ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF GRADUATE STUDIES DEPARTMENT OF ANESTHESIA

Effect of Ketofol versus propofol as an induction agent on ease of laryngeal mask airway insertion conditions and hemodynamic stability in children: A Prospective cohort study

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Research thesis prepared for partial fulfillment of the requirements for the masters of sciences degree in Advanced Clinical Anesthesia.

June, 2017,

Addis Ababa, Ethiopia

Addis Ababa University College of Health Sciences, School Of Graduate Studies, Department Of Anesthesia

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CERTIFICATION

The undersigned certify that the research entitled Effect of Ketofol versus propofol as an induction agent on laryngeal mask airway insertion conditions and hemodynamic stability in children, Addis Ababa, Ethiopia, 2017: A 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.

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ACKNOWLEDGEMENT

I would like to express my deepest appreciation and gratitude to my advisor Mr. Adugna Aregawi for his constant motivation, support, scientific inputs and guidance. I would also extend my appreciation to department of Anesthesia, Addis Ababa University for providing necessary supports. My special thanks also go to administrators of Menelik II Hospital, anesthesia department of the Hospital, for providing us useful information. Lastly, but not least, I would like to appreciate the data collectors for their help and for the time they gave.

Acronyms and Abbreviations

ASA: American Society of Anesthesiologists

BMA: Bone marrow aspiration

BIS: Bispectral index

DBP: Diastolic blood pressure

ECG: Electrocardiography

GA: General anesthesia

GABA: Gamma amino butyric acid

IRB: Institutional review board

KP: Ketofol

LMA: Laryngeal mask airway

LP: Lumbar puncture

LTS II: Laryngeal tube suction II

MAP: Mean arterial blood pressure

NMDA: N-Methyl-D-Aspartate

PLMA: Proseal Laryngeal mask airway

PSA: Procedural sedation

SBP: Systolic blood pressure

SpO2: Arterial oxygen saturation

SPSS: Statistical Package for social sciences

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ABSTRACT

Background: Laryngeal mask airway is a simple supraglottic device which has led to a radical change in the management of modern general anaesthesia. In the present study, we evaluated the laryngeal mask airway insertion conditions and hemodynamic changes comparing ketamine-propofol mixture (ketofol) with propofol.

Objective: The objective of this study was to compare ketamine–propofol mixture (ketofol) with propofol on the ease of laryngeal mask airway insertion conditions for induction of general anaesthesia (GA).The hemodynamic effects were also looked at.

Materials and Methods: In this prospective cohort study120 pediatric patients age 2 – 15 years undergoing general anesthesia with LMA for elective ophthalmic surgeries at Menelik II Hospital from Jan 25 -March, 25, 2017 were included. A six variable (mouth opening, ease of insertion, swallowing, coughing, movement and laryngospasm) three-point score was used to assess insertion conditions. LMA insertion summed score was prepared depending upon these variables. Hemodynamic variables Heart rate and mean arterial pressure were noted 1 min before induction (baseline), immediately after induction, immediately after insertion of LMA and 1,2 and 3 minute after LMA insertion. Insertion conditions were compared using Chi-square test while hemodynamic variables were compared using independent t test.

Results: LMA insertion summed score was nearly similar between the two groups. Mean blood pressure and heart rate were maintained higher in ketofol group while significant drop were observed in propofol group. The time from the LMA placement to the return of spontaneous ventilation was significantly longer in propofol group (240 seconds [range =60– 360 seconds]) compared with ketofol group (180 seconds [range= 30–320 seconds]) (p= 0.005).

Conclusion and Recommendations: LMA insertion condition summed score was comparable in both ketofol and propofol group. Ketofol provided equivalent LMA insertion conditions while maximizing hemodynamics and minimizing apnea time. When parameters such as LMA insertion conditions and hemodynamic stability are considered, ketofol can be used as an alternative to propofol for LMA insertion in pediatrics.

CHAPTER ONE: INTRODUCTION

1.1 Background

The major responsibility of an anesthetist is management of airway so as to provide adequate ventilation to the patient by securing airway when general anesthesia is administered. As such, no anesthesia is safe unless diligent efforts are devoted to maintain an intact functional airway (1, 2). Laryngeal Mask Airway (LMA) is a simple supraglottic device which is placed without requiring direct laryngoscopy either in adults or in children. In many cases, possibility of intubation or mask ventilation is poor; using LMA to control airway and make an adequate airway is effective in 94% of cases in patients (3). Several methods have been introduced for LMA insertion while no standard anesthesia induction method has been proposed to guarantee a proper placement of the device (4, 5).

LMA is a very safe device with the least complications (6). The most frequent anesthetic used for LMA placement is propofol (7, 8). Intravenous propofol can be successfully used as a sole induction agent to facilitate laryngeal mask airway (LMA) insertion even in children because of its predominant upper airway reflexes depressant action (9).

When administered alone for LMA insertion, propofol could be associated with undesirable complications including coughing, gag reflex, laryngospasm, and inability to provide analgesia which prevents it from being the sole anesthetic medication for any stimulating procedures (10, 11)

Numerous pharmacological agents and combinations have been introduced to decrease the hemodynamic instability throughout anesthesia (12, 13).

Ketamine is well-known for its airway reflexes maintaining activity and sympathetic stimulation so as to causes little or no cardio-respiratory depression and unlike propofol has pain relieving properties. It is unique in that it is a cardiovascular and respiratory stimulant. These are desirable in pediatric anesthesia (14, 15).

Ketamine in subanaesthetic doses with propofol has gained attention in total intravenous anaesthetic technique because of its powerful analgesic action without causing myocardial or respiratory depression (16-18)

"Ketofol" is a moniker for ketamine and propofol administered either independently or as a single-syringe admixture. Ketofol has been advocated as the ideal PSA combination because the need for lower doses of each agent combined with the opposing actions of both agents theoretically decreases the incidence of dose-related side effects (11). Effectiveness of the two agents – propofol and ketamine – in combination (ketofol) has been recently demonstrated and may provide a novel induction agent with favorable hemodynamics and reduced side effects attributed to either drug (19). By combining propofol and ketamine, there is additive effect of GABA agonism by propofol and NMDA antagonism by ketamine leading to lesser doses of propofol required along with ketamine (20). In addition, addition of analgesic doses of ketamine to propofol lowers the dose of propofol, provides better intubating conditions and overcomes the risk of adverse effects (21).

1.2 Statement of the problem

LMA insertion has been revolutionized with the development of induction agents like propofol which depresses pharyngeal and laryngeal reflexes (22).

Successful insertion of the LMA requires optimum anaesthetic depth to avoid unwanted airway reflexes such as swallowing, gagging, coughing or involuntary movements to severe complications such as laryngospasm (23, 24).

Satisfactory anesthetic induction conditions are best provided by propofol compared to other intravenous induction agents (23). However, when propofol is used as a single induction agent in unpremedicated patients, doses exceeding 3 mg/kg is required to allow smooth and atraumatic LMA insertion (3, 25). Elevated propofol doses are not desirable as the cardiorespiratory depression is dose dependent (22,26). Study shows up to 31.72% decrement in mean arterial pressure immediately after induction when anesthesia is induced with propofol alone). Therefore propofol as a single agent is unsatisfactory and to overcome problems associated with it, a number of other co-induction drugs have been introduced (27).

Ketamine, an N-methyl d-aspartate (NMDA) receptor antagonist, has beneficial airway-maintaining and sympathomimetic effects when used as a co-induction agent at sub-anesthetic doses (28, 29).

In our country some centers use the combination of ketamine and propofol as co-induction agent during LMA insertion, while its effect on LMA insertion condition and hemodynamic changes is not well studied. As to the knowledge of the investigators, there is also limited literature available on ketamine and propofol combination for LMA insertion. Therefore this study is aimed to compare the effect of ketamine–propofol mixture (ketofol) and propofol on the insertion conditions of LMA and hemodynamics pediatrics.

1.3 Justification of the study

Sufficient deepness of anesthesia and mouth openness is needed for correct insertion of supraglottic airway devices and prevents such complications as coughing, swallowing, head and extremity movements and laryngospasm. When propofol used alone it cannot provide LMA insertion conditions or high dose of propofol is needed to improve the insertion conditions. On the other hand, high dose of propofol cause cardiorespiratory depression. Ketamine increases heart rate and arterial blood pressure by virtue of increased centrally mediated sympathetic tone and increased centrally mediated release of catecholamines from the adrenal medulla. Clinical effects of propofol and ketamine seem to be complementary.

Therefore the finding of this research will help:

Anesthesia professionals

- To provide Safe and effective alternative induction agent for better LMA insertion conditions and improved hemodynamic stability.
- To enhance evidence based practice.

Health administrators

- To work on quality improvement to enhance good patient outcome.
- To supply cost effective anesthetic drugs with better patient outcome to enhance income generation and cost reduction.

Researchers

- Used as a footstep for next studies to be done on similar problems.

CHAPTER TWO: LITERATURE REVIEW

In study conducted to compare the effects of ketamine and alfentanil administered prior to induction of anesthesia with propofol, on the hemodynamic changes and ProSeal laryngeal mask airway (PLMA) insertion conditions, 80 children, aged between 3–132 months, were randomly allocated to receive either alfentanil 20 µg/kg or ketamine 0.5 mg/kg before induction of anesthesia. They found that the administration of ketamine 0.5 mg/kg with propofol 4 mg/kg preserved hemodynamic stability, and reduced the time to the return of spontaneous ventilation, compared with alfentanil 20 µg/kg during PLMA placement. In addition, the conditions for insertion of the PLMA with ketamine were similar to those found with alfentanil (30).

In a study conducted on 120 pediatric patients of ASA Grade I and II of either sex aged 3-12 years scheduled for pediatric surgeries under general anaesthesia showed that increasing dose of propofol decreases the adverse events like inadequate jaw relaxation, limb movements, coughing, gagging and laryngospasm. Midazolam when added to propofol further reduces the incidence of adverse events and provides more favorable environment for insertion of LMA. At higher doses of propofol (5 mg kg-1), hypotension is a major problem due to its cardiovascular depressant action. Therefore, 4 mg kg-1 propofol along with midazolam is the optimum dose because there is more hemodynamic stability to get better conditions for LMA insertion (31).

Randomized double blind comparison of ketamine-propofol and fentanyl–propofol for the insertion of laryngeal mask airway was done in children of age 3-13 years. Hundred ASA I and II patients were randomly allocated to receive intravenously either fentanyl 2µg/kg (group F,n=50) or ketamine 0.5 µg/kg (group K, n=50) before induction of anesthesia with propofol 3.5 µg/kg. Coughing/gagging was seen in 8% patients in group F as compared to 28% patients in group K. Limb /head movements were observed in 64% patients in the fentanyl group and in 76% patients in the ketamine group. Laryngospasm was not seen in any patient in either group. Incidence of apnea was 80% in the fentanyl group and 50% in the ketamine group. The heart rate, SBP, DBP and MAP were consistently higher in the ketamine group as compared to the fentanyl group. The combination of fentanyl and propofol provides better conditions for LMA insertion in children than a combination of ketamine and propofol (32).

In a clinical comparison of ketofol (ketamine and propofol admixture) versus propofol as an induction agent on quality of laryngeal mask airway insertion and hemodynamic stability in

children, Yousef and Elsayed showed that Ketofol is a safe and effective alternative induction agent for LMA insertion in children with rapid onset of action and lower incidence of injection pain. It provided better LMA insertion conditions, improved hemodynamic stability with less prolonged apnea when compared to propofol (15).

A prospective randomized double blinded study was done to compare ease of inserting LMA and the hemodynamic effects of etomidate with propofol for induction of general anaesthesia (GA) with LMA. Patients were induced with intravenous (I/V) fentanyl and induction agent either etomidate or propofol according to group randomization. LMA was inserted after 30 seconds. Intra-operative heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), number of attempts and duration of LMA insertion were monitored. There was no difference in the heart rate between the two groups. A significant drop was found for systolic blood pressure (SBP) in propofol group while diastolic blood pressure (DBP) was decreased in both the groups. In propofol group, successful insertion of LMA was achieved on the first attempt in 93.3% of patient as compared to 36.7% in etomidate group (33).

In another randomized double blind prospective study which included 90 ASA I & II patients aged between 15 and 50 years scheduled for ambulatory urological; ambulatory urogynaecological procedures, they concluded that among the two admixtures propofol ketamine has an edge over propofol-thiopentone because of its better hemodynamic stability and superior airway maintenance (34).

In a randomized double blind prospective study which included 100 children scheduled for LMA insertion the effects of ketofol and propofol were compared and concluded that ketofol is a safe and effective alternative induction agent for LMA insertion in children with rapid onset of action and lower incidence of injection pain. It provided better LMA insertion conditions, improved hemodynamic stability with less prolonged apnoea when compared with propofol (35).

In a randomized double blind prospective study which included 80 ASA I & II patients posted for laryngeal tube suctioning compared the effects of propofol and ketofol and concluded that ketofol provided better insertion summed score for LTS II than propofol with minimal haemodynamic changes (35, 36).

Prospective, randomised and double blind study was done to compare the effects of ketamine and midazolam as a co-induction agents with propofol for PLMA insertion. The ketamine-propofol group had significantly better mouth opening) and shorter duration of apnoea. Other conditions during PLMA insertion and the overall grading were comparable between groups. Haemodynamic parameters were comparable to baseline within each group. However, the ketamine-propofol group had more stable blood pressure readings and maintained a higher heart rate compared to the midazolam- propofol group (37).

A randomized double-blind study, in which 90 total patients having a laryngeal mask airway (LMA) placed received propofol (2.5 mg/kg) with either ketamine (0.5 mg/kg), fentanyl (1 ug/kg), or placebo normal saline (38) When measured vital signs and pre-determined time points and ease of LMA insertion, they found the ketofol group had a significantly higher systolic blood pressure than the other two groups and the incidence of prolonged apnea (>120 s) was higher in the fentanyl group (23.1%) than in either the ketofol group (6.3%) or the normal saline group (3.3%). They concluded that ketofol provided equivalent LMA insertion conditions while maximizing hemodynamics and minimizing apnea (39).

In another randomized double blind prospective study which included 68 ASA I & II patients undergoing elective general, orthopedic and gynecological procedures concluded that induction dose of propofol is reduced considerably by prior administration of small dose of ketamine compared to placebo using loss of verbal contact as end point of induction. Ketamine had the advantage of better hemodynamic stability (40).

In the 10 trials comparing the combination of ketamine and propofol with either agent alone for procedural sedation in the emergency department were examined. The evidence reviewed suggests that combining these agents may help to minimize adverse effects such as hypotension and respiratory depression. Ketamine is not commonly used as a single agent in adults because of the risk for emergence reactions; however, when combined with propofol, no significant increase in this adverse effect was found compared with propofol monotherapy (41).

In a randomized double blind prospective study which included 100 children, of age 3–14 years, American Society of Anesthesiologist physical status IE-IIE, posted for emergency short surgical procedures concluded that The combination of low-dose ketamine and propofol is more effective

and a safer sedoanalgesia regimen than the propofol–fentanyl combination in pediatric emergency short surgical procedures in terms of hemodynamic stability and lesser incidence of apnoea (42).

The study was done to compare the efficacy, respiratory and hemodynamic profiles, and side effects of two various combinations of ketamine and propofol in patients undergoing bone marrow aspiration (BMA) and lumbar puncture (LP). Patients received a slow bolus injection of a solution containing combination of equal amount of propofol and ketamine (1:1) (Group I) or two parts of propofol plus one part of ketamine (2:1) (Group II). Vital signs, oxygen saturation (SpO2) and incidence of any side effects were recorded. In this study there was an increase postoperative nausea, psychomimetic side effects, and increase recovery time with the largest ketamine dosage (Group I) (43).

A clinical trial comparing thiopentone with ketamine as adjuncts to propofol was conducted on 60 women, aged 18-50 years, American Society of Anesthesiologists (ASA) physical status 1 and 2, undergoing day- care gynecological surgeries. Both the propofol-thiopentone and propofol-ketamine admixtures provided adequate anesthesia. Propofol-ketamine proved superior to propofol-thiopentone in terms of hemodynamic stability and requirement of a lesser total dose of propofol. However, the patients in the propofol-thiopentone group had faster recovery (44).

A total of 120 American Society of Anesthesiologist physical status I and II patients 20–60 years of age were randomly allocated into one of four groups. The K0 group received only 2 mg/kg propofol. The K0.15 group received 0.15 mg/kg ketamine and 1.85 mg/kg propofol. The K0.3 group received 0.3 mg/kg ketamine and 1.7 mg/kg propofol. The K0.6 group received 0.6 mg/kg ketamine and 1.4 mg/kg propofol. Endotracheal intubation was performed after muscle relaxation. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR) and the bispectral index value were recorded. No significant differences were observed in SBP, DBP, MBP, or HR among the groups after endotracheal intubation. However, the number of patients with a decrease of MBP $>$ 20% from baseline after induction was significantly lower in the K0.6 group compared to that in the K0 group ($P < 0.05$).The results suggest that ketofol with 0.6 mg/kg ketamine and 1.4 mg/kg propofol can be used as an alternative to 2 mg/kg propofol (45).

Having adequate information about both ketofol and propofol on hemodynamic changes and LMA insertion conditions in anesthesia practice in order to provide better anesthesia service to improve anesthesia management and result in a better health service delivery.

2.1 Conceptual frame work

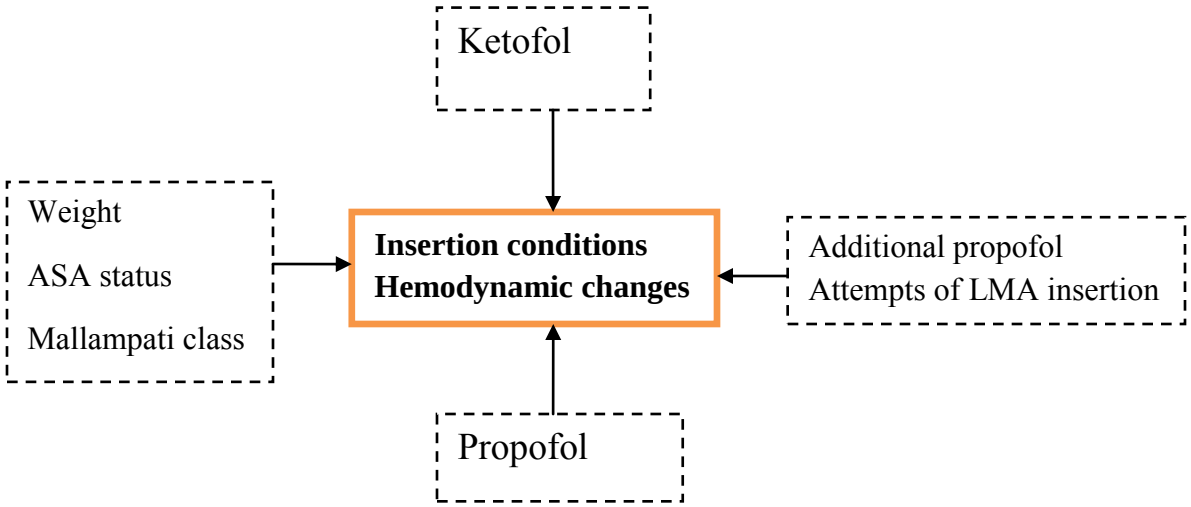


Figure 1: Conceptual frame work of the study

CHAPTER THREE: OBJECTIVES

3.1 General Objective

The aim of this study was to compare the effect of ketamine–propofol mixture (ketofol) and propofol on the insertion conditions of laryngeal mask airway and hemodynamic stability in children from Jan 25-March, 25, 2017.

3.2 Specific Objectives

- ✓ To compare the effect of ketofol and propofol on the insertion conditions of laryngeal mask airway
- ✓ To compare the effect of ketofol and propofol on hemodynamics stability

CHAPTER FOUR: METHODS AND MATERIALS

4.1 Study area and period

This study was conducted at Menelik-II Hospital. Menelik II hospital is one of largest hospital in the country. Menelik-II Hospital is now the main health provider center that offers high quality comprehensive health services to patient from all over the region of Ethiopia and there are two main operation departments, from which ophthalmic operation room has six operation tables. One of these is pediatric OR table which on average, 1920 pediatric patients operated under general anesthesia per year. The study was conducted from Jan 25-March, 25, 2017.

4.2 Study design

A prospective cohort study was employed from Jan 25-March, 25, 2017.

4.3 populations

4.3.1 Source population

All above 2 years old pediatric patients who underwent ophthalmic surgical operation under general anesthesia with LMA in Menelik-II Hospital

4.3.2 Study population

All above 2 years old pediatric patients who underwent ophthalmic surgical operation under general anesthesia with LMA in Menelik-II Hospital during the study period

4.4 Eligibility criteria

4.4.1 Inclusion criteria

Patients of ASA class I and II, age ranging from 2-15 years and undergoing elective surgical procedures under GA using LMA was included in the study

4.4.2 Exclusion criteria

- Patients with hyper-reactive airway disease
- Patients with anticipated difficult airway
- Patients on regular sedatives
- Patients on β-blockers

4.5 Study Variables

4.5.1 Dependent variables

- Ease of LMA insertion
- Hemodynamic changes

4.5.2 Independent variables

- Socio-demographic and operative data: Age, Sex Weight, ASA, Mallampati
- Exposure variable: type of anesthesia drugs used (ketofol vs. propofol)

4.6 Operational Definitions

1. Apnea(36)-Absence of spontaneous respiration for <20 seconds after induction
2. Ease of LMA insertion (33)
    a. Easy insertion- No adverse response, i.e., no gagging or coughing, no patient movement or laryngospasm
    b. Difficult- Moderate to severe adverse responses requiring additional boluses of drugs or more than two attempts is required for LMA insertion
3. Laryngospasm (33)
    a. Complete - when there is laryngeal spasm and no air entry on ventilation
    b. Incomplete - when there is laryngeal spasm but there is air entry
4. Coughing (33)
    a. Slight coughing - coughing which can occurs immediately after LMA and subside by it self
    b. Gross coughing - coughing which needs deepening of anesthesia to be relieved
5. Gagging (33)
    a. Slight gagging - Gagging which stays for short seconds can relieve on its own
    b. Gross gagging - Gagging which needs deepening of anesthesia to be relieved
6. Patient movement (33)

    a. Slight movement - movement from small muscles which can allow insertion of LMA without additional dose of the drugs

    b. Gross movement - movement which cannot be relieved without additional dose of the drugs.

7. Insertion condition summed score- Summing the insertion score for each patient then totaling the score for all patients in the groups and taking the mean

4.7 Sample size and sampling techniques determination

4.7.1 Sample size

Two independent sample size formula based on ease of LMA insertion condition and hemodynamic changes among two groups were used to calculate sample size for each group Having no previous study done in the study area, result adopted from literature has been used to calculate sample size based on the two outcome variable and the largest sample size were used for recruiting study subjects (9, 42). By assuming equal sample size for two groups, the sample size was determined by double population formula as,

$$n_1 = n_2 = f(\alpha, \beta) \times \frac{p1\,(1-p1) + p2\,(1-p2)}{(P1-p2)^2} = 54$$

Where, n1= number of patients taken propofol

n2 = number of patients taken ketofol

Z= 95% confidence interval =1.96

$f(\alpha, \beta)$ = the power function at 80%= 0.84

P1– subjects required additional propofol in propofol group =41.66

P2- subjects required additional propofol in ketofol group=18.33

Therefore, the total sample size was 60 patients in each group adding 10% contingency.

4.7.2 Sampling Technique

From situational analysis mean of midyear population was used to get total number of elective ophthalmic pediatric patients who underwent operation in 2 months duration. The midyear population from situational analysis was 960. So, the size of population in 2 months was 960 divided by 3 gives us 320. The study participants were selected using systematic random sampling technique from daily operation schedule list until the required sample size was obtained. The first study participants were selected by lottery method. We spent two extra weeks

to reach the number of propofol group equal to ketofol group to get equal sample size in both group

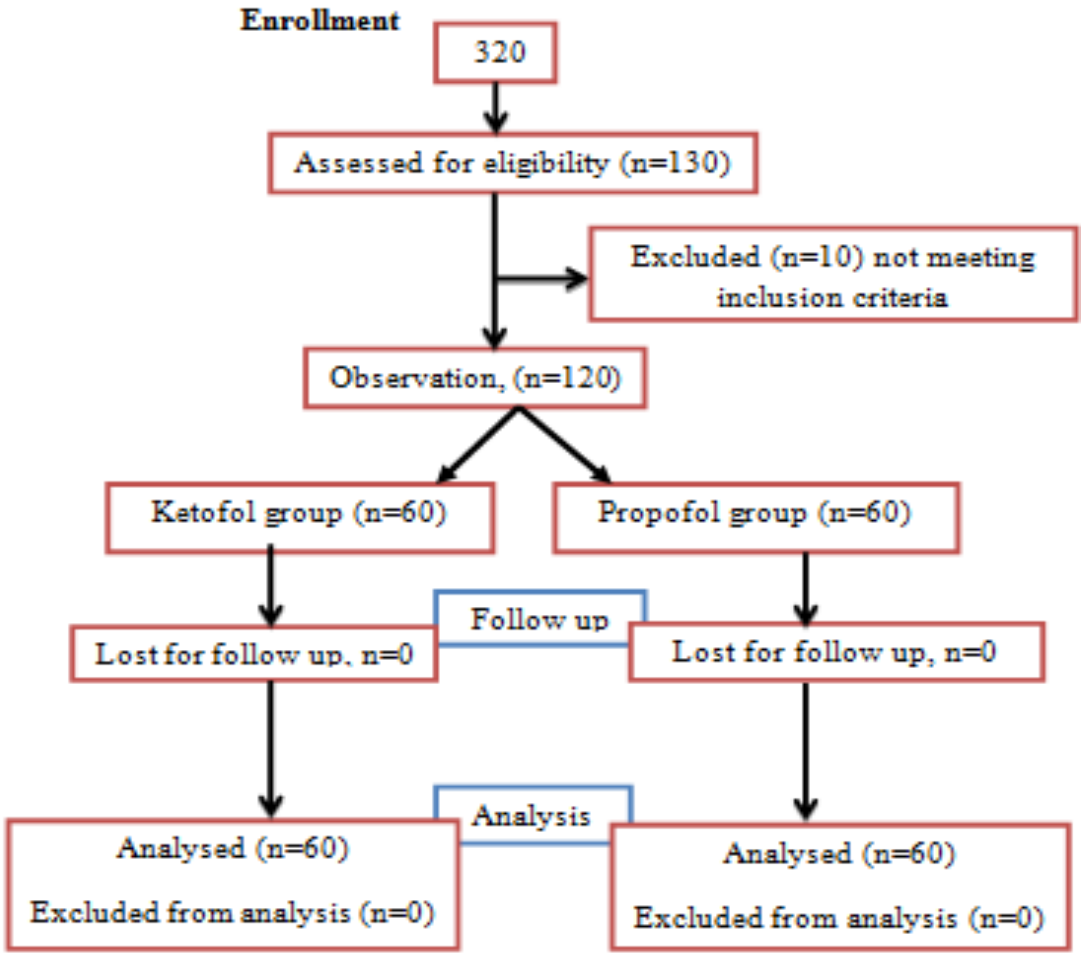


Figure 2: Flow of the study subjects

4.8 Implementation of observation and measurement variable

Children who underwent ophthalmic surgery under GA using LMA at Menelik-II hospital with exposure to either ketofol or propofol were compared to see different outcomes of both agents as an induction agent on ease of laryngeal mask airway insertion and hemodynamic stability. One hundred twenty ASA I and II patients who fulfilled the inclusion criteria were followed one minute before induction to start of spontaneous respiration in two months period.

The primary outcome measure was LMA insertion condition which was graded by the same anaesthetist who performs the procedure as (9).

a) Mouth opening: 1 – Full, 2 – Partial, 3 – Nil

b) Coughing: 1 – Nil, 2 – slight, 3 – gross

c) Swallowing: 1 – Nil, 2 – slight, 3 – gross

d) Movement: 1 – Nil, 2 – slight, 3 – gross

e) Laryngospasm: 1 – Nil, 2 – Mild, 3– Severe

f) Ease of LMA insertion: 1-Easy, 2-Difficult, 3- Impossible

Hemodynamic parameters were used as secondary outcome measures. Mean blood pressure, heart rate and arterial oxygen saturations were recorded 1 minute before induction (baseline), immediately after induction, immediately after LMA insertion, then at every minute for up to 3 minutes. The duration of apnoea was recorded via a digital timer as the time from the end of induction of anaesthesia until the return of adequate spontaneous ventilation.

In study hospital, after the patients are shifted to the operation room, standard monitoring such as electrocardiogram (ECG) leads, Non-Invasive Blood Pressure (NIBP) cuff and Pulse Oximetry always applied as routine protocol. Baseline vitals are recorded and I.V. fluids are administered. Patients are preoxygenated with 6L/min of Oxygen via face mask, for 3 minutes and given injection atropine 0.02mg/kg I.V. and Fentanyl 1µg/kg I.V prior to induction.

Insertion of LMA is performed 60 sec after induction. Following successful insertion, LMA position is assessed by observing chest movement and reservoir bag movement with both spontaneous and assisted ventilation. Patients are allowed to breathe spontaneously after successful LMA insertion. Assisted manual ventilation provided when the apnoeic period exceeded 20 seconds from time of LMA insertion to ensure that SpO2 remained > 95%. Manual

ventilation is ceased when adequate spontaneous respiration returned. Thereafter, anaesthesia is maintained with isoflurane 2% and oxygen 100% with flow rate of 3L/min.

The patients are either induced with ketofol (0.5mg/kg of ketamine plus 3.0mg/kg of propofol) or 3.5mg/kg or propofol alone. If the patients respond to stimulus after induction, further increments of propofol 0.5-1 mg/kg is given until loss of consciousness and loss of eye lash reflex in either technique. Our study used those patients induced with propofol as a cohort group, where the same checklist was used to observe the case.

4.9 Data collection technique and instrument

Data were collected by using pretested structured questionnaire. Data collectors were three BSc holder anaesthesia professionals and they were supervised by one MSc holder anaesthesia professional. All four anaesthetists participating in the study had at least five years of experience in conducting anaesthesia. Before recruiting patients into the study, training and orientation about the objective and process of data collection were provided by principal investigator. They were also instructed to declare loss to follow up when LMA is unable to be inserted within three attempts.

4.10 Data quality assurance

To ensure quality of data, pre-test of the questionnaire was performed on study populations. The completed questionnaire submitted and reviewed daily to avoid loss of data. Close supervision and daily information exchange were used as a means to correct problems during the course of data collection. Consent for the survey was obtained and confidentiality assured to improve the quality of data. Data consistency and completeness were made throughout the data collection, data entry and analysis.

4.11 Data processing and analysis

Data were checked manually for completeness and then coded and entered into epi info version 7 computer programs for cleaning. Descriptive statistics was used to summarize data, tables and figures. Data entry and cleaning was performed by principal investigator. Ten percent of the questionnaires were also cross checked with the already entered data to maintain its validity. All data were analysed by SPSS statistical package program (Version 20). Within the groups, normality of variables was measured using the Shapiro-Wilk test. Differences of numerical data between groups were evaluated using student's t-test and Mann–Whitney U-test when appropriate. Categorical data were analysed with the Chi-Square test. A p value of <0.05 was regarded as statistically significant.

4.12 Ethical Consideration

Ethical clearance and approval was obtained from ethical review committee, anesthesia department, Addis Ababa University. Permission to conduct was obtained from Menelik II hospital. The purpose of the study was explained to the family of patients under the study and written informed consent was obtained from family of each patient. The patients' family was informed that the care to be given was not be compromised in any way and confidentiality was assured. Name and other identifying information was not used in the study.

4.13 Presentation and dissemination plan

The final result of the study will be disseminated to AAU department of anesthesia, Addis Ababa health bureau and at large for Ethiopian Federal Ministry of Health. It will be presented in different workshops and seminars. Finally it will be submitted to a relevant scientific journal for publication.

CHAPTER FIVE: RESULTS

5.1: Socio-demographic features and operative conditions

A total of 120 patients were enrolled and none were excluded from the study as there was no incidence of failed LMA insertion. There were no statistically significant differences in age, sex, weight, and ASA or mallampati class between groups.

Table1: Socio-demographic features of the patients at Menelik II Hospital, Addis Ababa, Ethiopia, from Jan 25-March, 25, 2017.

Patient characteristics	Group KP (n=60)	Group P (n=60)
Age in years (median, Interquartile range)		
	5.5 (3-9)	7 (4-11)
Gender (n, %)		
Male	34(56.7)	35(58.3)
Female	26(43.3)	25(41.7)
Weight (median, Interquartile range) (kgs)	19.5(14-25)	26(15-30)
ASA (n, %)		
I	57(95.0)	59(98.3)
II	3(5.0)	1(1.7)
Mallampati class (n, %)		
Can't be assessed(<4years of, uncooperative)	18(30)	16(26.7)
I	40(66.7)	43(71.7)
II	2(3.3)	1(1.7)

ASA= American Society of Anesthesiologists

5.2: Comparison of ease of insertions conditions

In 12 (20%) of the propofol group patients, additional 0.5-1 mg/kg) propofol was required as compared to nine (15%) of those in ketofol group. However, no significant difference was noted between the two groups (p=0.631). The time from the LMA placement to the return of spontaneous ventilation was significantly longer in propofol group (240 seconds [range =60–390 seconds]) compared with ketofol group (180 seconds [range= 30–380 seconds]) (p= 0.005), expressed in median and range respectively. The LMA was inserted successfully and positioned correctly at the first attempt in 95% of patients receiving ketofol compared with 96.67% in patients receiving propofol [Table 2].

Table2: Requirement of Additional propofol, duration of apnea and attempts of LMA insertion at Menelik II Hospital, Addis Ababa, Ethiopia, from Jan 25 -March, 25, 2017.

	Group KP	Group P	p value
Required top up dose of propofol (n, %)			
	9(15)	12(20)	0.631
Duration of apnea (minutes)	180*(30–380 #)	240*(60– 390 #)	0.005
Attempts of LMA insertion(1/2/3)	57/3/0	58/2/0	0.648

**=Median, #=range*

LMA insertion summed score was nearly similar between the two group, which were statistically insignificant (p=0.511). No patient developed laryngospasm in ketofol group while 2 patients (3.33%) developed partial laryngospasm in propofol group but not statistically significant (p=0.154)

Table3: Comparison of insertion conditions of LMA between the ketofol and propofol groups at Menelik II Hospital, Addis Ababa, Ethiopia, from Jan 25-March, 25, 2017.

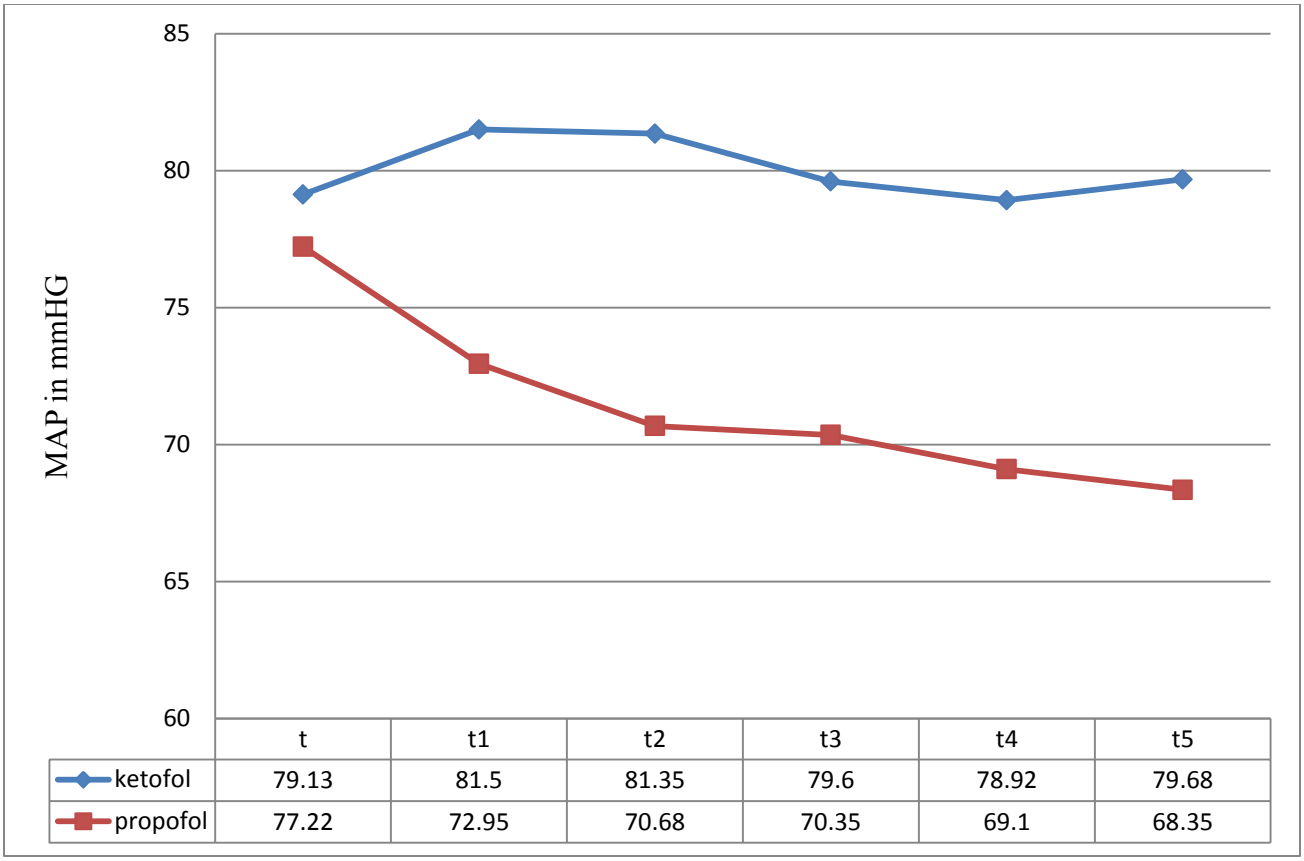
Assessment grades	Group KP	Group P	p value
Mouth opening (Full / Partial/None)	54/6/0	53/7/0	0.769
Coughing or gagging (Nil / Slight/Gross)	54/6/0	52/7/1	0.573
Swallowing (Nil / Slight/Gross)	55/5/0	54/5/1	0.604
Laryngospasm (Nil / Partial/Complete)	60/0/0	58/2/0	0.496
Ease of LMA insertion (easy/difficult/impossible)	59/1/0	58/2/0	0.956
Head or limbs movement (Nil / Slight/Gross)	57/3/0	58/2/0	0.648
Insertion condition summed score (ICSS)	6.35(6-10)	6.48(6-13)	0.607

5.3: Comparison of hemodynamic characteristics

Patients in both groups were comparable with respect to preoperative baseline hemodynamic conditions. The mean arterial pressure difference between the group is not significantly different before induction (p value = 0.263; is insignificant). With induction of anesthesia, significant drop in mean arterial blood pressure was observed in propofol group from baseline while in ketofol group, there was a rise in mean arterial pressure at all measurement times (P<0.001) [Figure 2]. Maximum mean blood pressure was 81.5±11.02 mmHg with ketofol group seen immediately after induction

Table4: Comparing the Mean of data on mean arterial blood pressure between ketofol and propofol at Menelik II Hospital, Addis Ababa, Ethiopia, from Jan 25-March, 25, 2017.

	Mean arterial pressure		P value
	Group KP (Mean ± SD)	Group P (Mean ± SD)	
Baseline MAP	79.13±8.96	77.22± 9.69	0.263
Immediately after induction	81.50±11.02	72.95± 12.349	<0.001
Immediately after LMA insertion	81.35 ± 11.339	70.68 ± 11.620	<0.001
One minute after LMA insertion	79.60 ± 11.036	70.35 ± 10.844	<0.001
Two minute after LMA insertion	78.92 ± 11.794	69.10± 10.188	<0.001
Three minute after LMA insertion	79.68 ± 11.978	68.35± 9.295	<0.001



	t	t1	t2	t3	t4	t5
ketofol	79.13	81.5	81.35	79.6	78.92	79.68
propofol	77.22	72.95	70.68	70.35	69.1	68.35

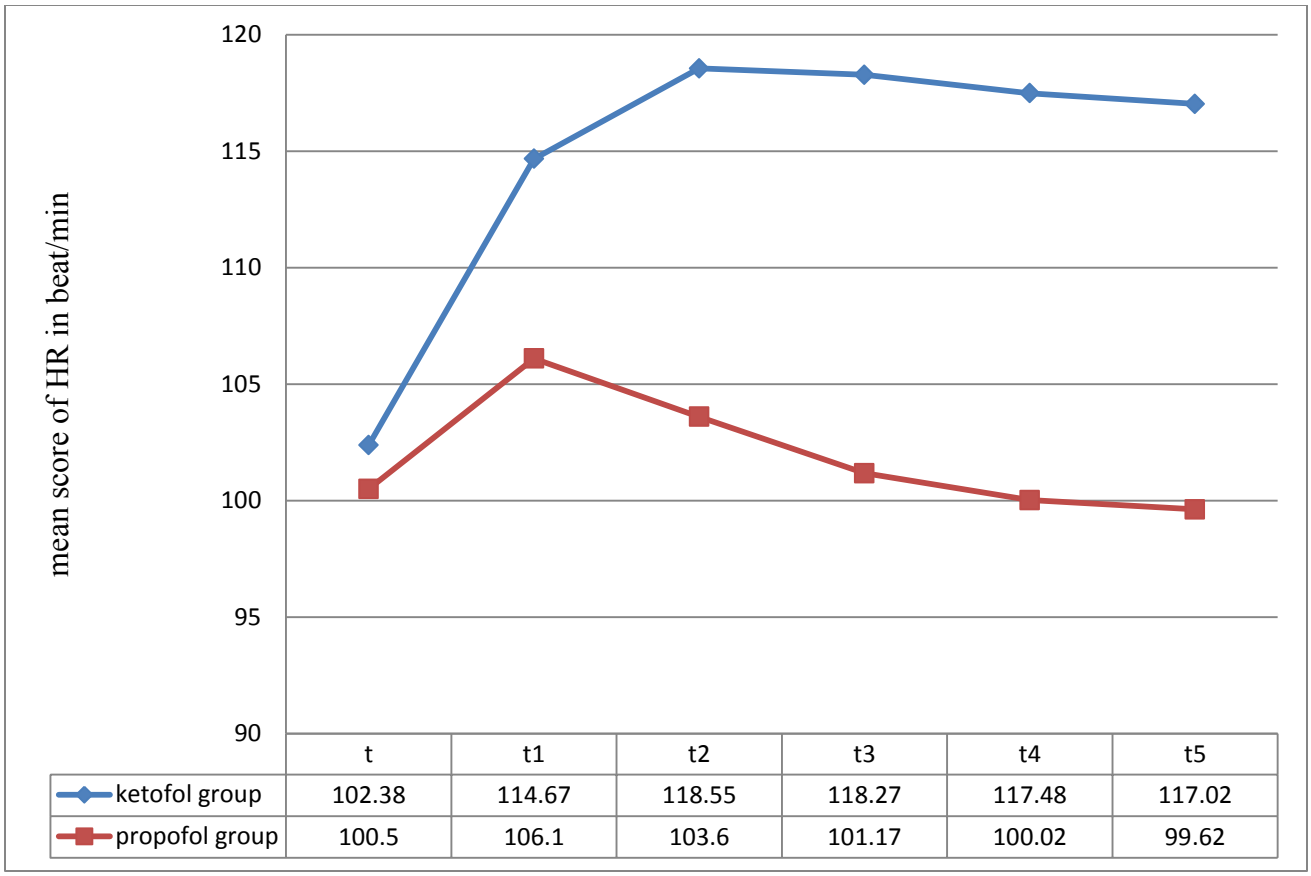
NB: t, baseline, t1, immediately following induction of anesthesia, t2, immediately after LMA placement, t3, t4, and t5,1,2 and 3 minutes after LMA placement.

Figure 3: Changes in mean arterial pressure between ketofol and propofol group

Pre operatively there was no statistically significance difference (p value > 0.05) between the HR of both groups. P values at all levels after induction were <0.05 and statistically significant. With induction of anesthesia, significant rise in heart rate was observed in ketofol group from baseline while in propofol group, there was a drop in heart rate at all measurement times (P<0.05) [Figure 3]. Increment in heart rate was seen immediately after induction comparing with baseline. Maximum heart rate was 118.55±24.86 beat/min with ketofol group seen immediately after LMA insertion. Minimum heart rate (99.62±25.071) was seen in propofol group 3 minute after LMA insertion

Table5: Comparing the Mean of data on heart rate between ketofol and propofol at Menelik II Hospital, Addis Ababa, Ethiopia, from Jan 25-March, 25, 2017

	Heart rate		P value
	Group KP (Mean ± SD)	Group P (mean ± SD)	
Baseline heart rate	102.38± 16.368	100.50± 17.070	0.539
Immediately after induction	114.67± 21.972	106.10± 21.802	0.034
Immediately after LMA insertion	118.55± 24.863	103.60± 23.449	<0.001
One minute after LMA insertion	118.27± 22.823	101.17± 24.668	<0.001
Two minute after LMA insertion	117.48± 20.994	100.02± 25.780	<0.001
Three minute after LMA insertion	117.02± 21.246	99.62± 25.071	<0.001



NB: t, baseline, t1, immediately following induction of anesthesia, t2, immediately after LMA placement, t3, t4, and t5,1,2 and 3 minutes after LMA placement.

Figure 4: Changes in heart rate between ketofol and propofol group

CHAPTER SIX: DISCUSSION

Smooth and successful insertion of LMA necessitates the adequate depth of anesthesia to suppress pharyngeal and laryngeal reflexes and prevent airway complications. Currently, propofol is the most widely used induction agent for LMA insertion as it provides rapid induction and excellent jaw relaxation, but it has many disadvantages such as swallowing, gagging, coughing or involuntary movements to severe complications such as laryngospasm, prolonged apnea, and hypotension (23-24).

In our study, LMA insertion summed score for ketofol and propofol group were nearly similar. This result coincides with the studies done by Goh et al. in their study of randomized double-blind comparison of ketamine-propofol, fentanyl-propofol and propofol-saline on haemodynamics and laryngeal mask airway insertion conditions (38).

In our study, in ketofol group we observed a decrease in requirement of additional dosage of propofol for induction, although it was not statistically significant ($p>0.05$).Consistent with our results, many researchers observed that, there was a significant decrease in additional requirement of propofol for induction, loss of consciousness and LMA insertion in ketofol group than propofol group. This less requirement of additional propofol dose is due to the combination effect of ketamine and propofol at both hypnotic and anesthetic end points (2, 15, 16). However, the reason for insignificant result in our study might have been due to the use of 3.5 mg/kg (high dose) of propofol for induction unlike Yousef et al (15). They administered initial 2mg/kg propofol and incremental doses of propofol until the target level of BIS 40 was obtained.

This study also shows that, apnea time was significantly longer in group P (median=240seconds [range =60– 390 seconds]) compared with ketofol group (median=180 seconds [range= 30–380 seconds]) (p= 0.005). Consistent with our study, Ozgul et al. in their study of comparison of propofol and Ketofol on laryngeal tube-suction II conditions and hemodynamics showed that apnea duration was longer in Group P (median=385 seconds [range =195–840 seconds]) compared with Group KP (median=325.5 seconds [range= 60–840 seconds]) but was not statistically significant(35). In their study we had observed that overall apnea time was higher than ours. This difference might have been due to the use of remifentanil (1µg/kg) 60 seconds after pre-oxygenation because remifentanil is known to have prolonged apnea time than fentanyl (47).

In another study done by Mohamad et al. on comparison between effects of ketamine and midazolam as co-induction agents with propofol for proseal^{TM} laryngeal mask insertion, the ketamine-propofol combination had a shorter duration of apnoea, better mouth opening and haemodynamic profile when compared to the midazolam-propofol combination (1).

Randomized double-blind comparison of ketamine-propofol and fentanyl-propofol for the insertion of laryngeal mask airway in children also concluded the combination of ketamine (0.5 mg/kg and propofol provides better conditions for LMA insertion in children than propofol and fentanyl (28).

Haemodynamic parameters can increase 20% after LMA insertion, with an additional 30% after orotracheal intubation (1). In our study, we observed that ketofol preserved mean arterial pressure at all measurement times while significant drop in mean arterial blood pressure was seen in propofol group [Figure 4]. Similarly several studies concluded that, ketofol is superior to propofol and propofol–thiopentone mixture because of its better hemodynamic stability (14,20,21,30,38).With induction of anesthesia, significant rise in heart rate was observed in ketofol group from baseline while in propofol group, there was a drop in heart rate at all measurement times ($P<0.05$). The cardiovascular stimulant effect of ketofol is desirable especially in pediatric anesthesia while unduly depressant effect of propofol is unwanted (14, 15).

Strength and Limitations of the study

The strength of this is the fact that the study participants were homogenous between the two groups and the study subjects were representative. The main limitation in this study is inability to conduct double blind control study. We feel further randomized double blind control studies should address to solve our limitations.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

The result of this study showed that, LMA insertion condition summed score was comparable in ketofol group and propofol group. There was a decrease in propofol requirement for induction in ketofol group. There was a more stable MAP picture in ketofol group when compared to that of propofol group. We conclude, by this study that ketofol (ketamine 0.5mg/kg administered with propofol 3mg/kg) compared with propofol 3.5 mg/kg provided equivalent LMA insertion conditions while maximizing hemodynamics and minimizing apnea.

7.2: Recommendations

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

- When parameters such as LMA insertion conditions and hemodynamic stability are considered, ketofol can be used as an alternative to propofol for LMA insertion in children.
- Researchers can use this study as a baseline data

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Annex II: Information Sheet

Title of the Research Project

Effect of Ketofol versus propofol as an induction agent on quality of laryngeal mask airway insertion and hemodynamic stability in children, Addis Ababa, Ethiopia, 2017: A Prospective Cohort Study

Name of Principal Investigator: Bacha Aberra (BSc in Anesthesia)

Name of advisor: Adugna Aregawi (Bsc, MSc)

Name of the Organization: Addis Ababa University, College of Medicine and Health Sciences, Department of Anesthesia

Name of the Sponsor: Addis Ababa University

Introduction:

This information sheet is prepared with the aim of comparing the effect of ketamine–propofol mixture (ketofol) and propofol on the insertion conditions of laryngeal mask airway and hemodynamics stability in children in Menelik II Hospital. The research group includes the principal investigator three data collectors, and one advisor

Purpose of the Research Project

The aim of this study was to compare the effect of ketamine–propofol mixture (ketofol) and propofol on the insertion conditions of laryngeal mask airway and hemodynamics stability in children from Jan 25, 2017-March, 25, 2017.

Procedure

All above 2 years old pediatric patients who underwent ophthalmic surgical operation under general anesthesia with LMA from Jan 25, 2017- March, 25, 2017 were involved in this study. Parents of each study participant were willing to participate in this study and gave written informed consent.

Benefits, Risk or Discomfort

There was no risk to the participants in participating in this research project because there was no any intervention taken other than observation.

Confidentiality

The information collected from study subjects were kept confidential and stored in a file, without their name by assigning a code number to it. And hence no report of the study ever identifies the participants.

Right to Refusal or Withdraw

They had full right to refuse participating in this research. They had also full right to withdraw themselves from this study at any time.

Person to contact

For any questions or concerns they can contact the principal investigator using the following addresses.

Name: Bacha Aberra

Telephone: +251 912391249

E-mail:bcabera11@gmail.com

Annex III: English Version Consent Form

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

Questionnaires prepared to compare the effect of ketamine–propofol mixture (ketofol) and propofol on the insertion conditions of LMA and hemodynamics stability in children undergoing elective ophthalmic surgery using LMA in Menelik II hospital, Addis Ababa Ethiopia.

Hello! My name is ----------I am one of the members of the research team. The purpose of this questionnaire is to gather information on the effect of ketamine–propofol mixture (ketofol) and propofol on the insertion conditions of LMA and hemodynamics stability in children undergoing elective ophthalmic surgery using LMA inMenelikII hospital. I have identified your child (family member) as a study participant hoping that you would be willing to give your assent during this observational study. Your participation on this study is definitely important to compare the effect of ketamine–propofol mixture (ketofol) and propofol on the insertion conditions of LMA and hemodynamics stability in children undergoing elective ophthalmic surgery using LMA in MenelikII hospital. It would help the government, policy makers and other stake holders to develop good health care delivery system. All information gathered will be kept confidential. I will not include any identifiers, such as your name or exact address. For your participation there is no specific benefit and if you find it not good you can quite the participation in between without any punishment. Indeed, your role in the success of the research is important and I appreciate your contribution to the research. Would this be okay with you?

I understood about the advantage of the research and the roles I will have in the research. I have agreed to participate in the research.

A. Agree ☐ B. disagree ☐

If Respondent agrees to be interviewed, the interview will be started

Questionnaire Code _____

Date of data collection _____Starting time _____finishing time _____

Name of data collector _____signature _____

Name of supervisor _____signature_____

Annex IV: Amharic Version Consent Form

በአዲስ አበባ ዩኒቨርሲቲ ጠፍ ሳይንስ ኮሌጅ፣ ህክምና ትምህርት ቤት፣ በደህረ-ምረቃ ፕሮግራም አንስቴዝያ ትምህርት ክፍል

የ ማ ዉ ይ ቅ ፈ ቃ ደ ኛ ነ ት ቅ ጽ

እንደምን ነዎት! ስሜ _____እባላለሁ፡፡ በአዲስ አበባ ዩኒቨርሲቲ በአንስቴዝያ ትምህርት ክፍል የምርምር ቡድን ዉስጥ አንድ አባል ነኝ፡፡ የዚህ ማዉይቅ አላማ በአፕራሲዎን ወቅት የአተነፋፈስ ስረዓትን ለማጠበቅ ከአየር ቧንቧ በላይ የሚቀመጥ የመተንፈሻ ቱቦ (LMA) ለሚከገባት የሚጠጡ ፕሮፖፎል ብቻ እና የፕሮፖፎልና ኬታሚን ድብልቅ ዉጠቃማነትን ለማወዳደር ጥናታዊ ምልከታ በማካሄድ ሚጃ ለማሳሰብ የሚገለግል ነዉ፡፡ ጥናቱን የሚካሂዳት በአዲስ አበባ ዩኒቨርስቲ አንስቴዝያ ት/ክፍል የሀለተኛ ድግሪ ተማሪ የሆኑት አቶ ባጫ አበራ ናቸዉ፡፡

የእርስዎን ልጅ (የቤተሰብ አባል) አንድ የጥናቱ ክፍል አድርጌ ስመጥ አስፈላጊ የሆኑ መጃዎችን እንደማገኝ በማሳብ ነዉ፡፡ለጥናቱ ፍቃድዎን ስለ ሰጠኝ ከወዲሁ አማሳግናለሁ፡፡

ከምልከታው የሚኝ ማንኛዉም መጃ በሚስጥር ይጠበቃል፡፡ ለዚህም ሲባል የእርስዎም ሆነ በጥናቱ ላይ የተሳተፈ የቤተሰብዎ አባል ሥማም ሆነ አድራሻ አይገለጽም፡፡ እርስዎ ያልፈቀዱትን ማንኛዉንም ምልከታ አናካሂድም፡፡ በማንኛዉም ሰዓት ከጥናቱ ሂደት እራስዎን ማገለል ይችላሉ፡፡ በጥናቱ በመሳተፍዎ የሚደረግ የተለየ ክፍያም ሆነ ጥናቱን በመቋረጥዎ የሚከፌሎዎት ቅጣት አይኖርም፡፡ ነገር ግን ቀደም ሲል እንደተገለጸው እርስዎ የተሳተፉበት ጥናት በአፕራሲዮን ጊዜ የሚጠጡ መድሃኒቶች ዉጠቃማነት ለማወዳደር ለሚደረገው ምርምር/ጥናት / በከፍተኛ ሁኔታ ያግዛል፡፡ እንድሁም ከጥናቱ በኋላ አፕራሲዎን ለሚደረግላቸዉ ታካሚዎች ዉጠቃማ ዬሆነ ወን መድሃኒት በተገቢዉ ጊዜ በማጠት ተገቢ የሆነ ወን እርምጃ ለመዉሰድ ይረዳል፡፡

የ ቃል ሥማማ ት

የዚህ ጥናት ዓላማው ገብቶኝ በጥናቱ ለመሳተፍ

ሀ. ፈቃደኛ ሆኛለሁ ☐ ለ. ፈቃደኛ አይደለሁም ☐

በጥናቱ ለማሳተፍ ፈቃደኛ ከሆኑ መቅጠል ይቻላል፡፡

የጥያቄው መለያ ቁጥር----------

ማዉይቁ የተካሄደበት ቀን ---------- የተጀመረበት ሰአት---------- ያለቀበት ስዓት----------

የጠየቂው ሥማ ፊርማ----------

የሱፐርቫይዘር ስማ ፊርማ----------

ጥናቱን በተመለከተ ማንኛዉም አይነት ጥያቄ ካላችሁ የሚከተለዉን አድራሻ ተጠቅመ፡፡

በዋናነት ምርምሩን የሚካሂዉ ሰዉ ስም፡ ባጫ አበራ

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Annex V: Questionnaires

Code no_____

Fill the blank spaces provided or put √ mark in the box when necessary and finally check the questions for completeness.

I: Socio-demographic characteristics and pre induction variables	
MRN_____	Ketofol ☐ propofol ☐
101.Age _____years	102. Sex M ☐ F ☐
103. Weight _____kg	104. height _____m
105. Diagnosis_____ _____	106. Planned surgery_____ _____
107. ASA Physical status ASA I ☐ ASA II ☐	108. Mallampati class MC I ☐ MC II ☐
109. Induction propofol dose _____mg/kg	110. Additional propofol dose _____mg/kg
111. Induction ketofol dose Ketamine _____mg/kg Propofol _____mg/kg	112. Additional propofol dose _____mg/kg
113. Premedication: Atropine _____mg/kg Other _____mg/kg	114. Opioid: Fentanyl _____mg/kg Other _____mg/kg
115. Maintainance Isoflurane _____% Halothane_____%	116. Size of LMA 1 ☐ 1.5 ☐ 2 ☐ 2.5 ☐ 3 ☐ 4 ☐

II: Conditions during insertion of LMA	
201.Use of lubricant jelly Yes ☐ No ☐	202.Experience of the anesthetist who perform LMA _____year(s)
203.Attempts during LMA insertion 1 ☐ 2 ☐ 3 ☐ >3 ☐	204.Mouth opening condition Full ☐ Partial ☐ Nil ☐
205.Gagging/coughing Nil ☐ Slight ☐ gross ☐	206.Swallowing Nil ☐ Slight ☐ Gross ☐
207.Laryngospasm Nil ☐ Partial ☐ Complete ☐	208.Ease of LMA insertion Easy ☐ Difficult ☐ Impossible ☐

III: Hemodynamic changes at different stages of anesthesia	
301.Mean arterial blood pressure changes in (mmHg) Baseline _____ Immediately after induction _____ Immediately after insertion _____ 1 min after LMA insertion _____ 2 min after LMA insertion _____ 3 min after LMA insertion _____	302.Changes in HR (beat per minute) Baseline _____ Immediately after induction _____ Immediately after insertion _____ 1 min after LMA insertion _____ 2 min after LMA insertion _____ 3 min after LMA insertion _____
303.Arterial oxygen saturation changes (%) Baseline _____ Immediately after induction _____ Immediately after insertion _____ 1 min after LMA insertion _____ 2 min after LMA insertion _____ 3 min after LMA insertion _____	304.Duration of apnea (time taken from loss of consciousness to return of spontaneous respiration) _____minute
Name of data collector _____ Signature _____	**Thank you!!!**