ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
DEPARTMENT OF ANESTHESIA

COMPARISON OF INTRAVENOUS FENTANYL AND LIDOCAINE ON ATTENUATION OF HEMODYNAMIC RESPONSES TO LARYNGOSCOPIC INTUBATION IN ADULT ELECTIVE SURGICAL PATIENTS AT TIKURE ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA.

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Full title of the research project	Comparison of intravenous fentanyl and lidocaine as an anesthetics adjuvant on attenuation of hemodynamic pressor responses to laryngoscopic intubation at Tikure Anbessa Specialized Hospital, Addis Ababa, Ethiopia
Source of found	Addis Ababa University
Total cost of the project	25,000 ETB
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Study Area	Tikur Anbessa Specialized Hospital (TASH)
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ABSTRACT

Back ground: Laryngoscopic intubation is an insertion of endotracheal tube in to the trachea for maintenance of airway during general anesthesia. Smooth intubation requires attenuation of pressor responses and maintenance of baseline hemodynamic stability. In order to control hemodynamic changes during tracheal intubation and extubation, local anaesthetics, opioids, beta-blocking agents, and calcium channel blockers have been used with varying success rates.

Objective: To compare intravenous fentanyl and lidocaine on attenuation of hemodynamic responses to Laryngoscopic intubation in elective surgical patient at Tikur Anbessa Specialized Hospital (TASH) Addis Ababa, Ethiopia.

Methods: An institutional based observational prospective cohort study was conducted on one hundred and Fourteen eligible adult patients at TASH from January 1, to March 30, 2018. The study participants were allocated in to two group; Group F (n =57) patients received fentanyl 2mcg/kg and Group L (n =57) patients received lidocaine (2%) 1.5mg/kg three minute before intubation. Observation and chart review were employed for data collection. Data was entered in to Epi info version 7.2 software by investigators and transported to SPSS version 20 program for analysis. Normality of the data was checked by Shapiro wilk test. Independent t- test was used to determine the mean differences between two groups while paired sample t- test was used to determine the mean differences within the groups. Chi square test was used for categorical variables. Those variables with p-value < 0.05 were considered as statistically significant.

Results: The heart rate was significantly lower in fentanyl group (98.91±15.6 bpm) compared to lidocaine (107 ±15.45 bpm) at first minute after intubation, t (112) =2.8, p = 0.006. Systolic blood pressure was also significantly lower in fentanyl group (141.9±18.9 mmHg) compared to lidocaine (150mmHg ±18.098 mmHg), t (112) = 2.45, p = 0.016. At third minute after intubation heart rate was lower in fentanyl group compared to lidocaine, t (112), p= 0.037. No difference in heart rate and blood pressure among the group at 5^{th} minute after intubation (p>0.05).

Conclusion and recommendations: Fentanyl was better on attenuation of hemodynamic pressor responses to intubation when compared to lidocaine. Therefore, using fentanyl pre-operatively to attenuate pressor responses especial during intubation is important.

Key word: - Hemodynamic Pressor responses, Laryngoscopic intubation, Fentanyl, Lidocaine

Declaration

The under signed certify that the research entitled comparison of fentanyl and lidocaine on attenuation of hemodynamic responses during endotracheal tube intubation at Tikur Anbessa Specialized hospital, Addis Ababa, Ethiopia Institutional based observational prospective cohort study is my original work and any literature and/or data cited in this article were listed in the reference section and any assist done during this period has been given an acknowledgement.

Investigators

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Approval of the Board of Examiners

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Acronyms

ASA - The American Society of Anesthesiologists physical state classification

CI- confidence interval

DAP- diastolic arterial pressure

ETT- Endotracheal tube

GA- General Anesthesia

GC – Gregorian calendar

HR- heart rate

IV- intravenous

LETI- Laryngoscopic and Endotracheal tube intubation

L&I- Laryngoscopy and Intubation

LI- laryngoscopic intubation

M- Mean difference

MAP- Mean arterial pressure

SAP – systolic arterial pressure

TASH - Tikur Anbessa Specialized Hospital.

Chapter one: Introduction

1.1. Back ground:

Manipulation of the airway is one of the most stressing moments of general anesthesia. Laryngoscopy, tracheal intubation and other airway manipulations (e.g., placement of a nasopharyngeal, oropharyngeal or supralaryngeal airway) may cause significant cerebral and systemic hemodynamic responses, including tachycardia, hypertension and increased intracranial pressure (1). This pressor responses are described as an increase in hemodynamic parameters (Heart rate (HR), Systolic blood pressure (SAP), Diastolic blood pressure (DAP) and Mean arterial pressure(MAP)) in 20% and above from baseline value immediately after Laryngoscopy and Endo tracheal tube intubation (LETI) (2). Although these changes are only short-lived and of little consequence in healthy individuals, they may have detrimental effects on the coronary or cerebral circulation of high-risk patients (3).

It has been suggested that distension of the supraglottic tissues is the major cause of the sympatho adrenal response to Laryngoscopy (4). In adults and adolescents, the more common responses to airway manipulation are hypertension (HTN) and tachycardia mediated by the cardio accelerator nerves and sympathetic chain ganglia. This responses includes widespread release of norepinephrine from adrenergic nerve terminals and secretion of epinephrine from the adrenal medulla (5).

Many drugs and techniques have been used to prevent the hyperdynamic responses induced by Laryngoscopy and Endotracheal intubation (1) but no single technique has gained universal acceptance. Topical anesthesia applied to the upper airway is effective in blunting hemodynamic responses to Endotracheal intubation (ETT) (6), but it has almost invariably proved to be less effective than systemic administration of lidocaine. Endotracheal intubation by inhalational anesthetics using doses in the range of the minimum alveolar concentration (1 MAC) resulted in marked cardiovascular stimulation. It should not be surprising that 1 MAC is insufficient, because it is known that approximately 1.5 to 1.6 MAC is needed to block the adrenergic and cardiovascular responses to a simple surgical skin incision (MAC-BAR) (7).

Accordingly, it appears that the dose of volatile anesthetics required to block the cardiovascular response to endotracheal intubation must be inordinately high, this resulting in profound cardiovascular depression before endotracheal intubation (8). Propofol, barbiturates, and benzodiazepines are all associated with profound hypotension at doses that suppress the hemodynamic and intra cranial pressure (ICP) responses to intubation (9).

Cochrane Database of Systematic Reviews in Pakistan (2013) shows effectiveness of multiple pharmacological adjuvants for attenuation of pressor responses; among those Opioids are the adjuvants most commonly administered in addition to other intravenous (IV) or inhaled agents to facilitate induction of anesthesia and subsequent airway manipulation (10). Local anesthetics, calcium channel blockers, beta blockers and narcotics reduced the risk of arrhythmia in the intervention group compared to the control group p-value<0.0001. IV lidocaine may also blunt hemodynamic and cerebrovascular responses to intubation. When given in a bolus of 1.5 mg/kg IV, it adds approximately 0.3 MAC of anesthetic potency (11).

1.2. Statement of the problem:

Hemodynamic pressor responses are a common problem in patients undergoing general anesthesia with laryngoscopic intubation (LI). The mean blood pressure and heart rate is increased by 30% and 22% respectively from baseline values during laryngoscopic intubation (12). This may results in significant moribund outcome including tachycardia, hypertension, ventricular tachycardia and myocardial ischemia.

It is clinically impractical to achieve sufficient anesthetic depth for preventing a hyper dynamic responses to intubation solely with an intravenous (IV) or inhalational agent. Therefore, a wide variety of anesthetics drug combinations, adjuvants, or both have been used in attempts to potentiate anesthetics effects while minimizing hemodynamic depression with varying success rates. Among those dexmedetomidine, beta blocker, opioids and lidocaine are usually used adjuvants (13).

Event though, there were a variety of agent which was used for blunting hemodynamic stress responses to intubation with acceptable outcome, without depressing respiratory and cerebral hemodynamics most of this agents are not available in our country. Thus, considering for good drug with better outcome on attenuation of hemodynamic pressor responses to intubation from the available anesthetics adjuvants in our setup is essential.

Fentanyl acts at opioid receptors and predominantly acts on μ receptors. Fentanyl brings hemodynamic stability during perioperative period by its action on cardiovascular and autonomic regulatory areas. It decreases sympathetic tone and increases parasympathetic tone. Fentanyl inhibits pituitary adrenal response directly or indirectly via hypothalamus. Low doses of fentanyl were employed because a large dose was lead to muscular rigidity, bradycardia, nausea and vomiting. Large doses may also cause postoperative respiratory depression; especially in surgery with short duration of less than 1 hour (14).

Lidocaine attenuates the hemodynamic response to tracheal intubation by its direct myocardial depressant effect, central stimulant effect, and peripheral vasodilatory effect and it also suppresses the cough reflex, an effect on synaptic transmission(15). There was a study done in Nigeria (2001) which shows that lidocaine was effective on attenuation of heart rate response to intubation but it was ineffective on attenuation of blood pressure response to intubation(16).

But a study done in china (2013) shows lidocaine was effective on attenuation of blood pressure response to intubation but not heart rate response and 1.5mg/kg IV lidocaine was popular in clinic(17). There was also a study done in India (2015) shows that lidocaine was ineffective on attenuation pressor response to laryngoscopic intubation and heart rate was above baseline until five minute after intubation(18). In contrary a study done in Turkey (2012) show that when administered before induction and emergency of anesthesia 1 mg kg–1 of lidocaine and 1μg kg-1 of fentanyl are effective in suppressing the hemodynamic response to laryngoscopy, intubation and extubation, but they recommended furthermore studies regarding the dose of those drugs should be required (19). Thus, our study was proposed to investigate and compare intravenous lidocaine and fentanyl on attenuation of hemodynamic responses during intubation.

1.3. Justification of the studies:

Manipulation of the airway is one of the most stressing moments of general anesthesia. Elevation in blood pressure and heart rate due to laryngoscopic intubation are transient but may have significant effects.

The technique, besides minimizing the cardiovascular responses to laryngoscopic intubation may satisfy applicable universally and easily, available in the setup, and attenuate pressor response to intubation with minimal effect on respiratory, cerebral and hemodynamic depression.

Among many cardiovascular drugs which have been evaluated by different literature with respects to their ability to blunt the acute hemodynamic responses to tracheal intubation, lidocaine and fentanyl are widely available in our set up.

There were also literatures which show conflicting results on effectiveness of lidocaine for blunting the acute hemodynamic responses to laryngoscopic intubation.

As far as my knowledge no published data exist on comparison and evaluation of the effects of lidocaine and fentanyl on attenuation of hemodynamic responses to laryngoscopic intubation in my study area.

Since the main task of this study was to assess the effects of fentanyl and lidocaine on attenuation of hemodynamic pressor responses, the result will have an effect on anesthetists to better consider their management protocols. This study might be used as a baseline for further country wide study on this topic.

Chapter two: Literature review

2.1. Hemodynamic response to laryngoscopy and ETT intubation.

Induction of general anaesthesia and endotracheal intubation for maintenance of airway and prevention of aspiration is carried out frequently by the anesthesia professional in day to day practice. Although endotracheal intubation adds tremendous safety to the administration of general anaesthesia, it has deleterious effects especially on cardiovascular system(13).

A prospective study in Britain (2005) show that, sudden increase in blood pressure during LETI may cause rupture of aortic/cerebral aneurysm, increase cerebral blood flow due to increased cerebral metabolic activity and systemic cardiovascular effects. Patients with raised intracranial pressure who have minimal compliance are at risk for herniation and sudden death during LETI unless otherwise attenuated (20).

A randomized control trial (RCT) study in Pretoria (2008) on 80 American Society of Anesthesiologists physical state classification (ASA) I and II patients aged 18 to 65 years scheduled for elective surgery and requiring general anesthesia with intubation show that Blood pressures and heart rates were significantly greater (p value < 0.002 and < 0.009 respectively) after Laryngoscopy followed by Intubation than after Laryngoscopy of the same duration not followed by Intubation (21).

In Tanzania (2013) single blind RCT study on 100 ASAI/ASAII patients, aged 15 to 50 years and mallmapatti I and II found that LETI produces statistically significant rise in hemodynamic parameters as compared to classic LMA insertion in selected patients scheduled for various elective surgeries p value< 0.01 (12). Systemic review in Indian (2016) found that even though, Laryngoscope design, duration and the forces applied on the laryngoscope contribute to hemodynamic fluctuations; pressor response produced by Macintosh laryngoscopy is superior than others (22).

2.2 Lidocaine as an anesthetics adjuvant for attenuation of hemodynamic response.

The effectiveness of lidocaine to blunt the intubation response (IR) is contentious. Numerous studies dating from 1960 have looked at different doses, timing and routes of administering lidocaine. A prospective study done in Nigeria (2001) on effectiveness of intravenous lidocaine in obtunding the circulatory response to intubation found that compared to control (placebo)

group IV lidocaine significantly attenuated the post intubation rise in HR ($p<0.01$) and RPP ($p<0.05$). But the post intubation rise in SAP,DAP and MAP were not significantly affected (16).

A systemic review of 37 randomized controlled trials in china (2013) concluded that, intravenous lidocaine is effective in preventing cardiovascular response to LETI. In the elderly, especially who suffer from cardiovascular and cerebrovascular co-morbidities, lidocaine is effective in blunting the elevation of SAB, DBP and MAP but not HR. In children 1.5 mg/kg dosage of lidocaine is effective and seems to be most popular in clinic (17).

In contrary, analytical study on effects of intravenous lidocaine on pressor response during LETI in Indian (2015) which were undertaken on 50 ASAI and ASAII adult patient undergoing various surgical procedure indicated that IV lidocaine is less effective to attenuate the pressor response and they recommend a better alternative should need to be used after further comparative studies (18). The principal limitation when comparing studies is heterogeneity of the studies. Various doses, timings, pre medications and induction agents are used.

But in contrary a study done in Iran (2015) on 86 ASA II hypertensive patients which compare clonidine and lidocaine on attenuation of pressor response to laryngoscopic intubation show that lidocaine 1.5 mg/kg was effective on attenuation of pressor response immediately after intubation(23).

2.3 Fentanyl as an anesthetic adjuvant for attenuation of hemodynamic response.

Numerous studies have looked at various doses and timing to administer Fentanyl and its effect on the intubation response. In normotensive ASA I/II patients various authors indicate that a dose of 2μg/kg given between 3-5 min prior to LETI suppress the pressor response.

Prospective study in Japan (2002) indicated that fentanyl suppresses the hemodynamic response to endotracheal intubation more than it suppresses the response to laryngoscopy. When an anesthesiologist attempts to reduce hemodynamic responses to orotracheal intubation by avoiding laryngoscopy, the co administration of a small dose of fentanyl is recommended before the induction of anesthesia (24).

Randomized and double-blinded study done in Indian (2006) reported that given 5 minutes prior to intubation, lidocaine (1.5 mg/kg) and fentanyl (2 μg/kg) both attenuated the rise in pulse rate, SBP and DBP. But the fentanyl group showed clinical significantly lesser rise (5.46%) in HR

compared to lidocaine (16.23%) (p=0.018) and Control group (43.68%) (p=0.000). The rise persisted for 2, 5 and 10 minutes in fentanyl, lidocaine & control groups respectively (25).

Prospective study of hundred and twenty patients (aging from 18 to 65, ASA class I or II) in Turkey (2012) was randomly divided into 4 groups. Fentanyl 1μg kg-1 (n = 30), Esmolol 1 mg kg-1 (n =30), Lidocaine 1 mg kg-1 (n = 30) and NaCl 0.9% 10 mL (Control group, n = 30) were administered before induction and extubation. They concluded that When administered before induction and emergency of anesthesia 1 mg kg–1 of esmolol and lidocaine, and 1μg kg-1 of fentanyl are effective in suppressing the hemodynamic response to LETI and extubation when compared with control group (P< 0.01) (19).

Prospective randomized study in Indian (2017) to compare Fentanyl, Lidocaine and Placebo for attenuation of cardiovascular response to direct LETI during General Anaesthesia reported that the heart rate, systolic and diastolic blood pressure responses during laryngoscopy and intubation have shown significant difference with fentanyl and lidocaine when compared with the placebo group (26). This study confirms that Fentanyl attenuates both the heart rate and blood pressure responses effectively to direct laryngoscopy and intubation, whereas with Lidocaine blood pressure was effectively controlled than heart rate.

Various drugs combination and techniques have been used for blunting the hemodynamic response to LETI with variable degrees of success. A prospective, randomized, double-blind trial on 37 patients with hypertension in Iran (2013) to evaluate and compare the efficacy of fentanyl and fentanyl plus lidocaine in attenuating the hemodynamic responses to LETI reported that Fentanyl and fentanyl plus lidocaine effectively decreased the hemodynamic response to tracheal intubation, however, neither fentanyl nor fentanyl plus lidocaine, could inhibit all hemodynamic responses, moreover fentanyl plus lidocaine was not more effective than fentanyl alone (27).

Research Hypothesis:

- ✓ **HO:** There is no a significant difference between intravenous fentanyl and lidocaine on attenuation of hemodynamic pressor response to Laryngoscopic intubation.
- ✓ **HA:** There is a significant difference between intravenous fentanyl and lidocaine on attenuation of hemodynamic pressor response to Laryngoscopic intubation.

Chapter three: Objective of the study

3.1 General objective:

To compare intravenous fentanyl and lidocaine on attenuation of hemodynamic responses to laryngoscopic intubation in elective surgical patient undergoing general anesthesia at TASH, Addis Ababa, Ethiopia, 2018

3.2 Specific objectives:

To compare intravenous lidocaine and fentanyl on attenuation of heart rate response to laryngoscopic intubation.

To compare intravenous of lidocaine and fentanyl on attenuation of blood pressure response to laryngoscopic intubation

Chapter Four: Methods and material

4.1 Study Area and period:

This study was conducted in Tikur Anbessa specialized Hospital (TASH) which is one of the largest teaching and referral hospital in the country since its establishment in 1972. TASH is now the main teaching hospital for clinical and preclinical trainings of most disciplines. Annually more than 6,000 people are operated for different surgical conditions in the Hospital. The hospital has 12 operation rooms which include 9 in the main operation room, 1 in obstetric unit and 2 in orthopedic department. The study was conducted from January 1, 2018 to March 30, 2018G.C.

4.2 Study design:

An institutional based observational prospective cohort study was conducted. The non-exposed group/comparison group where lidocaine group (took lidocaine 1.5mg/kg) and as it was usually used fentanyl group (took fentanyl 2mcg/kg) where considered exposure

4.3. Source and study Population:

4.3.1 Source population: All adult patients who were scheduled for elective surgeries under general anesthesia with Laryngoscopic intubation in Tikur Anbessa Specialized Hospital.

4.3.2 Study population: All adult patients who underwent elective surgeries under general anesthesia with Laryngoscopic intubation in the study period and those who fulfilled inclusion criteria were included in the study.

4. 4 Eligibility Criteria:

4.4.1 Inclusion criteria were:

- ✓ Elective surgeries under general anesthesia with laryngoscopic intubation during the study period.
- ✓ Patients age between 18 and 65 years
- ✓ American society anesthesiology physical status I and II

4.4.2 Exclusion criteria were:

- ✓ Patients with history of cardiac disease; a three-fold increase in plasma noradrenaline levels which returned to baseline nearly 10 minutes following laryngoscopic intubation was observed in hypertensive patients(5). Therefore these patient groups need to be studied exclusively.
- ✓ Patients with uncontrolled hypertension;
- ✓ Patients on beta blocker,
- ✓ Patients with difficult intubation,
- ✓ Obstetric patient, and
- ✓ Neurosurgical patient were excluded.

4.5 Variables:

4.5.1 Dependant variable:

Hemodynamic responses (HR, SBP, DBP)

4.5.2 Independent variable:

- Age, sex , weight
- ASA physical status
- IV induction agent
- Exposure variable; Lidocaine or Fentanyl

4.6 Sample size and sampling technique:

4.6.1 Sample size determination

Sample size was calculated using the following formula (Comparison of two means) for continuous outcomes based on a previous study done in India(26) which showed a DBP mean and standard deviation of 86 $\pm$ 4.04 mmHg and 84 $\pm$3.27 mmHg among the Lidocaine and Fentanyl groups respectively after intubation. With level of significance being 5%, Z= confidence level at 95% (standard value of 1.96) and power of 80%.

$$n = \frac{(S_1^2 + S_2^{2)}(Z\,\alpha/2 + Z\beta)^2}{(\mu_1 - \mu_2)^2}$$

Where

$Z \alpha/2 = 1.96$ for a $p = 0.05$ (95% confidence interval)

$Z\beta = 0.84$ for 20% beta error

S = standard deviation

μ= SBP mean

$$n = \frac{(4.04)^2 + (3.27)^2}{(86 - 84)^2} (1.96 + 0.84)^2$$

$n = 53.015956 \approx 54$ patients in each group

By adding 5 % for non-respondent rate in each group, 57 patients were included in the each group. Totally 114 patients were included in this study.

4.6.2. Sampling technique:

Systematic random sampling technique was used till to get the required sample size during the study period. The daily operation schedule list was used as a sampling frame. The situational analysis showed that 18 patients who fulfill our inclusion criteria were operated in TASH per week; according to this data we had 216 patients in our study period from whom we collected data from only 114 patients. So, sampling interval (**k**) was calculated as K=N/n= 216/114 = 2, where N= total study population, n= total sample size. The first participant (random start) was selected using lottery method. Then, every second patients were included in this study from the daily operation schedule list.

4.7 Data collection technique and instrument:

Checklists which prepared in English were used to collect data. After providing training for data collectors, data were collected by one MSc and two BSc Anesthetists. Both observations and chart reviews were used to collect the appropriate data. Reviewing Patients' chart where employed for demographic, anesthesia and surgery related factors whereas the observation including recording of hemodynamic parameters (HR, SBP and DBP) before intubation(baseline), and immediately at first minute after intubation, third minute after intubation and fifth minute after intubation from anesthesia monitoring. If the anesthesia providers gave fentanyl 2mcg/kg three minute before intubation for the patients, the data were

recorded as group F as well as if lidocaine 2% (1.5mg/kg) was given three minute before intubation the data were recorded as group L.

Any surgical interventions like catheterization, nasogastric tube insertion, and incision were requested to do five minutes after intubation to avoid disturbances in data recording.

4.8 Data quality control:

To ensure quality of data, pre-test of the checklist have been performed with 5% of total sample size on patients who fulfill the inclusion criteria at TASH. Training and orientation about the objectives and relevance of the study were provided for data collectors and supervisors. During data collection the completed questionnaire has been submitted and reviewed daily to avoid loss of data. Data consistency and completeness have been made throughout the data collection, data entry and analysis.

4.9 Data analysis and interpretation:

Data was checked manually for completeness and then coded and entered into Epi-info version 7.2. Data was cleaned and analyzed with SPSS version 20 computer program. Normality of the distribution of data was tested by the Shapiro-wilk test and Histogram with superimposed curve. Comparison of numerical variables within the study group and between study groups was done with paired student t- test and unpaired student t- test respectively. Data was expressed in terms of mean ± SD. Categorical data were assessed by Chi-square tests. P value <0.05 is considered statistically significant for all analysis. Descriptive statistics was used to summarize data, tables and figures for display results.

4.10 Ethical consideration:

The study was conducted after obtaining ethical approval from Addis Ababa University, department of anesthesia ethical committee. After the permission from department ethical committee, Official support letter was written to Tikur Anbessa Specialized Hospitals and permission for data collection was sought from the hospital authorities. The purposes and the importance of the study were explained & verbal informed consent was obtained from each participants. Confidentiality was maintained at all levels of the study by using anonymous questionnaire. In addition all the responses were kept confidential and anonymous.

4.11 DISSEMINATION PLAN:

This paper will be disseminated to Addis Ababa University College of health science, Ethiopian Association of Anesthetists and Federal Ministry of Health. After presentation on workshops and seminars, Great effort will be made to publish the finding on international rebuttable journal.

4.12. Operational definition:

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 (Khan AA and Khan FA, 2009) (2).

Hemodynamic parameters: heart rate , systolic blood pressure ,diastolic blood pressure and mean arterial blood pressure which are measured before intubation (base line), 1 minute after intubation ,3 minute after intubation and 5 minute after intubation.

Fentanyl 2mcg/kg: The usual dose most commonly used for attenuation pressor response during induction of anesthesia.

Lidocaine (2%) 1.5 mg/kg: Intravenous preparation plain lidocaine used for attenuation of per operative arrhythmia.

Intubation: insertion of flexible tube or airway device in the trachea or supra glottis. **Laryngoscopy:** A device which are used to see a trachea during placement of ETT.

Endotracheal tube: Advice (plastic tube which are placed in the trachea) which are used to secure airway during GA.

Laryngoscopic intubation (LI): Insertion of flexible tube or airway device in the trachea by using laryngoscopy.

ASA I: patient with mild systemic and medical illness unless otherwise, indication for surgery

ASA II: Patient with moderate systemic/medical illness which don't affect daily activity

Attenuation: Decrease hemodynamic responses induced by laryngoscopic intubation

Hypotension and bradycardia: Decrease in SBP and HR by 20 % and 15% from baseline respectively(2).

Chapter five: Results

5.1. Demographic and clinical characteristics of the patients.

A total of one hundred and fourteen respondents were participated in this study. Out of 114 respondents 57 were group "F" and 57 were group " L", all were included in the study as they were complete and showed consistency of responses. There was no significant difference between two groups in mean age, mean difference (M) = 0.667, 95% CI [-3.97, 5.3], t (112) = 0.285, p = 0.776, the minimum and maximum ages were 18 and 65 years respectively in group ''F'' and 18 and 62 years in group ''L''. The demographic status and clinical characteristics of data were comparable between groups with p value greater than 0.05 (table 1).

Table 1 Demographic and clinical characteristics of the study participants who underwent elective surgery under general anesthesia with laryngoscopic intubation at TASH, from January 1- March 30, 2018

Characteristics		Fentanyl (n=57)	Lidocaine (n=57)	P-value
		Frequency (%)	Frequency (%)	
Sex	Female	35 (61.4)	38 (66.7)	0.558*
	Male	22 (38.6)	19 (33.3)	
Age(years) (mean ± SD)		38.5±12.53	39.19±12.45	0.776¥
Weight (kg) (mean ± SD)		68.9±8.3	67.9±8.5	0.53¥
ASA	I	37 (64.9)	37 (64.9)	0.32*
	II	20 (35.1)	20 (35.1)	
Mallapatti classification	I	42 (73.3)	42 (73.3)	0.33*
	II	15 (26.3)	15 (26.3)	
Induction agent	Propofol	30 (52.6)	32 (56.1)	0.50*
	Thiopental	27 (47.4)	25 (43.9)	

Surgical procedure	GI surgery	23 (40.4)	15 (26.3)	0.372*
	Gynecology	17 (29.8)	16 (28.1)	
	ENT surgery	4 (7)	7 (12.3)	
	Urology	5 (8.8)	10 (17.5)	
	Other surgery	8 (14)	9 (15.8)	

(n = number of participant, (%) = percentage, ASA=American society of anesthesiology physical status, s = second, SD = standard deviation, * p value for chi-square (X^2) test of independence, ¥ p value for independent t-test).

According to this study, there were no significant difference between the two groups regarding before induction (base line) Heart rate (HR), Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) of the study participants (table 2).

Table 2 Base line hemodynamic parameters among fentanyl and lidocaine groups.

Baseline hemodynamic parameter	fentanyl (Mean ± SD)	Lidocaine (Mean ± SD)	p-v
Baseline HR	92.26±18.314 bpm	95.68±15.830 bpm	0.288
Baseline SBP	132.19±15.113mmHg	132.84±16.049 mmHg	0.824
Baseline DBP	84.07±10.871 mmHg	84.91±13.644 mmHg	0.716

(HR= Heart rate, SBP= systolic blood pressure, DBP=diastolic blood pressure, SD = standard deviation, bpm = beat per minute, mmHg = millimeter mercury, p-v = p value for independent t-test).

5.2. Comparison of hemodynamic responses between and within the group.

The following assumptions were fulfilled for our data to ran (perform) independent and dependent sample t-test and present the result in this research paper.

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

- ✓ Our outcome variables was measured on a continues scale(HR, SBP and DBP)
- ✓ Our independent variable (anesthetics adjuvant) was contained two categorical (independent group), group F and group L

- ✓ 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 dependent sample t-test:

- ✓ Our outcome variables was measured on a continues scale(HR, SBP and DBP)
- ✓ Our independent variable contained two categorical, related groups or matched pairs (HR before and after, SBP before and after, DBP before and after)
- ✓ There were no significant outliers in the difference between two related groups for all data that we ran dependent t-test.
- ✓ The distribution of the difference in the dependent variable between the two related groups were checked by Shapiro wilk W-test for each and every data that we ran dependent t-test and normality was approximately assumed ($p > 0.05$)

5.2.1. Mean heart between and within the group.

In this study the result of independent sample t-test shows that mean heart rate was significantly lower in fentanyl group (98.91 bpm ± 15.6 bpm) compared to lidocaine group (107 bpm ±15.45 bpm) in mean ± SD at first minute after intubation, mean difference (M) = 8.2 bpm, 95% confidence interval (CI) [2.45, 13.97], $t(112) = 2.8$, $p = 0.006$.

Mean heart rate was also lower in fentanyl group compared to lidocaine group at third minute after intubation, mean difference (M) = 5.9 bpm , 95% CI [0.36, 11.4], $t(112) = 2.1$, $p = 0.037$. At fifth minute after intubation there was no significant different between the group in mean heart rate (table 3).

In this study the paired sample t-test result showed that there was initial rise in heart rate from baseline at first minute after intubation (mean increment of 11.4 bpm ± 9.5 bpm), $t(56) = 9$, $p<0.01$ and third minute after intubation (mean increment of 4.9 bpm ± 10.56 bpm), $t(56) = 3.5$, $p<0.01$ in lidocaine group.

There were also initial raise in heart rate from baseline at first minute after intubation (mean increment of 6.65 bpm ± 12.9 bpm), t (56) = 3.9, p<0.01 and third minute after intubation (mean increment of 2.5 bpm ±12.5 bpm), t (56) = 1.5, p = 0.141 in fentanyl group (table 3). The heart rate fluctuation slightly returned to the baseline value by 3 minutes in F group and by 5 minute in L group as shown in figure 1 below.

Table 3 Mean heart rate between and within fentanyl and lidocaine group in study participants who underwent elective surgery under GA with LI, TASH, from January 1- March 30, 2018

Heart rate	Fentanyl (Mean ± SD)	Magnitude of raise from baseline F-group	P-value for mean differenc-e with in F-group	Lidocaine (Mean±SD)	Magnitude of raise from baseline L-group	P-value for mean differen-ce within L-Group	P-value for Mean difference b/n F and L groups
Baseline HR	92.26±18.3 bpm		-	95.68±16 bpm		-	0.288
At 1Min.	98.91±15.6 bpm	7.2% ↑	0.001	107±15.45 bpm	12%↑	0.001	0.006
At 3Min.	94.7±15 bpm	1.11%↑	0.141	100.6±15 bpm	5.14%↑	0.001	0.037
At 5Min.	91.25±15.3 bpm	1.1%↓	0.565	93.84±15 bpm	1.9%↓	0.230	0.362

(%, percentage, b/n = between, SD= standard deviation, F = fentanyl, L = lidocaine, HR =heart rate, At 1min = at 1 minute after intubation, At 3min = At 3minute after intubation, at 5 min = at 5 minute after intubation, ↑ = increase, ↓ = decrease)

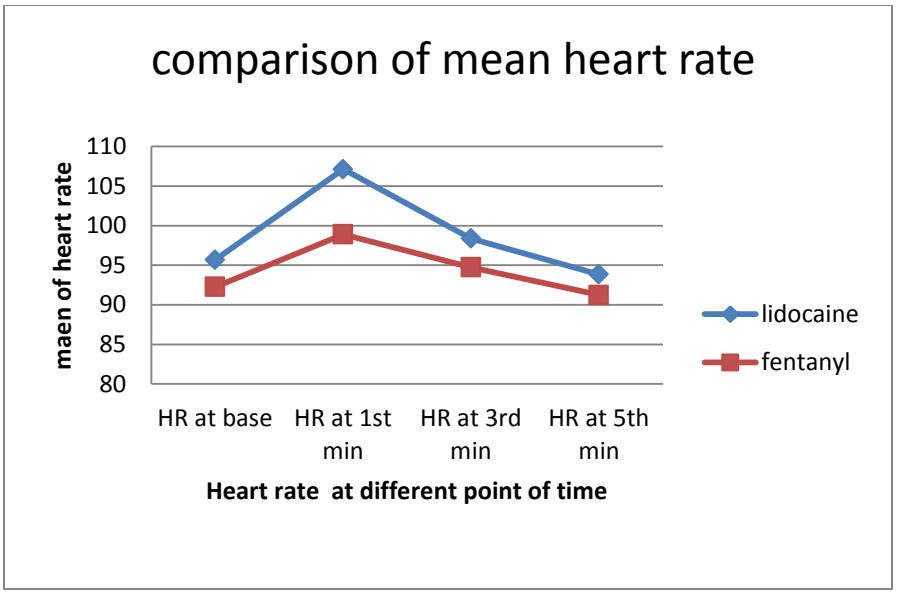

Figure 1 Comparison of mean heart rate at baseline and at first, third and fifth minute after intubation between fentanyl and lidocaine group.

5.2.2. Mean SBP between and within the group.

The result of this study showed that systolic blood pressure was significantly lower in F group (141.9 mmHg ±18.9 mmHg) compared to L group (150 mmHg ±18.098 mmHg) in mean ± SD at first minute after intubation, M = 8.5 mmHg , 95% CI [1.609,15.34], t (112) = 2.45, p=0.016. Elevation elicited in lidocaine group was persisted until three minute after intubation. But there were no significant different in SBP at 3rd and 5th minute after intubation between fentanyl and lidocaine group with p value of 0.094 and p=0.313 respectively (table 4). Decrement in SBP was comparable in both groups at 5 minute as shown in figure 2.

Paired sample t-test showed that there was initial rise in SBP from baseline at first minute after intubation (mean increment of 17.5 mmHg ± 10.2mmHg) in lidocaine group, t (56) = 13, p < 0.01. There were also initial raise in SBP at first minute after intubation (mean increment of 9.68 mmHg ± 9.4 mmHg) in fentanyl group, t (56) = 7.76, p < 0.01(table 4).

Table 4 Mean SBP within and between fentanyl and lidocaine group in study participants who underwent elective surgery with under GA with LI, TASH, from January 1- March 30, 2018.

SBP	Fentanyl (Mean ±SD)	Magnitude of raise from baseline F-group	P-value for mean differenc -e within F-group	Lidocaine (Mean±SD)	Magnitu -de of raise from baseline L-group	P-value for mean difference within L group	P-value for mean difference b/n F and L group
Baseline	132.19±15 mmHg		-	132.8±16 mmHg		-	0.824
At 1Min.	141.9±18.9 mmHg	7.35 %↑	0.001	150 ±18.098mm Hg	13 %↑	0.001	0.016
At 3Min.	127.7±15.2 mmHg	3.4%↓	0.05	132.65±16 mmHg	0.1 %↓	0.896	0.094
At 5Min.	120.25±16.8 mmHg	6 %↓	0.001	123.19±14.1 mmHg	7 %↓	0.001	0.313

(b/n = between, SD= standard deviation, % = percentage, SBP =systolic blood pressure, mmHg = millimeter of mercury, At 1min = at 1 minute after intubation, At 3min = at 3minute after intubation, At 5 min = at 5 minute after intubation, ↑= increase, ↓ = decrease)

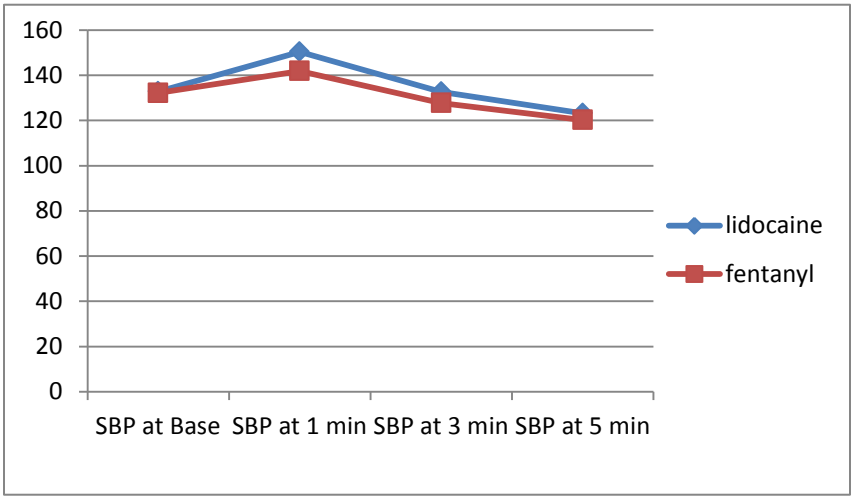

Figure 2 Comparisons of mean SBP at base line and after intubation between fentanyl and lidocaine.

5.2.3. Mean diastolic blood pressure between and within the group.

This study showed that there were no significant different in mean DBP between the group throughout the study period, t (112) = 1.3, p<0.01, t (112) = 1.36, p = 0.177 and t (112) = 1.55, p = 0.125 at 1st, 3rd and 5th minute after intubation respectively. But the mean DBP was significantly increased from base line at first minute after intubation both in fentanyl and lidocaine group, t (56) = 5.75, p < 0.01 and t (56) = 7.36, p<0.01 respectively (table 5).

Table 5 Mean DBP in fentanyl and lidocaine group in study participants who underwent elective surgery with ETT, TASH, from January 1- March 30, 2018.

DBP	Fentanyl (Mean ±SD)	Magnitude of raise from baseline in F-group	P-value for mean difference within F group	Lidocaine (Mean±SD)	Magnit-ude of raise from baseline L-group	P-value for mean difference within L group	P-value for mean difference b/n F and L group
Baseline	84.07±10.9 mmHg		-	84.91±14 mmHg		-	0.716
At 1Min.	91.7±13 mmHg	9.07 % ↑	0.001	95.06±14 mmHg	12 % ↑	0.001	0.194
At 3Min.	82.11±12.6m mHg	2.3 % ↓	0.232	85.63±15 mmHg	1% ↑	0.896	0.177
At 5Min.	77.02±12 mmHg	8 % ↓	0.05	80.7±13.4 mmHg	5 % ↓	0.19	0.125

(SD= standard deviation, % = percentage, DBP =diastolic blood pressure, At 1min = at 1 minute after intubation, At 3min = at 3minute after intubation, At 5 min = at 5 minute after intubation, ↑ = increase, ↓ = decrease).

Chapter six: Discussion, Limitation and Strength

6.1. Discussion

Stress responses to laryngoscopy and endotracheal intubation in form of tachycardia, hypertension, ventricular tachycardia and arrhythmias may be associated with significant moribund outcome. This hemodynamic change is due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation(4). Thus, a variety of anesthetics agent combinations and anesthetics adjuvants have undergone many prospective study and clinical trials in relation to study attenuation of pressor responses to laryngoscopic intubation (28).

In our study there was significant difference in heart rate with mean ± SD was lower in fentanyl group (98.91 bpm ± 15.6 bpm) when compared to lidocaine group (107 bpm ±15.45 bpm) at first minute after intubation with p value of 0.006. SBP with mean ± SD was also lower in fentanyl group (141.9 mmHg ±18.9 mmHg) than lidocaine group (150 mmHg ±18.098 mmHg) at first minute after intubation (p =0.016). Heart rate was also lower in fentanyl group at third minute after intubation (P = 0.037). The possible explanation for this may be Fentanyl brings hemodynamic stability during peri-operative period by its action on cardiovascular and autonomic regulatory areas. It decreases sympathetic tone and increases parasympathetic tone.

A randomized control trial study by Jyothsna Yadav et al (2017) shows similar finding to our study, comparing fentanyl and lidocaine on attenuation of hemodynamic response to laryngoscopic intubation observed that heart rate in lidocaine group after intubation was 89 bpm ±2.33 bpm, which was significantly higher compared to fentanyl group 82.40 bpm ±1.66 bpm (p=0.000). The average increase in heart rate above baseline was significantly lower in fentanyl group compared to lidocaine group (p=0.000). The magnitude of increase in SBP above baseline in lidocaine group and fentanyl group were (9.9%) and (7.07%) mmHg respectively which was statistically significant (p=0.000) (26).

Our study was also in line with the study done in Korea (2007) on 150 ASAI/II patients aged 20 to 65 years, undergoing elective surgery requiring tracheal intubation. That compared effects of Lidocaine, Fentanyl, Nicardipine, and Esmolol on hemodynamic and bispectral index responses during induction with Thiopental Sodium. The result of their study found that all the adjuvant drugs in the study attenuated with a various degree of the tracheal responses. Heart rate was

significantly lower in fentanyl group compared to lidocaine group at first, second and third minute after intubation ($p > 0.05$) (29).

Our study was in contrary with study done in India (2016) a prospective, randomized, double-blind study on 120 patients that compare, the effects of lidocaine, fentanyl, and Esmolol on hemodynamics and bispectral index when used before laryngoscopy and intubation to prevent stress responses stated that there were no significant different between fentanyl (109.80±11.78 bpm) and lidocaine (103.63±13.813 bpm) in producing hemodynamic stability at first minute after intubation when compared to each other ($p = 0.305$) (30). The difference with our study may be due to a difference in study design and types of induction agent that was used in ours and their study. Etomidate, one of induction agent with known cardiovascular stability effect was used in their study.

According to the result of the present study there were no significant different in SBP and DBP at third minute after intubation between fentanyl and lidocaine group ($p=0.413$ and 0.194 respectively). In contrary to this study, the randomized control trial study done in Turkey (2012) stated that there were significant different in SBP and DBP at Third minute after intubation between fentanyl and lidocaine group ($p<0.05$) (31). This discrepancy might be due to high dose of fentanyl (4 mcg /kg) that was used in their study rather than 2mcg/kg which was mostly used in our set up. A linear relationship exists between increasing opioid dose and cardiovascular response reduction. But the risk of prolonged postoperative respiratory depression must be weighed against the advantages of perioperative cardiovascular stability.

Our study found that heart rate was slightly returned to baseline at third minute and fifth minute after intubation in fentanyl and lidocaine group respectively. Our study was in line with prospective studies done in Iran (2017) on 96 patients stated that lidocaine effectively prevent HR fluctuations following the endotracheal intubation at 3^{rd} and 5^{th} minute after intubation (32). The similarity with our study may be due to the similarity with study design and anesthetics adjuvant.

In our study, IV fentanyl 2 mcg/kg administered three minute before induction was found to be the most effective in attenuating the hemodynamic response. As the result of our study shows in group L maximum increase in heart rate was 12% at first minute after intubation whereas in group F heart rate increase only 7 % after intubation at first minute which was significantly smaller ($p = 0.001$) as compare to baseline. This might be due to the fact that fentanyl administration affects the plasma concentrations of anesthetics during induction by changing circulatory variables. This study was in line with the study done in United Kingdom (2015) randomized control trial study on 75 ASAI and ASAII patients to evaluate and compare effects of 2 different doses of fentanyl 1mcg/kg and 2mcg/kg in attenuating pressor response to laryngoscopy and intubation. The result of their study revealed that intravenous fentanyl 2 mcg/kg body weight provides better attenuation of hemodynamic response to laryngoscopy and endotracheal intubation without any adverse effects (33). The similarity with our study may be due to the similarity with induction agent and dose of fentanyl used.

In contrary to our findings, Siddiqui et al (2015) found intravenous lidocaine is less effective to attenuate the pressor responses at fifth minute after intubation and at the end of 5 minutes, the heart rate was still higher in lidocaine group ($p < 0.05$). This discrepancy might be due to the difference in study designed and time point for lidocaine injection in ours and their study which was one minute before intubation in their study and three minute before intubation in our setup (18).

6.2. Limitation of the study:

- ✓ Making blind for data collectors was not possible due to operation theatre setup.
- ✓ Lack of control group.

6.3. Strength of the study:

- ✓ It will be helpful as baseline information for other researchers.

Chapter seven: Conclusion and Recommendation

7.1. Conclusion

The findings of our study demonstrate that fentanyl 2 μg/kg IV, administered three minute before intubation, was better in attenuating hemodynamic response to laryngoscopic intubation compared with lidocaine 1.5 mg/kg IV in patients undergoing elective surgeries under general anesthesia with laryngoscopic intubation. However, clinically lidocaine provides a consistent and reliable attenuation of pressor responses at fifth minute after intubation as comparable to fentanyl.

7.2. Recommendation

Even though, fentanyl and lidocaine are commonly used anesthetics adjuvant for blunting hemodynamic stress responses and maintenance of hemodynamic stability, each drug has variability on attenuation of hemodynamic response to intubation. Therefore, based on the findings of this study the following recommendations were drawn.

For anesthetists

- Fentanyl administration three minutes before intubation for elective surgeries undergoing general anesthesia with laryngoscopic intubation is better in attenuating hemodynamic response to intubation.
- It is better to use fentanyl in patients undergoing elective surgery under general anesthesia with laryngoscopic intubation to attenuate pressor responses while reserving lidocaine for those who are contraindicated to use fentanyl.

For further researchers

- Further study with Randomized control trial may need to be conducted.

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Annexes:

Annex I: Informed consent:

Addis Ababa University College health Sciences, School of graduate studies, Department of anesthesia. Questionnaire prepared to assess the effectiveness of fentanyl and lidocaine on attenuation of Laryngoscopic and endotrachal tube intubation induced hemodynamic pressor response.

This questionnaire is to be used as a guide to collect information for the data collectors.

Hello! My name is ----------I am one of the members of the research team. The purpose of this questionnaire is to gather information on controlling post intubation hemodynamic pressor response. I have identified you as a study participant hoping that you would be willing to help me by providing with some information. I have some questions which I would like to fill from your chart and intraoperative data monitoring screen if you are willing. All information your chart and data monitoring screen provide will be kept confidential. I will not include such as your name or exact address. Only honest data would contribute to improvement of health planning. Your role in the success of the research is important and I appreciate your contribution to the 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: 0928786677, Gmail: Samuelhirbo1@gmail.com.

አመሰግናለሁ::

ስሜ ሂርቦ ሳሙኤል እባላለሁ::

እኔ በአዲስ አበባ ዩኒቨርሲቲ በአንስቴሽያ ት/ት ሳይንስ የማስትሬስ ድግሪ ተማሪ ሲሆን የመመረቅያ ፅሁፌን በቀዶ ህክምና ወቅቲ የአየር ቧንቧ ለ መቆጣጠር በጉሮሮ ዉስጥ በሚገባ ቱቦ ምክንያት የሚከሰቱ ችግሮችን ለመቅረፍ ለህመሙማን በምሰጥ መድሀንት ዙርያ አቀርባለሁ:: ከዚሁ ጥናት የሚገኘዉ መረጃ የጤና ባለሙያዎች በጥሩ ሁኔታ በሽተኞችን እንድረዱ ያግዛቸዋል በተጨማሪም ታካሚዎቹ ለአንስቴሽያዉ የተሻለ ዕዉቀት እንድኖራቸዉ ያደርጋል::ስለዝህ የርስዎ በ ጥናት ዉስጥ መካትተ ለዚህ ጥናት መሳካት ከፍተኛ አስተዋጾ አለዉ:: ከርስዎ እና ከ ሕክምና ካርዶዎ በ ሕክምና ወቅት የሚናገኘዉ ማንኛዉም መረጃ ለምርምር አገልግሎት እንደምዉል እየገለጽኩኝ በማንኛዉም ሁኔታ የርስዎ የግል መረጃ ለሌላ አገልግሎት እንደማይዉል ለማሳሰብ እወዳለሁ:: እንድንቀጠል(የ ሕክምና መረጃዎን እንድንዎስድ) ይፈቅዳሉ ? አዎ---------- አልፈልግም----------

(ስለ ዕርዳታዎ በቅድሚያ ላቅ ያለ ምስጋና አቀርባለሁ::)

የ አጥኝዉ ስም ና አድራሻ

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Annex II- checklists:

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

Code…….

Part I: Questions on socio-demographic characteristics of the patient

101	Age (years)	---------- years
102	Sex	A, Male , B, Female
103	Weight in Kg	…….
104	Diagnosis	……..
105	ASA physical status	A, ASA I B, ASA II

Part II: Questions about anesthetic and surgical characteristics of the patient.

201	mallampatti class of patient	A, class 1 B, class 2
202	Planned Surgical procedure to be done	……..
203	The used anesthetic adjuvant three minute before intubation	A, fentanyl B, Lidocaine
204	Induction agent	A, propofol B, thiopental C, ketamine D, Halotahen

Part III per-operative hemodynamic parameter measurements.

3, Hemodynamic parameter

Hemodynamic parameter	Heart rate	Systolic blood pressure	Diastolic blood pressure	Mean arterial blood pressure
301 , Before intubation (base line)				
302 , 1 minute after intubation				
303 , 3 minutes after intubation				
304 , 5 minutes after intubation				

4, Maintenance inhalational agent opened immediately after intubation

401, Haloten	A, 1% B,1.5 % C, 2% D, specify any other MAC…….
402, Isoflurane	A, 1% B,1.5 % C, 2% D, specify any other MAC…….

Annex III dummy tables:

1. **Pre induction variable (data will be presented as mean± SD or ratio as appropriate)**

Variables	GROUP F (fentanyl group) (n=57)	GROUPL (lidocaine) group(n=57)	P–value(x^2- test)
Sex M			
F			
Age			(t-test)
Weight			(t-test)
ASA status ASA I			
ASA II			
Surgical procedure			
Abdominal			
Gynecology			
Urology			
Induction agent			
Thiopental			
Propofol			

2, Intraoperative hemodynamic variables at baseline and immediately after intubation (mean ± SD):

Heart rate (beats/minute)	Group I		Group 2		P - value
	mean ± SD	% change from baseline	**mean ± SD**	% change from base line	
Base line					
1 minute after intubation					
3 minute after intubation					

5 minute after intubation					

SBP	Group I		Group 2		P - value
	mean ± SD	% change from baseline	**mean ± SD**	% change from base line	
Base line					
1 minute after intubation					
3 minute after intubation					
5 minute after intubation					

DBP	Group I		Group 2		P - value
	mean ± SD	% change from baseline	**mean ± SD**	% change from base line	
Base line					
1 minute after intubation					
3 minute after intubation					
5 minute after intubation					