 8.679	0.957

Data are analyzed by independent sample test and Pearson chi-square (X2) test

Hint: (n = number of participants, (%) = percentage, ASA=American society of anesthesiology physical status, SD = standard deviation, F= Fentanyl, FP= Fentanyl with paracetamol.

5.2. Comparison of mean heart rate at different point of time among fentanyl vs fentanyl with paracetamol groups.

In this study, the independent samples t-test results indicated that the mean heart rate increased in both groups compared to their baseline values. However, the mean heart rate was significantly lower in the fentanyl with paracetamol group (90.09±5.027 bpm) compared to the fentanyl alone group (92.21±4.930 bpm) at the first minute after intubation. The mean difference (M) was 2.4 bpm, with a 95% confidence interval (CI) of [0.617,4.176], t=2.668, and p=0.024.

Mean heart rate was also lower in fentanyl with paracetamol groups compared to fentanyl alone group at third minute after intubation, mean difference (M) = 2.31bpm,95% CI [0.449,4.121], t = 2.527, p = 0.013.

However, there were no statistically significant difference in mean heart rate between fentanyl alone and fentanyl with paracetamol groups at pre-induction(baseline), before intubation,5^{th} min and 10^{th} min post intubation time intervals (p =0.608, 0.234, 0.11, 0.773) respectively (Table 2).

Table 2.Comparison mean heart rate between fentanyl alone and fentanyl with paracetamol

HR (time interval)	F groups (mean ± SD)	FP group (mean ± SD)	P-value
Pre-induction(baseline)	81.47 ±4.835	81.93 ±4.923	0.608
Before intubation	78.76 ±4.570	79.83 ±5.044	0.234
1^{st}min after	92.21 ±4.930	90.09 ±5.027	0.024

intubation			
3rd min after intubation	89.17 ±4.874	86.86 ±4.972	0.013
5th min after intubation	86.09 ±4.547	84.64 ±5.132	0.111
10th min after intubation	82.55 ±4.585	82.81 ±5.045	0.773

Data analyzed by independent sample t-test.

Hint: *PCM=Paracetamol, SD=Standard deviation, F=Fentanyl, FP= Fentanyl with paracetamol, HR=Heart rate*

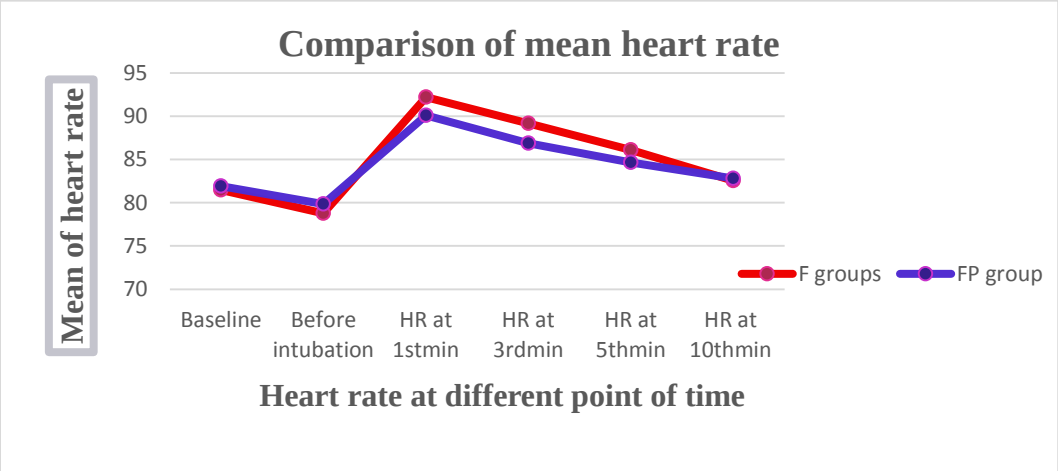


Figure 2.Comparison of mean heart rate at baseline, before intubation, 1st ,3rd, 5th and 10th minutes after intubation between fentanyl and a combination of fentanyl with paracetamol groups

5.3. Comparison of mean blood pressure among fentanyl alone vs fentanyl with paracetamol group.

The independent samples t-test results revealed that the mean blood pressure rose in both groups relative to their baseline measurements. However, the mean blood pressure was lower in fentanyl with paracetamol group (96.57mmHg ± 4.543mmHg) compared to fentanyl alone group

(98.78mmHg ± 4.413) in mean ± SD at first minutes after intubation, mean difference (M) = 2.2bpm,95% CI [0.559,3.854], t = 2.654, p = 0.009. Elevation of MAP also persisted in the fentanyl group up to three minutes after intubation, with a p-value of 0.01. However, there were no statistically significant differences in MAP between the fentanyl alone group and the fentanyl with paracetamol group at baseline, before intubation, and at the 5th and 10th minutes after intubation, with p-values of 0.801, 0.307, 0.163, and 0.416, respectively (see Table 3).

Table 3.Comparison of mean MAP between fentanyl and fentanyl with paracetamol group in study participants who underwent elective laparascopic cholestectomy under laryngoscopic intubation at governmental hospital, Addis Ababa, from February 1- April 30, 2025.

MAP (time interval)	F groups (mean ± SD)	FP group (mean ± SD)	P-value
Baseline	90.69 ±4.362	90.90 ±4.475	0.801
Before intubation	82.98 ±4.470	83.79 ±4.025	0.307
1stmin after intubation	98.78 ±4.413	96.57 ±4.543	0.009
3rdmin after intubation	96.67 ±4.148	94.55 ±4.554	0.01
5thmin after intubation	94.74 ±4.451	93.57±4.451	0.163
10thmin after intubation	92.02 ±4.571	91.33 ±4.524	0.416

SD= Standard deviation, F= Fentanyl, FP= Fentanyl with paracetamol, data was analyzed by independent sample t-test.

5.4. Comparison of 1st analgesic request time between two groups

There was a statistically significant difference in postoperative patient analgesic request time between the two groups. Patients in the fentanyl with paracetamol group requested analgesia at an average of 48.88±2.968 minutes, compared to 46.98±4.951 minutes in the fentanyl alone group (p=0.014) as shown table 4.

Table 4.Comparison of 1st analgesic request minutes between fentanyl and a combination of fentanyl with paracetamol groups.

	F groups	FP groups	P-value
1st analgesia request time(min)(mean ± SD)	46.98 ± 4.951	48.88± 2.968	0.014

F= fentanyl, FP= Fentanyl with paracetamol, SD= standard deviation, data was analyzed by independent sample t-test.

5.5. Comparison of postoperative pain severity by using the Numerical rating scale between two groups.

As post-operative pain severity assessed by NRS the median pain score was comparable between fentanyl group and fentanyl with paracetamol groups at 1st hour, 2nd hour, 4th hour,6th hour, 12th hour & 24th hours post-operatively and showed that there were no differences observed between the two groups in the adequacy of analgesia as assessed by NRS scores. However, the median pain scores were significantly lower in the fentanyl with paracetamol group (Group FP) at the 1st and 2nd hour post-operatively as shown in the table 5.

Table 5.Comparison of post operative pain severity by using the numerical rating scale between fentanyl alone and fentanyl with paracetamol groups.

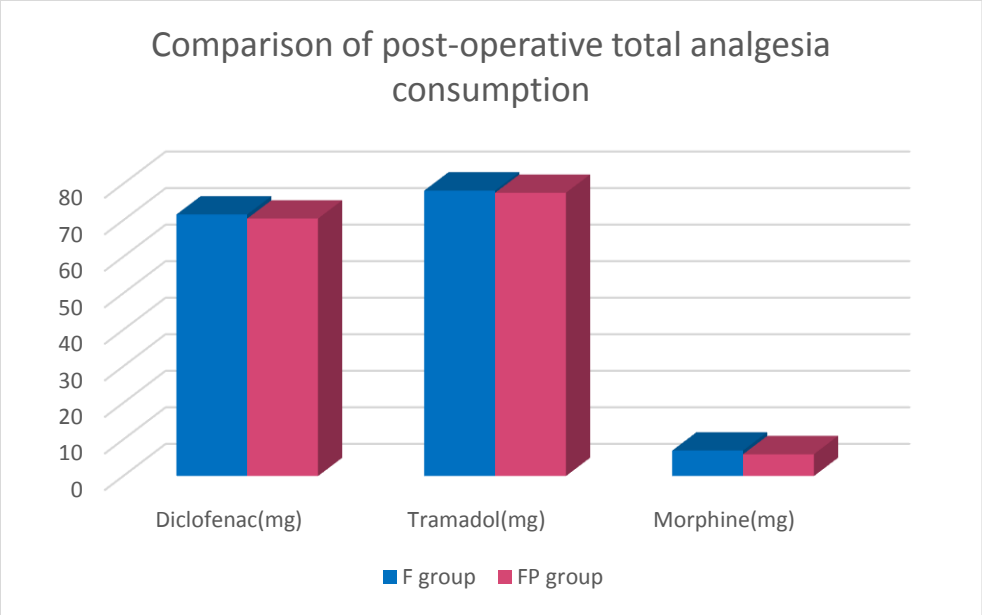
Time interval for	F groups: M(IQR)	FP groups: M(IQR)	P-value

NRS			
1st hour post-operative	5(2)	3(2)	0.243
2nd hour post-operative	3(3)	2(1)	0.120
4th hour post-operative	2(2)	2(1)	0.182
6th hour post-operative	2(1)	2(1)	0.404
12th hour post-operative	2(1)	2(1)	0.311
24th hour post-operative	2(1)	2(1)	0.560

Hint: F= Fentanyl, FP= Fentanyl with paracetamol, NRS= Numerical rating scale, M(IQR)= Median & Inter-quartile range. Data was analyzed by Mann Whitney u-test, P-value <0.05 is statistically significant.

5.6. Comparison of postoperative total analgesic consumption between groups

Independent sample test showed that post-operative morphine consumption was significantly lower in fentanyl with paracetamol group compared to fentanyl group with p-value<0.05. However, there was no statistically significance difference in post-operative diclofenac and tramadol consumption.



Hint: F=Fentanyl, FP= fentanyl with paracetamol

Figure 3: Comparison of the first 24hour post-operative total analgesia consumption in between groups.

CHAPTER SIX. Discussion, Limitation and Strength

6.1. Discussion

Laryngoscopic intubation is a strong painful stimulus that triggers the sympathetic nervous system, leading to catecholamine release and a resulting rise in heart rate and blood pressure. Effective attenuation of this hemodynamic response, as well as adequate post-operative pain management, is especially important in procedures like laparoscopic cholecystectomy, where pain can increase analgesic requirement, prolong hospital stays, and delay recovery(3).

We recognized that several confounding variables such as socio-demographic profiles, clinical characteristics of the patients, and anesthesia-related variations could potentially impact our study outcomes if not addressed. However, these variables were comparable between the two groups, and strengthening the validity of our results.

This study findings revealed that the combination group (FP group) had significantly lower HR and mean arterial pressure (MAP) values at 1st minutes post-intubation compared to fentanyl alone group. Specifically, the mean HR in paracetamol-fentanyl group was 90.09 ±5.027 versus 92.21 ±4.930in the fentanyl group with (p=0.024). Similarly, MAP was also significantly lower in the FP group (96.57±4.543 than in the fentanyl group (98.78±4.413) with p-value=0. 009. These differences persisted at 3 minutes post-intubation for both heart rate and MAP (p=0.013 and p=0.01, respectively). The improved hemodynamic stability in the combination group might be due to the synergistic effect of fentanyl and paracetamol in reducing nociceptive input during laryngoscopic intubation, thereby decreasing sympathetic outflow and promoting cardiovascular stability during the perioperative period.

These findings align with a randomized controlled trial conducted by Gupta et al. (2022), which also demonstrated significantly lower heart rates (85.53 ± 5.03 vs. 90.87 ± 8.40) and systolic blood pressure in the fentanyl-paracetamol group compared to the fentanyl group after intubation ($p<0.01$)(43). There by supporting the synergistic effect of the combination in blunting the stress response.

Several studies have supported these findings: A randomized controlled trial conducted by Pourfakhr et al. (2014) demonstrated that administration of IV paracetamol 30 minutes before

intubation significantly reduced MAP and HR post-intubation compared to placebo with $p<0.05$ (31). This supports the idea that paracetamol may help suppress sympathetic activity, likely through its central pain-relieving effects and its ability to inhibit prostaglandin production.

Similarly, a randomized controlled trial carried out in India in 2017 comparing fentanyl and lidocaine found that the fentanyl group had significantly lower heart rate (82.40 ± 1.66 vs. 89 ± 2.33 bpm) and systolic blood pressure after intubation compared to the lidocaine group, with a p-value of 0.000(44).

In a 2019 randomized controlled trial conducted in India, researchers observed that nalbuphine and fentanyl had comparable effects on heart rate during laryngoscopic intubation. Heart rates for both groups were statistically insignificant and similar at 1, 3, 5, and 10 minutes post-intubation (P = 0.748, 0.685, 0.062, and 0.651, respectively).However, the mean heart rate in the nalbuphine group at the 1st minute after intubation was 95.76 ± 9.31 bpm (12.84%), which was slightly higher compared to the fentanyl group, which recorded 94.96 ± 7.25 bpm (12.97%).Additionally, the mean blood pressure between fentanyl (99.27 ± 5.31 (+5.80%)) mmHg and nalbuphine groups (104.61 ± 6.86 (+10.86%) mmHg) at the above time interval were statistically significant ($P < 0.001$)(27).

In contrast, a study conducted in India in 2021 comparing fentanyl with esmolol found that the mean heart rate after intubation was significantly lower in the esmolol group (80.43 ± 7.682) compared to the fentanyl group (99.90 ± 16.283), with a p-value of 0.000. Although the mean blood pressure was slightly lower in the esmolol group (85.20 ± 6.509) than in the fentanyl group (92.43 ± 20.051), this difference was not statistically significant ($p > 0.05$)(10). However, esmolol might not be the ideal choice because of its potential to cause bradycardia or hypotension in certain patients, thereby supporting the use of fentanyl as a safer and more reliable option in our study.

In the current study, we found no significant difference in postoperative pain severity between the fentanyl group and the fentanyl with paracetamol group. Median pain scores, assessed by NRS, were comparable at 1, 2, 4, 6, 12, and 24 hours post-operatively ($p > 0.05$), indicating similar pain relief between the two treatments. However, significantly lower median pain scores were observed in the fentanyl-paracetamol group during the first and second hours after surgery.

Additionally, the time to first analgesic request was longer in the combination group (48.84 ± 2.29 minutes) compared to the fentanyl group (46.98 ± 5.02 minutes), with a p-value of 0.016.

These results were consistent with findings from Choudhuri and Uppal (2014), who reported that patients receiving a combination of fentanyl and paracetamol had significantly lower pain scores in the early postoperative period compared to fentanyl alone, but not statistically significant and also there were similar finding in terms of first analgesic request time with statistically significant difference between groups, fentanyl group mean analgesic request time was 48±15.8 and the fentanyl with paracetamol group was 76±24.7min with $p<0.05$ (3).This might be due to the initial loading dose of paracetamol, intended to achieve a higher concentration in the plasma.

Similarly, a study conducted by Gousheh et al. (2015) showed that intravenous paracetamol significantly lowered postoperative pain scores and prolonged the time before patients required rescue analgesia following laparoscopic cholecystectomy with $p=0.01$(38)

A single-blind, randomized, prospective case-control trial carried out in Bangladesh in 2019 involved patients undergoing laparoscopic cholecystectomy who were randomly divided into two groups. Group A received intravenous paracetamol before the skin incision, while Group B was given a placebo (normal saline). The findings revealed that pain scores were consistently lower in Group A compared to Group B throughout the 24-hour postoperative period ($p = 0.027$) and also, statistically significant difference was observed, with the paracetamol group having a longer time to first analgesic request than the placebo group ($p < 0.001$) (35). This might also be due to paracetamol works centrally by inhibiting prostaglandin synthesis in the brain and possibly activating descending serotonergic inhibitory pathways.

Furthermore, Aweke et al. (2020) compared paracetamol with other combinations like tramadol and diclofenac in multimodal regimens and found paracetamol-tramadol to be superior in reducing pain and opioid consumption with $p < 0.001$ (39). While this does not directly contradict the findings of this study, it raises the possibility that combinations with other agents may yield even better outcomes than paracetamol-fentanyl alone. The reason for this might be the complementary and synergistic actions of paracetamol and tramadol.

In contrast, a randomized controlled trial by Rajoria et al. (2023), which compared the analgesic effects of preoperative intravenous paracetamol versus ketorolac in patients undergoing

laparoscopic cholecystectomy, showed significantly lower VAS scores and time for need of first rescue analgesic throughout 24 hours postoperative evaluation in the ketorolac group compared to the paracetamol group ($p < 0.05$ (37). This is may be due to ketorolac reduces significantly in prostaglandin synthesis that play a key role in pain sensitization and prolonged duration of action than paracetamol.

In this study the additive effect of combining intravenous paracetamol with fentanyl on post-operative analgesia consumption showed that post-operative morphine consumption was significantly lower in fentanyl with paracetamol group (5.974±1.1973) compared to fentanyl group (6.974 ± 1.4762) in mean ± SD, p-value=0.029. However, there was no statistically significance difference in post-operative diclofenac and tramadol consumption between two groups with p-value> 0.05. The lower need for morphine in the combination group might be due to the synergistic analgesic effects of the two medications working through different mechanisms: paracetamol's inhibitory effect on prostaglandins and activation of descending serotonergic inhibitory pathways, combined with fentanyl's analgesic effect on opioid receptors in the central nervous system.

These findings align with a study conducted by Choudhuri A, Uppal R et al, in comparison of post operative analgesia consumption between fentanyl group and fentanyl with paracetamol group in patient underwent laparascopic cholestectomy observed that the post-operative analgesia consumption was lower in fentanyl with paracetamol group than fentanyl group with p-value < 0.05(3)

A single-blind, randomized, prospective, case-control trial conducted in Bangladesh (2019) underwent laparoscopic cholestectomy were randomly allocated into two groups. Group A was given intravenous paracetamol before the skin incision, while Group B received a placebo (normal saline). The finding revealed that post- operative opioid consumption was significantly lower in paracetamol group than placebo group with p-value<0.001(35).

In contrast to this study finding, randomized controlled trial conducted in 2013 involving a total of 30 patients undergoing laparoscopic cholecystectomy, who were randomly assigned to receive either intravenous paracetamol or standard opioid analgesia. They found that there was no significant difference for intravenous morphine consumption for the post-operative pain control

(P = 0.24)(38). This difference could be because of variations in study design and the smaller sample size of 30 patients.

6.2. Strength

- ✓ Reduces recall bias and allows accurate data collection in real-time
- ✓ Improves the generalizability of the findings across different hospital settings, as it was a multi-centered study
- ✓ Use of validated tools like NRS for pain and standard hemodynamic parameters enhances reliability
- ✓ Addresses a common clinical problem with practical implication for anesthesia practice.
- ✓ Provides evidence on the added value of combing paracetamol with fentanyl.

6.3. Limitation

- ✓ The main limitation in this study is the inability to conduct double blind control study.
- ✓ Most studies used for comparison were randomized control trial.
- ✓ Short follow-up duration: The study only assessed post-operative pain for the first 24 hours, so long-term pain outcomes weren't evaluated.

CHAPTER SEVEN: Conclusion and Recommendation

7.1. Conclusion

The findings of this study demonstrate that a combination of intravenous fentanyl (2μg/kg) and paracetamol (15mg/kg), administered before intubation, was more effective in attenuating the hemodynamic response to laryngoscopic intubation and post-operative pain severity in patients undergoing laparoscopic cholecystectomy compared to intravenous fentanyl (2μg/kg) alone.

7.2. Recommendation

Based on the finding of our study the following recommendation was drawn.

- For better hemodynamic stability, improved early pain control, and less opioid consumption, we recommend routinely giving a combination of intravenous paracetamol and fentanyl during induction.
- Further study with Randomized control trial may need to be conducted to avoid bias.

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ANNEX I: INFORMATION SHEET

Title of the Research Project: Effect of iv fentanyl versus a combination fentanyl with paracetamol in attenuating the hemodynamic response to laryngoscopic intubation and post-operative pain relief in patient undergoing elective laparoscopic cholecystectomy at governmental hospitals, Addis Ababa, Ethiopia, 2025; a prospective cohort study.

Name of Principal Investigator: Demisu Dejene

Name of the Organization: Addis Ababa University, College of Medicine and health science. Department of Anesthesia

Introduction: Greetings! My name is Demisu Dejene. I am a student at Addis Ababa University College of medicine and healthy science Département of anesthesia in MSc in clinical anesthesia. As part of this degree, I am undertaking a research project "Effect of intravenous fentanyl versus intravenous fentanyl and paracetamol in attenuating the hemodynamic response to laryngoscopic intubation and post operative pain in patient undergoing elective laparoscopic cholecystectomy at governmental hospital, Addis Ababa, Ethiopia."

Purpose of the Research Project: To compare effect of intravenous fentanyl versus a combination of intravenous fentanyl and paracetamol in attenuating the hemodynamic response to laryngoscopic intubation and post operative pain at governmental hospital. The information gained from this research will be used to minimize perioperative complications and improving patient outcomes and to select the best alternative solution.

Procedure: The data collection was conducted in Zewditu Memorial Hospital, Menelik Referral hospital and Yekatit 12 Hospital Medical college. Standard questioner was prepared to collect necessary information from patient, chart and from the monitoring device used in the operation room.

Risk and /or Discomfort: The data was taken from patient, medical records and vital sign monitoring device, so it will not impose any harm on patients.

Confidentiality: During data collection the patients name was taken, instead they were identified by their card number in the chart. All questionaries collected were kept confidential and destroyed two years after the end of the project. The information collected was used only for research purpose. The thesis will be submitted for marking to Addis Ababa University Department of Anesthesia College of Medicine and Health Sciences and displayed in the University Library and website. This study will be intended to be submitted for publication in scholarly journals.

Right to Refusal or Withdraw: Approval of the manager of the hospitals and participants were required to start data collection.

Person to contact: If you have any further questions or would like to receive further information about the project, please contact:

1. Demisu Dejene (Principal investigator): +251913567641
2. Dr. Eyayalem(Advisor)
   Ms. Bethelihem (BSc, MSc, Lecturer of anesthesia) (Advisor)

Thank you for reading the Information Sheet, and asking any questions that you might have had.

ANNEX II: CONSENT FORM (ENGLISH VERSION)

Addis Ababa University College of health Sciences, School of graduate studies, Department of anesthesia. Questionnaire prepared to compare the effect of fentanyl and a combination fentanyl with paracetamol on attenuation of hemodynamic response to laryngoscopic intubation and post operative pain in patient undergoing elective laparoscopic cholecystectomy.

This questionnaire will guide data collectors in gathering information.

Dear participant!

Hello! my name is _____ as a member of this research team, I can tell you this questionnaire aims to collect data on how intravenous fentanyl (alone or combined with intravenous paracetamol) affects hemodynamic responses during laryngoscopic intubation and postoperative pain in patients undergoing elective laparoscopic cholecystectomy at a governmental hospital.

I have identified you as a potential study participant and hope you'd be willing to help. With your permission, I'd like to gather some information from your chart, intraoperative data monitoring screen, and your postoperative pain levels. Please be assured that all information from your chart and data monitoring screen will be kept strictly confidential. I won't collect identifying details like your name or exact address. Accurate data directly helps us improve health planning. Thank you for your important role and contribution to this research.

I understood about the purpose of the research. Are you voluntary to participate in the study?

A. YES B. NO

If Respondents are voluntary to participate, the data collection will be started.

For any question or concerns, you can contact the principal investigator using the following address.

Phone number: +251913567641 Email: demisdejen08@gmail.com

ANNEX III: AMHARIC INFORMATION SHEET

የመጠይቅ ፈቃድ

የተከበራችሁ የጥናቱ ተካፋዮች

ጤና ይስጥልን እኔ----------እባላለሁ፡፡

በአዲስ አበባ ዩኒቨርሲቲ በአንስቴዥያ ት/ት ሳይንስ የማስትሬስ ድግሪ ተማሪ ሲሆን የመመረቅያ ፅሁፌን በቀዶ ህክምና ወቅት የአየር ቧንቧ ለመቆጣጠር በጉሮሮ ዉስጥ በሚገባ ቱቦ ምክንያት የሚከሰቱ ችግሮችንና የሚሰማዎትን ህመም ለመቅረፍ ለህሙማን በሚሰጥ መድሀኒት ዙሪያ አቀርባለሁ፡፡ ከዚ ጥናት የሚገኘዉ መረጃ የጤና ባለሙያዎችን በጥሩ ሁኔታ በሽተኞችን እንድረዱ ያግዛቸዋል በተጨማሪም ታካሚዎቹ ለአንስቴዥያዉ የተሻለ ፅዉቀት እንድኖራቸዉ ያደርጋል፡፡ ስለዝህ የርስዎ በ ጥናቱ ዉስጥ መካተት ለዚህ ጥናት መሳካት ከፍተኛ አስተዋጾ አለዉ፡፡ ከርስዎ እና ከ ሕክምና ካርዶዎ በ ሕክምና ወቅት የሚናገኘዉን ማንኛዉም መረጃ ለምርምር አገልግሎት እንደምዉል እየገለጽኩኝ፣ በማንኛዉም ሁኔታ የርስዎ የግል መረጃ ለሌላ አገልግሎት እንደማይዉል ለማሳሰብ እወዳለሁ፡፡

እንድንቀጠል (የ ሕክምና መረጃዎን እንድንዎስድ) ይፈቅዳለ?

አዎ---------- አልፈልግም---------- (ስለ ዕርዳታዎ በቅድሚያ ላቅ ያለ ምስጋና አቀርባለሁ፡፡)

የ አጥኝዉ ስም ና አድራሻ

ደምሱ ደጀኔ

ስልክ ቁጥር (+251)- 913567641

ኢሜይል፡ demisdejen08@gmail.com

አመሰግናለሁ!

ANNEX IV. CHECKLIST

Date: __/____/__

Code. _____

Instruction: For each of the questionaries, please Encircle the number of alternative(s) that fit the response and fill the blank space provided or provide appropriate response accordingly.

PART I: Questions on socio-demographic and physical characteristics of the patient

Sr.no	**Questions**	**Response**	**Code**
1	Age(years)	_____years	
2	Pt.ID	……..	
3	Sex(M/F)	A. Male B. Female	
4	Weight in kg	_____	
5	Height in cm	_____	
6	BMI in kg/m^2	_____	
7	Diagnosis	_____	

8	ASA physical status	A. ASA I B. ASA II	
9	Mallampati class of patient	A. Class I B. Class II	
10	Is there any co existing medical disease?	A. YES B. NO	
11	If yes; specify the disease	_____	

PART II. Questions about anesthetic and surgical characteristics of the patient

Sr.no	Question	Response	Code
1	The used anesthetic adjuvant ten minutes before intubation	A. Fentanyl…….mg B. Paracetamol……mg C. Induction with out fentanyl or paracetamol D. Other (……)	
2	Induction agent	A. Propofol B. Thiopental C. Diazepam D. Halothane E. Other	

3	Intubating muscle relaxant	A. Suxamethonium B. Vecuronium C. Pancuronium D. Specify any others (…….)	
4	Number of attempts to intubate	A. 1 B. 2	
5	Internal diameter of the ETT (mm)	**……**	
6	Anesthesia provider experience	**……..**	

PART III. Peri-operative hemodynamic parameter measurements.

3.Hemodynamic parameter

Sr.no	**Time**	**Hemodynamic parameters**			
		Hert rate	Systolic blood pressure	Diastolic blood pressure	Mean arterial blood pressure
1	Pre-induction (baseline)				

2	Before intubation				
3	1st minutes after intubation				
4	3rd minutes after intubation				
5	5th minutes after intubation				
6	10th minutes after intubation				

4 Maintenance of muscle relaxant and inhalational agent opened immediately after intubation

Sr.no	Question	Response	Code
1	Halothane	A. 1% B. 1.5% C. 2% D. Specify other MAC……	
2	Isoflurane	A. 1% B. 1.5% C. 2% D. Specify other MAC……	

3	Muscle relaxant within 10^{th} minutes of intubation. If there, specify minutes	A. Suxamethonium B. Vecuronium C. Pancuronium D. Atracurium E. No relaxant within 6minutes	
3	Is surgery started within 10^{th} minutes of intubation?	A. YES B. NO if no specify minutes……..	
4	Is opioid given within 10^{th} minutes of intubation?	A. YES B. NO if yes specify minutes……..	
5	Intraoperative fentanyl given in micg/kg?	……	
6	Duration of surgery in minutes?	……	

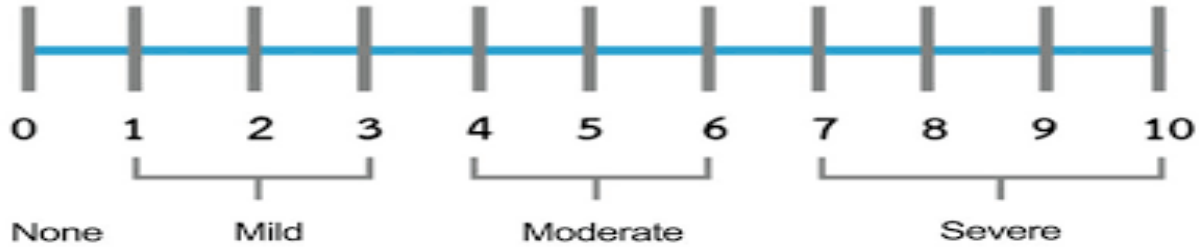
6. Hemodynamic parameters and analgesia requirement at point of time post-operatively

Sr.no	**Follow up time**	**HR**	**BPmmHg**	**NRS**	**Analgesic dose**	**Analgesic time**

1	1st hr post op					
2	2nd hr post op					
3	4th hr post op					
4	6th hr post op					
5	12th hr post op					
6	24th hr post op					
7	Total analgesic consumption(mg) and types of agents					
8	First analgesia required time(min)				Local time……	

ANNEX V. English version: Pain assessment tool(NRS)

Numeric rating scale (NRS)



The scale will be taken 5 times within the first 24 hours. Patients were asked to rate their pain and recorded at 2nd,4th,6th,12th and 24th hr. post-operatively.

The patients were 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:

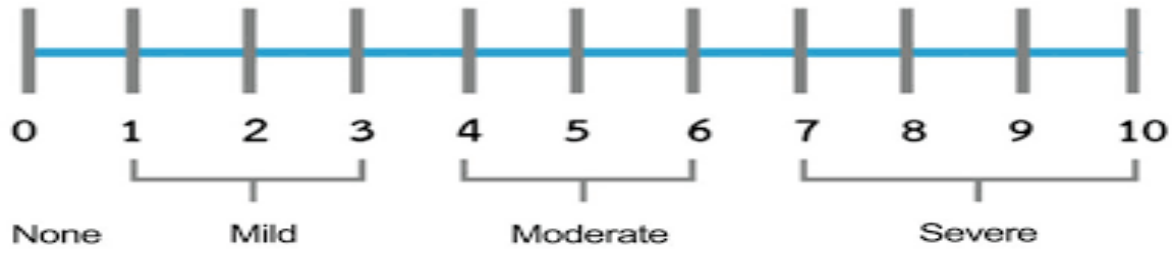
0 = No Pain

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)

ANNEX VI: አማርኛ ትርጉም: በቁጥር አምሳያ መለኪያ (NRS)



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

Name of data collector……Signature

Name of supervisor……Signature