ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE
DEPARTMENT OF ANESTHESIA

Effectiveness of ketamine and propofol (ketofol) in 1:2 versus 1:3 combinations for Procedural sedation and analgesia in pediatric patients undergoing Bone marrow aspiration and / or Biopsy: A Prospective Cohort Study

Investigator: Meron Woubshet (Msc Anesthesia candidate)

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

June, 2020
Addis Ababa, Ethiopia

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Declaration

I, the undersigned declare that the research effectiveness of ketamine and propofol (ketofol) in 1:2 versus 1:3 combination for Procedural sedation and analgesia in pediatric patients undergoing BMB and/or Biopsy at Tikur Anbessa Specialized Hospital Addis Ababa Ethiopia : An institutional based Prospective cohort study, is my original work in partial fulfillment of the requirements for the master of science degree in anesthesia .I understand that plagiarism will not be tolerated and all directly quoted material has been appropriately referenced.

Investigator

Name: _____

Signature: _____

Approval of the Board of Examiners

1. Advisors

Name _____ Signature _____ Date _____

Name _____ Signature _____ Date _____

2. Internal Examiner

Name _____ Signature _____ Date _____

3. External Examiner

Name _____ Signature _____ Date _____

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Abbreviations/Acronyms

BMA	Bone Marrow Aspiration
BMB	Bone Marrow Biopsy
PSA	Procedural Sedation and Analgesia
KETOFOL	Ketamine and propofol single syringe combination
ALL	Acute Lymphoblastic Leukemia
LP	Lumbar puncture
ED	Emergency Department
ASA	American Society of Anesthesiologists
RSS	Ramsay Sedation Score
MAP	Mean arterial pressure
IQR	Inter quartile range
BP	Blood Pressure
HR	Heart Rate
ECG	Electrocardiography
SpO2	Arterial oxygen saturation
SPSS	Statistical Package for social sciences

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ABSTRACT

Background: *Bone marrow aspiration and Biopsy is a painful procedure done in children with hematologic disorders. The ideal drug administered during this procedure should have sedative and analgesic effect including hemodynamic stability and recovery with minimal side effects. Ketamine and propofol mixture is widely used for its combined effect of amnesia and analgesia as well as heamodynamic stability and decreased post procedural adverse events . This study mainly aims to compare the effectiveness of ketofol in 1:2versus 1:3 combinations for pediatrics undergoing BMA and/or Biopsy .*

Objectives: *The objective of this study was to compare the effectiveness of ketofol in 1:2 versus 1:3 combinations for Procedural sedation and analgesia in children undergoing Bone marrow aspiration and/or Biopsy at Tikur Anbessa Specialized Hospital.*

Methodology :*In this prospective cohort study128 pediatric patients age 1– 12 years undergoing BMA and/or Biopsy with ketofol 1:2 or 1:3 combination at Tikur Anebessa Specialized Hospital from December 2019-March 2020 were included. Hemodynamic and respiratory variables, were noted 1 min before induction (baseline) and every 10 minute until the procedure ends. Ramsay sedation score immediately after induction and every 10 minute during the procedure was recorded. Total sedative and analgesia use was recorded intraoperativley. Post procedural adverse events occurrence was followed in the postoperative period. Normality of the data was checked using Kolmogorov-smirnov test and analyzed using student t test for normally distributed data and chi-square test for categorical data. Non- parametric data was analyzed using Mann –Whitney U test with 95% CI and p- value less than 0.05 is considered as statistically significant.*

Results*: - ketofol 1:2 group (n=64) compared with ketofol 1:3 group (n=64) had similar sedation level assessed by RSS , heamodynamic and respiratory outcome, as well as general postoperative adverse events profile, but the total intraoperative analgesia consumption was significantly higher in ketofol 1:3 group (29.7%) when compared to ketofol 1:2 group (7.8%) with p=0.002.*

Conclusion and recommendation*: -Sedation level, general hemodynamic and respiratory profile including post procedural adverse events were comparable between groups. Higher intraoperative analgesia use in ketofol 1:3 group shows the need for additional analgesia in this combination. We recommend ketofol 1:2 combination for pediatrics undergoing BMA and/or Biopsy, due to decreased intraoperative analgesia requirement seen in the group.*

CHAPTER ONE

INTRODUCTION

1.1. Background

Bone marrow aspiration(BMA) is a cytological preparation of bone marrow cells obtained by aspiration of marrow and a smear of the cells. It is used to diagnose, confirm, and/or stage hematologic malignancies. It helps to evaluate cytopenias, thrombocytosis, leukocytosis, anemias, and iron status. It is also a diagnostic tool in non-hematological disorders such as storage disorders and systemic infections (1). During Bone marrow biopsy(BMB) a sample is taken from the bone to be examined under microscope.

BMA and Biopsy is is an invasive procedures often done in children. This procedure leads to considerable pain and distress in children, which is why they require adequate sedation and analgesia during the procedure. Sedation in children needs special considerations, and some drugs used for sedation are not as reliable as those for anaesthesia(2)**.**

Anesthetic agents for procedural sedation should have quick onset and recovery time, while providing satisfactory analgesia and sedation with cardiopulmonary homeostasis, amnesia, and motor control throughout the procedure. Although many pharmacological agents have some of these qualities, none possess all of them (3)**.**The question of "why not use one drug instead of two?" remains to be answered. There is no perfect drug at present, so one needs to find the right combination to achieve the perfect sedation(4)**.**

Ketamine and propofol mixed in the same syringe (ketofol) is gaining interest as the agent of choice for procedural sedation and analgesia (PSA), in hematological oncology interventions(5)**.** Propofol is an agent with rapid onset and short duration of action. It can be used for induction and maintenance of general anesthesia as well as for procedural sedation and mechanically ventilated adults. The unwanted effects include dose-related cardiovascular and respiratory depression and bradycardia. It has amnesic but no analgesic effect which for some clinicians is a potential concern when performing painful procedures. Ketamine is a phencyclidine anesthetic that produces intense analgesia and sympathetic nervous system stimulation, resulting in increased blood pressure and heart rate. Unlike propofol, ketamine causes minimal

cardiovascular and respiratory depression. Patients maintain protective airway reflexes as well as spontaneous respiration intraoperatively. A major adverse effect of ketamine is the incidence of emergence reactions at increasing doses such as nightmares or vivid hallucinations(6).

The combination of ketamine and propofol has received interest as a PSA regimen that allows the provision of the procedure using drug doses lower than typically required for each agent alone, while the nausea and psychic recovery effects of ketamine are counterbalanced by the sedative and antiemetic effects of propofol(7).

1.2. Statement of the Problem

Procedures done outside the operation theater have had an increasing trend in the recent years. Sedation, analgesia or both may be necessary to perform the majority of these diagnostic or interventional procedures like BMA and Biopsy(8). According to a study done by GohilM et al, pediatric age group (<15 years)were 34.52% of patients operated for BMA (9).

Invasive procedures like BMA and Biopsy can lead to considerable pain and distress in children, which is described by the patients as the most painful experience relating to their malignancy. In a retrospective study of childhood cancer survivors, invasive procedures have been reported as the most difficult part of treatment, leading to post traumatic stress symptoms in some long term survivors(10).Combination of Sedative and analgesic agents are often used for procedural sedation, which calls for cautious tittration of the drugs (11).

According to a study done by Bhatt et al the overall incidence of adverse events in procedural sedation in children due to pharmacologic agents was 11.7% where Oxygen desaturation [5.6%] and vomiting [5.2%]were the most common events. Some clinicians believe the sedation experience is improved because combination use offsets each individual agent's limitations (12). Prolonged sedation or recovery and failed sedation rates were also reported in the data, occurring 36 and 89 times per 10,000 sedation encounters, respectively (13).

Wide range of agents are available for pediatric PSA including more than a dozen pharmacological agents. (14). Nowadays, a combination of benzodiazepines and opioids are commonly used for sedation and analgesia. This combinations can be associated with prolonged

time of drugs' effect and delayed discharge after intervention; moreover, they may cause nausea, vomiting, apnea and muscle rigidity(8).

ketamines' safety, availability and potent analgesic effect makes it the preferable anaesthetic agent for many minor painful operations done indeveloping countries(15)**.** Ketamine has been compared with other procedural sedatives like ketamine/propofol for children undergoing procedural sedation. Mono therapy with ketamine had more adverse effects (49% vs. 25%) than ketamine/propofol respectively(16)**.** propofol is a popular sedative agent despite its potential for respiratory depression and hypotension. Many researches suggests that combining ketamine and propofol might produce hemodynamic stability, decrease respiratory depression, while stabilizing respiratory drive (17)**.**

New combinations like ketamine and propofol may replace older regimens. when used alone Ketamine could potentially cause hallucination, nystagmus and myoclonus, , but in combination with hypnotics, these side effects could be avoided (18)**.**

If a formulation of ketofol were identified that produced fewer adverse effects than either agent alone, it would improve sedation safety (19)**.** Different combination ratios of Ketamine and propofol have been studied before, butthe optimal mixture and dosing of ketamine and propofol has yet to be determined. The safety and efficacy of ketofol as a sedoanalgesic agent are dependent on the dose and the ratio of the mixture (11).

Ketofol is a relatively new idea for most medical practitioners. There is little in the scientific literature on its clinical efficacy for its use in children PSA during BMA and BMB, although other situations such as in emergency department and pediatric orthopedic surgery has previously been described(3).

As to the knowledge of the investigators, no data was found on the trend and practice of procedural sedation and analgesia for pediatricsin our country. Besides the favorable combined effect of ketofol its availability in our setup makes it the better drug of choice among other agents. Studies hypothesis addition of low dose ketamine to propofol produce good intraoperative and postoperative outcome . The common practice seen in our setting is using ketofol in either 1:2 or 1:3 combination, which calls for standardized guideline in order to achieve safe and desirable perioperative outcome.

1.3. Justification of the study

Common problems associated with different sedative and analgesic agents used for therapeutic and diagnostic procedures such as Bone marrow aspiration and Biopsy include respiratory depression, hemodynamic instability, emergence phenomena and post operative nausea and vomiting. These problems causing a prolonged hospital stay with additional drugs used to treat the symptoms are one of the major cost drivers in the postoperative period. Optimal sedation and analgesia allowing normal physiologic function cannot be achieved by a single agent without imposing additional risks on the patients. A combination of ketamine and propofol (ketofol) has garnered a favorable position for PSA. Despite this there is still different opinion among researchers on the effective combination of ketofol in terms of hemodynamic stability and decreased adverse events. Some authors suggested that shorter recovery time and lower heart rate makes the Combination of ketofol in 1:3for children sedation better than a combination of 1:2,whilesome authors showed that a 1 to 1 combination of propofol and ketamine has the same hemodynamic effects as a 1 to 3 proportion. Other authors also found Combination of 1:2 Ketamine-Propofol an appropriate ratio because of its hemodynamic and respiratory safety. These controversies and interracial difference in groups is one of the reasons which call for the study. There is no previous study done in Tikur Anbessa Specialized Hospital as well as in our country Ethiopia to assess the Effect of two different concentration of ketamine and propofol (ketofol)combination in pediatric patients undergoing Bone marrow aspiration and Biopsy, even though it has been studied in different parts of the world.

Therefore conducting such a research which intends to find the optimal ketamine and propofol combination is expected to have a value since it will improve the sedation experience for patients who undergo repeated procedures, increase perioperative outcomes by providing hemodynamic stability and decrease adverse events in the postoperstive period . On the other hand, it will open an opportunity to bring quality education, training, and further research activities by clinical professionals and researchers in their working environment. At least, it will create an expert transition of theoretical procedures to be done practically by providing additional knowledge.

CHAPTER TWO

2. LITERATURE

2.1. Efficacy of ketofol for PSA when compared with ketamine and propofol alone

Ketamine and propofol are pharmacologically compatible and have been used together as ketofol since the early 1990s for surgical anesthesia. Since then, ketofol's signature of combined sedation-analgesia with hemodynamic stability and preserved airway reflexes has led to popularity among those performing brief painful procedures (20)**.** Ketamine is a dissociative anesthetic that has been used with increasing frequency in EDs since the early 1990s. It isa phencyclidine derivative and provides sedation, analgesia, and amnesia. It does have several disadvantages, however, including vomiting, sialogogue properties, and a relatively long recovery time.The use of propofol for PSA in the ED was first described in 1996. Propofol (2,6-diisopropylphenol) is an ultra Yshort-acting, soy based intravenous hypnotic agent. Propofol's sedative and amnestic properties make it ideal for brief, non painful procedures. It does not, however, provide analgesia and thus cannot be used as the sole agent in PSA(14).

A combination of ketamine and propofol (ketofol) has several ideal anesthetic properties, as several clinical studies evaluated (11).

A study done to compare total sedation time when ketamine/propofol is used compared with ketamine alone for pediatric procedural sedation and analgesia found that ketamine/propofol is an effective combination for pediatric procedural sedation, providing a slightly shorter total sedation time than ketamine alone, with fewer adverse events and higher satisfaction scores (21)**.**

Meta-analysis and systematic review of ketofol versus propofol in PSA proved that addition of ketamine to propofol provided respiratory protection. Co administration of ketamine and propofol had lowered the incidence of hypotension and bradycardia , and prevalence of emergence phenomenon, was lower with ketofol than with ketamine alone (5.91% vs 10%-20%). Pooled data in the study showed that nausea and vomiting has been reduced to 3.49% in ketofol, probably due to antiemetic effect of propofol administration (22)**.**

According to a study conducted in Italy lumbar puncture performed in children under deep sedation with propofol and ketamine (in a 2:1 ratio with further doses of 1.0 mg/kg propofol administered in the case of agitation or complaint), during the procedures the evaluation of vital parameters (heart rate, respiratory rate, and blood pressure) did not show any significant variation compared to baseline values. Mean (heart rate) HR values were 111 ± 6 beats per minute. No apnea episode was recorded, and SpO2 ranged between 94 and 99 %.In all patients, satisfactory sedation was obtained; the mean Ramsay score was 6.15 ± 1. The mean time to awakening was 25 ± 10 min. After awakening, no child reported pain or discomfort during the procedures (23)**.**

In a prospective study that was conducted in Sudan for assessment and evaluation of the effectiveness and safety of the combination of ketamine and propofol in patients who undergone minor painful operations, the incidence of respiratory complications were low. This matches the result of another study done by Willman EV, and Andolfatto G. The study concluded that Ketofol appears to be safe, with fewer adverse side effects that were either self-limited or responded to minimal interventions (15).

2.2. Ketofol compared with other commonly used drug combinations for safe and effective procedural sedation

A prospective, randomized, double-blind trial was conducted in 100 children, of age 3–14 years, posted for emergency short surgical procedures in India,to compare the effectiveness and safety of intravenous infusion of the ketamine– propofol(PK) combination with the conventional fentanyl– propofol(PF) combination for emergency short surgical procedures in pediatric patients. Seven patients (14.6%) in group PK and 17 (38.6%) patients in group PF developed hypotension (P=0.009). Intraoperative MAP was significantly lower in group PF than group PK when compared with baseline. The study concluded that low-dose ketamine and propofol is more effective regimen than the propofol–fentanyl combination in paediatric emergency short surgical procedures in terms of haemodynamic and respiratory stability (24).

A study done in Iran to compare the ketamine/propofol (ketofol) combination with the midazolam/fentanyl (MF) combination in Emergency department (ED) in adult patients requiring procedural sedation and analgesia (PSA), most of the patients in the ketofol group underwent PSA with a Ramsay score between IV and VI (87.1%), while most of the patients in the MF

group had a Ramsay score of III or less (58.1%). Among the two study groups, reduction in the heart rate and respiratory rate values was not statistically significant compared with baseline values and there was no hypotension or evidence of poor perfusion in either group. The study concluded that coadministration of propofol and ketamine provided adequate sedation and analgesia for painful ED procedures with less oxygen desaturation than the combination of midazolam and fentanyl and a deeper level of sedation and analgesia according to the Ramsay score (25).

According to a study done in Saudi Arabia in the Pediatric Intensive Care Unit who received moderate sedation using ketamine and midazolam, adverse events including apnea, laryngeal spasm, hypotension, and recovery agitation were observed during moderate sedation. It has been noticed in four sessions ,i.e., 1.6%, which includes hypoxia, laryngeal spasm, and hypotension (26).

On the other hand a study done in Nigeria to compare the occurrence of hypoxia, apnea, and pain between ketamine–propofol and ketamine–midazolam combination conducted in 60 children aged 1–15 years scheduled for bone marrow aspiration and, or intrathecal chemotherapy showed that the oxygen saturation decreased to 83 and 88% in ketamine–propofol and ketamine–midazolam groups, respectively. This was accompanied by bradycardia with a heart rate of 56 and 58 beats/min, respectively. Both events responded to oxygen therapy. There was no episode of apnea, and all maintained spontaneous respiration. Hallucinations were more common in the ketamine–propofol group [4(6.7%)] than the ketamine–midazolam group [0 (0%)] (P=0.05). The occurrence of hypoxia, apnea, and pain was comparable following the administration of ketamine–propofol and ketamine–midazolam combination (5).

In a study conducted in Ethiopia assessing the effect of ketofol versus propofol as an induction agent on ease of laryngeal mask airway insertion conditions and hemodynamic stability in pediatrics, showed that there was a more stable MAP picture in the ketofol group when compared to that of propofol group. It was observed that ketofol preserved mean arterial pressure at all measurement times while a significant drop in mean arterial blood pressure was seen in the propofol group(27).

2.3. Different ketamine and propofol single syringe combinations for PSA

Studies have used a range of ketamine to propofol ratios from 1:1 to 1:10 and have evaluated its acceptability when used alone or have compared ketofol directly with ketamine**,** propofol, or other commonly used PSA combinations suchas fentanyl plus propofol. The wide range of doses used in these studies indicates a lack of consensus on how much ketofol to administer. The optimal ratio of propofol to ketamine for single-syringe administration has yet to be established (20).

According to a study done in Iran comparing 2 different intravenous concentrations of Ketofol group I (1:1) and group II (1:3) in patients aged 10 to 50 years undergoing closed reduction of the nose, a slight decrease of oxygen saturation occurred in some patients (Group II>Group I) who improved with respiratory support. The hemodynamic parameters showed no statistically significant difference between both groups. Vomiting and hallucination was considerably lower in Group II (P/K 3/1) when compared with Group I (P/K 1/1). Recovery duration was lower in Group II (28).

In another randomized double blind controltrial done in Iran, 80 Children were studied in two groups Ketamine and propofol in 1:3 and 1:5 group, for Intrathecal injection of chemotherapy drugs. Hemodynamic parameters, recovery time, and drug side effects were compared between two groups. The study demonstrated there were no significant differences in Spo2 ($p = 0.74$) and Ramsay score ($p = 0.62$) between two groups and concluded combination of ketamine and propofol (ketofol) in 1:5 ratio for sedation in the children undergoing intrathecal injection of chemotherapy drugs is better in terms of shorter recovery time, lower heart rate and minimal psychomimetic side effects (6).

Another study done in Iran comparing (Ketofol) in(1:2) (group I) and (1:3) (group II) Concentrations in Pediatric Patients under Lumbar Puncture or Bone Marrow Aspiration, showed that the Mean of procedure durations were not different in both groups (P-value= 0.57), but mean of recovery time was longer in group I. This difference was significant (P-value <0.001). Three patients in group I and one patient in group II experienced nausea (P-value= 0.41). Seven patients in group I and 1 in group II had hallucination (P-value= 0.05). No Respiratory problem and vomiting were seen in both groups. Ramsay scores were similar in two

groups after injection of 0.07 ml/kg, and additional drug was required to achieve Ramsay score of 5 (29).

Another study done in Iran to compareketofol in 1:1 (Group I) and 1:2 (Group II) combinations for procedural sedation and analgesia in children with hematological diseases, mean arterial blood pressure (MAP) showed minimal decrease from baseline in both groups following the initial dose of ketofol. All the patients had decrease in pulse rate compared to the baseline. The change was least in group II (89.91+/- 7.21 vs. 116.63+/-8.48) (p =0.06), but no patient had severe tachycardia requiring treatment in both groups. Patients in both groups did not have decrease in arterial oxygen saturation (SpO2) and hypoxia after induction (SpO2 <95%). In group I, two patients (4.1%) complained of postoperative nausea, 12 patients (50%) experienced hallucinations. In group II no patient complained of postoperative nausea but 6 patients (24%) experienced hallucinations(P-value=0.059)(8).

Here, the available evidence will be presented from a clinical perspective, the goal is to put the reported findings in a context relevant for the practicing anaesthetist and anesthesiologist and to provide new skills, filling knowledge gaps and evidence. It provides safe and effective alternative induction agent for procedural sedation and analgesia with improved hemodynamic stability when using different combination of ketofol in paediatrics undergoing bone marrow aspiration and biopsy.It also helps health administrators to work on quality improvement, enhancing good patient outcome, supplying cost-effective anesthetic drugs with the better patient outcome .

2.4. Hypothesis

1. **H.O**: There is no difference in level of sedation between the two groups.

   H.A: There is a difference in level of sedation between the two groups.
2. **H.O**: There is no difference in intraoperative Mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (SPO2) between the two groups.

   H.A: There is a difference in intraoperative Mean arterial pressure (MAP), heart rate (HR) and oxygen saturation (SPO2) between the two groups.
3. **H.O**: There is no difference in total analgesia requirement between the two groups.

   H.A: There is a difference in total analgesia requirement between the two groups.
4. **H.O**: There is no difference in postoperative adverse events(respiratory depression, hallucination, nausea and vomiting) between the two groups.

   H.A: There is a difference in postoperative adverse events(respiratory depression, hallucination, nausea and vomiting) between the two groups.

CHAPTER THREE

3. OBJECTIVE

3.1 General Objective

The General objective of this study was to compare effectiveness of ketofol 1:2 versus 1:3 combination for Procedural sedation and analgesia in pediatrics undergoing bone marrow aspiration and/or biopsy at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

3.2 Specific Objective

- To compare level of sedation
- To compare total analgesia requirement
- To compare intraoperative respiratory (spo2) and hemodynamic profiles (MAP and HR)
- To compare post procedural adverse effects (Nausea, vomiting, hallucination and respiratory depression)

CHAPTER FOUR:

4. METHODS AND MATERIALS

4.1 Study Area and period

This study was conducted at Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia. This hospital is multi-specialist tertiary care teaching hospital in Ethiopia, since 1972. Now a days; it is serving as main referral hospital and teaching facility to the country. The hospital has a total of 12 functional operating theaters and more than other 11 public hospitals situated in Addis Ababa. The sedation room is found in the pediatrics oncology department which on average, 256 pediatric patients undergo BMA and BMB within four months . The study was conducted from December 2019 - March 2020.

4.2 Study design

An institutional based Prospective observational cohort study design was conducted from December 2019 -March 2020.

4.3 Population

4.3.1 Source Population

All pediatric patients who underwent Bone Marrow Aspiration and/ or Biopsy with ketofol 1:2 or 1:3 sedation at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

4.3.2 Study population

Selected Pediatric patients who underwent Bone Marrow Aspiration and Biopsy with ketofol 1:2 or 1:3 sedation and fulfilled inclusion criteria during the study period at Tikur Anbessa specialized Hospital were included.

4.4 Eligibility criteria

4.4.1 Inclusion criteria

Patients of ASA class I and II, age ranging from 1-12 years and undergoing BMA and Biopsy with ketofol 1:2 or 1:3 combination were included in the study.

4.4.2 Exclusion criteria

- Pediatrics whounderwent Bone Marrow Aspiration and Biopsy with Local Anesthesia
- Previous allergic reaction to propofol and ketamine
- Other ketofol combinations used for sedation
- Chronic opioid use

4.5 Study variable

4.5.1 Dependent Variable

- Level of sedation
- Total analgesia requirement
- Intraoperative hemodynamic and respiratory profile
- Post procedural adverse events

4.5.2 Independent Variable

- Age
- Sex
- Weight
- ASA Status
- Additional study drug given
- Total doses of study drugs used intraoperatively
- Ketofol combination used (ketofol 1:2 vs 1:3)

4.6 OPERATIONAL DEFINITION

Ketofol 1:2- ketamine 0.5mg/kg and propofol 1mg/kg combination in a single syringe.

Ketofol 1:3- ketamine 0.5mg/kg and propofol 1.5mg/kg combination in a single syringe.

Sedation level : level of sedation will be assessed by Ramsay sedation scale.

ASA status: is a surgical risk stratifications validated by American Society of Anesthesiologist; described as follows:

ASA I: a healthy patient with no organic/physiological/psychiatric problems.

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

Ramsay sedation scale: The Ramsay scale assigns a score of 1–6 based on the clinical assessment of the level of sedation (1=anxious, agitated, restless; 2=awake, but cooperative, tranquil, orientated; 3=responds to verbal commands only). Scores 4–6 apply to sleeping patients and are graded according to the response to loud noise or a glabella tap (4=brisk response; 5=sluggish response; 6=no response)(5).

Additional study drug: ½ of the original study drug (ketofol 1:2 or 1:3) given.

Total analgesia requirement: Analgesia used in the intraoperative and postoperative period.

Post procedural adverse events : Nausea, vomiting, respiratory depression and Hallucination.

Respiratory Depression: Respiratory rate less than 8 breaths/min of more than or equal to 10 s in duration and/or apnea greater than 6 s (defined as no visible respiratory effort)(5).

Nausea : The urge to vomit.

Vomiting : Expulsion of stomach contents.

Hallucination : A profound distortion in a person's perception of reality.

4.7 Sample size and sampling procedure

4.7.1 Sample size calculation

Sample size was calculated using comparison between two means (Equal sample sizes) formula. Having no previous study done in the study area, result adopted from literature has been used to calculate sample size. According to results from recent study in Iran [6], the mean and standard deviation of Ramsay sedation scale were 4.17 and 0.64 respectively for group Iand 3.87 and 0.57 respectively for group II, which means $\mu 1$ (4.17), $\sigma 1$ (0.64) and $\mu 2$ (3.87) ,$\sigma 2$ (0.57) with

an alpha error of 0.05 at a power of 80%, when this value is incorporated into the formula for continuous outcome,

$$n_1 = n_2 = \frac{(z_{\alpha/2} + z_{\beta})^2 (\sigma_1^2 + \sigma_2^2)}{\Delta^2}$$

$$n1=n2= \frac{(1.96+0.84)^2(0.64^2+0.57^2)}{(4.17-3.87)^2} = n=63.89 \approx 64$$

Total sample size of 134 adding 5% of non-response for two groups.

4.7.2 Sampling Technique

The daily operation schedule list was used as a sampling frame. The situational analysis showed that 16 patients who fulfill the inclusion criteria were operated in Tikur Anbessa Hospital per week, according to this data we had 256 patients in our study period. Data was collected from 134 patients. So sample interval (k) was calculated as K=256/134, approximately 2. 1st participant selected by a lottery method, then every two patients were included in this study from the daily operation schedule list until the required sample size was met.

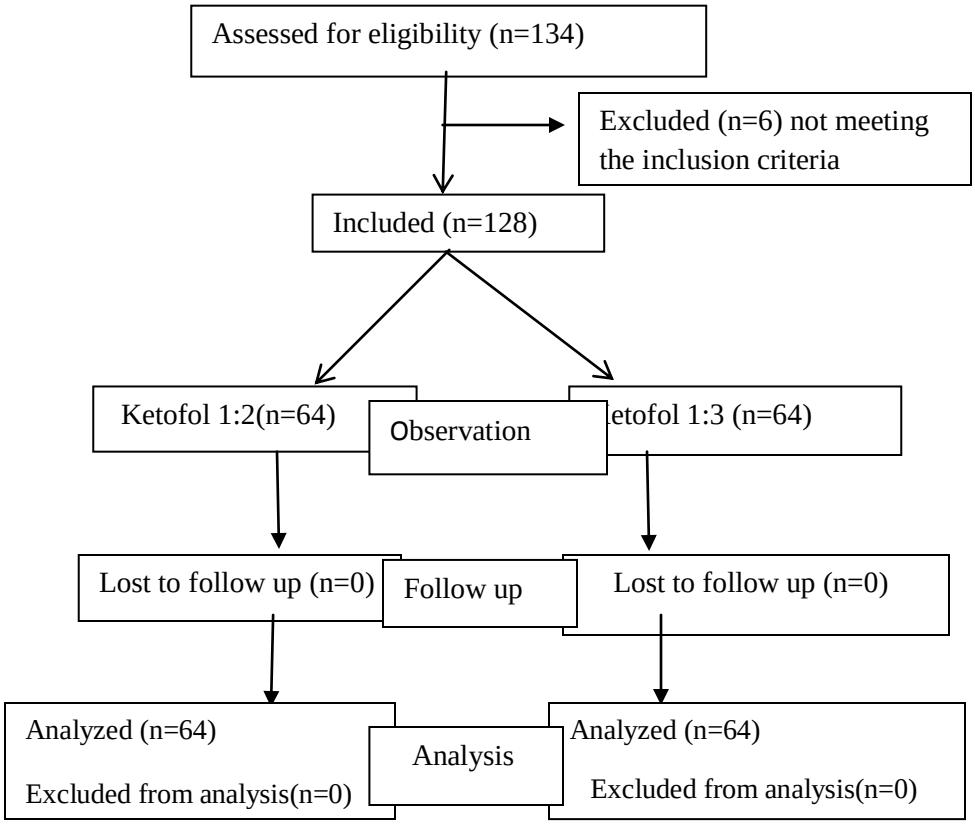

Figure 1: Flow of the study subjects

4.8 Implementation of observation and measurement variable

Children who underwent BMA and Biopsy at Tikur Anbessa hospital under sedation with ketofol 1:2 or ketofol 1:3 were compared to see sedative effect, total analgesia requirement and hemodynamic and respiratory stability as well as post sedation adverse event profile of both agents. One hundred twenty eight ASA I patients who fulfilled the inclusion criteria were followed one minute before induction up to recovery period in four months period. Ramsay sedation score was recorded immediately after induction and every 10 minute until the procedure ended. Mean arterial pressure, heart rate and arterial oxygen saturation were recorded 1 minute before induction (baseline) and at 10 ,20 and 30 minutes after induction. Total analgesia requirement was recorded in the perioperative period. Post procedural adverse event was followed for 20 up to 30 minutes in the recovery period.

In the study hospital, after the patients are shifted to the sedation room, standard monitoring such as, Non-Invasive Blood Pressure (NIBP) cuff, Pulse Oximetry and precordial stethoscope always applied as routine protocol. I V line is secured with 22 or 24-gauge cannula for those without an IV line and baseline vitals are recorded . Patients are preoxygenated with 4-6L/min of Oxygen via face mask for 2-3 minutes. After preparation of the surgical team sedative agents in the form of ketofol in either 1:2 (ketamine 0.5 mg/kg and propofol 1 mg/kg), 1:3 (ketamine 0.5 mg/kg and propofol 1.5 mg/kg) or other combination is injected. Patients are assessed for level of sedation using the Ramsay sedation score. After adequate level of sedation is reached the procedure will be started. 100 % oxygen by face mask is applied throughout the procedure and Patients are allowed to breathe spontaneously. Assisted manual ventilation provided for those who doesn't have adequate spontaneous breathing. During the procedure if the patient moves or responds to stimuli ½ of the study drug is addedby the same anaesthetist who performs the procedure. If the anesthetist observes any sign of pain, analgesia in the form of ketamine 0.5 mg/kg is given. At the end of the procedure patients are moved to recovery bed and followed for signs of adverse events. 100 % oxygen by face mask is applied until the patient is discharged. For patients who develop postoperative adverse events, treatment is provided by the recovery nurse per recovery room practice.

4.9 Data collection technique and instrument

Data was collected from December 2019 to March 2020 in selected study participants using pretested questionnaire, which have been performed with 5% of total sample size in Tikur Anbessa Specialized Hospital, 2 weeks before data collection started.

Anesthesia management for pediatric sedation in the study hospital is carried out by B.Sc. and M.Sc. anesthesia professionals. The drug selection and dosage for sedation depends on the personnel assigned to each case. Most anesthetist used one to three and one to two combination of ketamine and propofol , while the rest use other combination .

Baseline blood pressure using noninvasive blood pressure (NIBP), heart rate(HR) and oxygen saturation (Spo2) using pulse oximetery was recorded and continued every 10 minutes after then, until the end of procedure. The level of sedation was evaluated using the Ramsay sedation score. The occurrence of adverse events such as nausea and vomiting, hallucination and respiratory

depression was assessed and reported for the responsible clinician for management . The data collection was done by two Anesthetists after being familiar with the questionnaires and appropriate training was given on assessment tool. The principal investigator checked completeness of data every day.

4.10 Data quality assurance

To assure the quality of data training on the objectives and relevance of the study, brief Orientations on the assessment tool was provided for data collectors and supervisor. Data was checked for completeness accuracy and clarity on the day of the collection by supervisor and crosschecked by the principal investigator. The data collectors were instructed to write card number on the questionnaire during the data collection if further cross check is needed.

4.11 Data processing and analysis

Data was coded, edited and then entered to Statistical package for Social Sciences (SPSS) software version 22. Using SPSS Numeric data was described in terms of mean ± SD for symmetric and median (Interquartile range) for asymmetric numeric data. Comparison of numerical variables between study groups was done using unpaired student t- test and Manny Whitney U test for symmetric and asymmetric data respectively. Frequency and percentage was used to describe categorical variable and statistical difference between groups was tested using Chi square. Fishers exact test or pearsons chi square test were used depending on the cell value. Significance was determined at P value <0.05. The findings of the study was presented using narratives, graphs, tables and charts.

4.12 Ethical consideration

The study was conducted after approval by Addis Ababa University Ethical review board to conduct the study. A legal letter was submitted to Tikur Anbessa Specialized Hospital, where the study took place. Informed consent was obtained from all parents of patients after full explanations of the goals and procedures of the study. After taking permission from the hospital and study participants, data collection was conducted.

4.13 Result Dissemination plan

The result of the study will be submitted to the collage of medical and health science of Addis Ababa University, to the Hospital medical administration office, Addis Ababa city health bureau, Ethiopian Anesthetist Association and other responsible bodies. The result will be presented at collage of medical and health science in different seminars, meeting, conferences and workshops. Moreover, efforts will be done to publish the findings of the study and send to different reputable journals and scientific publications.

CHAPTER FIVE

5. RESULTS

5.1 Socio-demographic characteristics of the participants

A total of 128 patients (64 patients in each group) were finally involved for data analysis and interpretation of the study. There was no statistically significant difference among the groups with respect to age, sex, weight, ASA status, preoperative anticholinergic use, type of procedure and procedure time as shown in [Table1 and 2].

Table1: Socio-demographic features of the patients at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from December 2019 to March 2020

Groups	Group I	Group II	P value
Age in years (n, %)			
1-4	28(43.8%)	24(37.5%)	
5-8	18(28.1%)	25(39.1%)	
9-12	18(28.1%)	15(23.4%)	
Sex (n, %)			
Male	35(54.7%)	33(51.6%)	0.723
Female	29(45.3%)	31(48.4%)	
ASA Status			
ASA I	64(100%)	64(100%)	
ASA II	0	0	
Weightin kg (Mean ± SD)	19.02 ± 6.876	18.03 ± 6.402	0.404

Table 2: Operative and anesthetic data of group I (ketofol 1:2) and group II (ketofol 1:3) patients at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from December 2019 to March 2020

Groups	Group I	Group II	P value
Procedure (n, %) **BMA** **BMB** **Both**	 7(10.9%) 1(1.6%) 56(87.5%)	 11(17.2%) 1(1.6%) 52(81.3%)	
Preoperative anticholinergic use(n,%)	16(25.0%)	10(15.6%)	0.187
Duration of procedure (Median, IQR)	(20,15-25)	(20,15-25)	0.511

5.2 Comparison of intraoperative hemodynamic and respiratory profile

Patients in both groups were comparable with respect to preoperative baseline hemodynamic (HR and MAP) and respiratory conditions (Spo2) . Although not statistically significant, the mean heart rate in group II (ketofol 1:3) was higher when compared to group I (ketofol 1:2), after sedation started (p=0.052 and p=0.092 at10 minute and 20 minute respectively).

Fig.2: Changes in Heart rate between Group I(ketofol 1:2) and Group II(ketofol 1:3) patients at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from December 2019 to March 2020

There was no statistically significant difference in mean arterial blood pressure at all measurement times between the groups as shown in table 3.

Table 3: Comparing the Mean of data on mean arterial pressure between group I(ketofol 1:2) and group II(ketofol 1:3) patients at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from December 2019 to March 2020

Groups	MAP		P value
	Group I	Group II	
Baseline MAP	74.06* ± 7.694#	73.78* ± 7.371#	P=0.833
After 10 minute	74.69* ± 7.698#	74.92* ± 8.197#	p=0.868
After 20 minute	74.19* ± 6.506#	73.81* ± 6.645#	p=0.828

*= Mean, # Standard deviation

Since the intraoperative oxygen saturation and Ramsay sadation score was not normally distributed as checked by kolmogorov-smirnov test, Mann-Whitney U test was used to compare the mean difference. There was no statistically significant difference in oxygen saturation at all measurement times during the procedure between the groups as shown in table 4.

Table 4: Comparing the Mean of data on spo2 between group I(ketofol 1:2) and group II(ketofol 1:3) patients at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from December 2019 to March , 2020

Groups	Spo2		P value
	Group I(ketofol 1:2)	Group II(ketofol 1:3)	
Baseline spo_2	(97*,96-98#)	(97*,96-98#)	0.544
After 10 minute	(99*,99-100 #)	(100*,99-100#)	0.450
After 20 minute	(100*,99-100#)	(100*,99 -100#)	0.235

*Median, # Range

5.3 Comparison of Ramsay sedation scale

Ramsay sedation scale throughout the procedure was not significantly different between the two groups as shown in table 5.

Table 5: Comparing the Mean Ramsay sedation score between group I (ketofol 1:2) and group II (ketofol 1:3) patients at Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from December 2019 to March 2020 G.C

Groups	RSS		p value
	Group I (ketofol 1:2)	Group II(ketofol 1:3)	
Immediately after induction	(6*,6-6#)	(6*,6-6#)	0.652
After 10 minute	(5*,4-5#)	(5*,4-5#)	0.507
After 20 minute	(4*,4-4#)	(4*,4-5#)	0.198

*Median, # Range

5.4 Additional study drug use and total analgesia consumption

Total intraoperative propofol used between the two groups was not significantly different, while the total intraoperative ketamine used was greater in group II and significantly different than group I (p=0.030). Additional intraoperative study drug use between the groups was not significantly different. Preoperative analgesia was not given for either of the groups. 26 patients in group II and 5 patients in group I required intraoperative analgesia, which was statistically significant with (p=0.002). Post operative analgesia was given for 3 patients in group I and 1 patient in group II (p=0.272, not statistically significant) as shown in table 6.

Table 6: Comparing additional study drug use and total analgesia consumption between group I (ketofol 1:2) and group II (ketofol 1:3) patientsat Tikur Anbessa specialized Hospital, Addis Ababa, Ethiopia, from December 2019 to March 2020

Groups	Group I	Group II	P value
Additional study drug given	31(48.4%)	33(51.6%)	0.215
Preoperative analgesia consumption	0	0	
Intraoperative analgesia consumption	5(7.8%)	19(29.7%)	0.002
Total propofol (mg) (Mean ± SD)	49.84*±15.93#	51.72*±17.733#	0.530
Total ketamine (mg) (Mean ± SD)	19.64* ±8.214#	23.08*±9.447#	0.030
Postoperative analgesia consumption	3(4.7%)	1(1.6%)	0.619

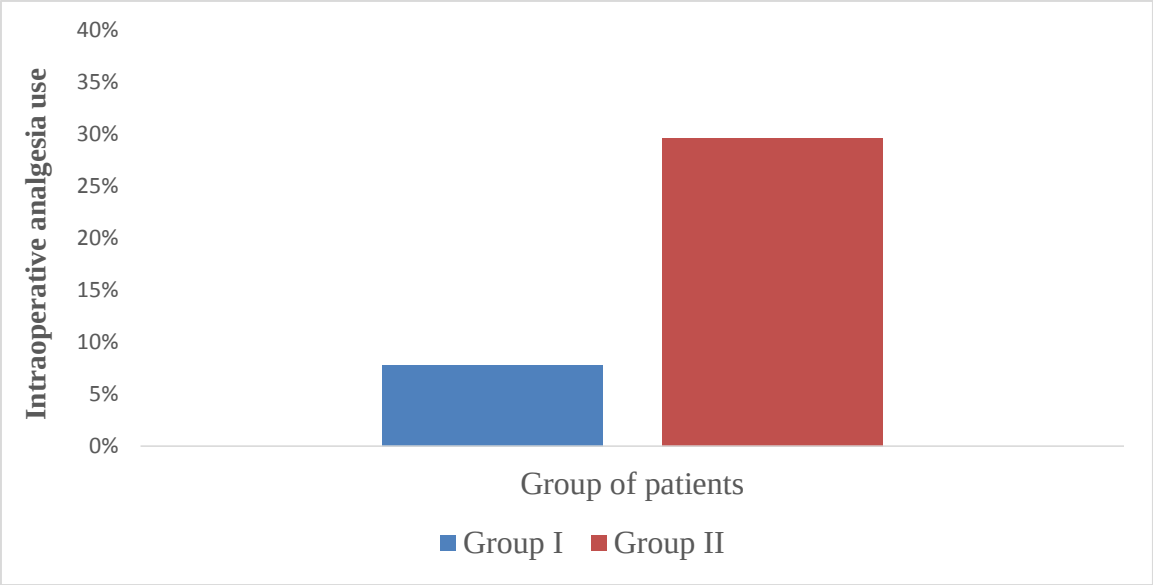

Fig.3: Intraoperative analgesia use between Group I(ketofol 1:2) and Group II (ketofol 1:3) patients at Tikur Anbessa specialized Hospital Addis Ababa, Ethiopia, from December 2019 to March 2020 G.C

5.5 Comparison of postoperative adverse events

No patient in either of the groups has developed Postoperative nausea, vomiting as well as respiratory depression . 5(7.8%) patients in group II only developed postoperative hallucination. However no significant difference was noted between the groups(p=0.058).

CHAPTER SIX

6. DISCUSSION

The components of Procedural sedation and analgesia should include adequate level of sedation and analgesia, minimal adverse drug-related events, and a stable cardiovascular and respiratory status (7). Since there is no one ideal agent present, it is common to use combination of different drugs.

Several Studies which investigated ketofol mixtures with various proportions of ketamine and propofol, suggest combining low dose ketamine with propofol produces adequate sedation and analgesia with minimal adverse events. However, no consensus has been reached on an optimal Ketamine- Propofol ratio (30) .

The findings of the present study showed that the combination of ketamine and propofol (ketofol) in 1:2 proportion produced a decreased additional analgesia requirement with stable intraoperative hemodynamic and respiratory status and safe post procedural adverse events profile.

The Ramsay sedationscore (RSS) was the tool used to assess level of sedation, during the current research. Median RSS was not significantly different at all measurement times throughout the procedure between the two groups. This result coincides with a study done by Yazdi G et al. in the randomized double blinded study designed to compare the effect of two different concentration of ketamine and propofol combinations in 1:2 and 1:3 groups in pediatric patients under lumbar puncture or BMA (29).

In another randomized, double blinded study done by Hashemi A et al designed to compare the quality of analgesia and side effects of intravenous ketofol in 1:1 and 1:2 group, Ramsay sedation scores were similar in both groups (7).

Cardiovascular depressant effects of propofol can be offset by the sympathomimetic effects of ketamine, resulting in stable hemodynamic and respiratory profiles(7) . Therewas no statistically significant difference found in mean arterial pressure at all measurement times between groups

in the current study. Consistent with ourresult, a study done by Yazdi et al. and Behdad S et al. comparing different concentrations of ketamine and propofol combinations in pediatric patients , MAP was similar at different times during the procedure ($p>0.05$) (6,29). A similar result was found by Aberra et al comparing effect of ketofol versus propofol as an induction agent on ease of laryngeal mask airway insertion conditions and hemodynamic stability in pediatrics. The researcher observed that ketofol (0.5mg/ kg of ketamine plus 3.0mg/kg of propofol) preserved mean arterial pressure at all measurement times while a significant drop in mean arterial blood pressure was seen in the propofol group (27).

In the current study,although the mean Heart rate in group II was higher than group I , it was not statistically significantly between the groups throughout the procedure. Consistent with our results, a study done by Kip G et al. Comparing three Different Proportions of Ketofol in 1:1, 1:2 and 1:4 ratio in Children Undergoing Dental treatment,mean HR values of patients in study groups were found similar ($P > 0.05$) (30).

In contrast to our findings, a study done by Behdad S et al. found the mean of heart rate in ketofol 1:3group (109.43 ± 6.65) was greater compared to ketofol 1:5group (100.73 ± 8.26) with ($p = 0.0001$, statistically significant), the researchers related higher ketamine dose in ketofol 1:3 group for the significant difference in mean HR between the groups (6). where as in the current study increased in mean heart rate seen in group II was perceived as sign of inadequate analgesia by the anesthesia provider, hence higher additional intraoperative ketamine (0.5 mg/kg) use for analgesic purpose in the group .

In the current study , while total doses of propofol between the groups was not significantly different, the total ketamine in group II (ketofol 1:3) was higher and significantly different than group I, which was due to ketamine 0.5 mg/kg use for intraoperative analgesia in group II (29.7%) than in group I (7.8%) as practiced in the sedation room. The result of this study shows increased intraoperative analgesia requirement in the group which received ketofol 1:3 combination. There were no other studies found which compared the total analgesia requirement between different ketamine and propofol combinations, which made it difficult to compare the current findings.

48.4% patients in group I and 51.6% patients in group II were given additional study drugintraoperatively, which was not statistically significant. Different from the current finding, in a study done by Kip G et al. additional mean ketofol doses used in groups were significantly different from each other (P = 0.005). In Group 3 (ketefol 1:4), additional doses were used in 14 patients (46.7%), where additional doses were used in only 3 patients (10.0%) in Group 1(ketofol 1:1) (X2 = 10.569, P = 0.001)(30).

However, when comparing the results, it must be pointed out that the study drugs were administered using infusion technique in the above study, where as bolus technique was used to deliver the study drugs in the current study . The researchers suggested that constant and continuous dose delivered by continuous infusion may lead to a more steady‐state sedation level with fewer additional bolus doses.

The addition of ketamine to propofol during PSA seems to reduce the frequency of hypoxia and airway compromise (8). In the present study there was no statistically significant difference between groups in oxygen saturation levels at all measurement times.Consistent with the current findings, there was no significant difference between groups regarding peripheral oxygen saturation levels (P > 0.05) in the study done by Kip et al (30) .

In contrast to the present study, a study done by Daabiss M et al. on assessment of different concentration of ketofol (1:1) and (1:4) in procedural operation, five patients (10%) in group I (1:1) and three patients (6%) in group II (1:4) had apnea and hypoxia after induction (SpO2 <95%). The researchers speculate that apnea and desaturation which happened in group I (10%) could be due to the excessive salivation related to higher dose of ketamine (31). The reason for insignificant result in our study might have been due to the routine use of 100 % oxygen by face mask throughout the procedure.

It is thought that the sedative effects of propofol mitigate adverse events such as recovery agitation and vomiting that are associated with ketamine use (7). In the current study there was no post procedural nausea and vomiting recorded in both groups.This is consistent with what has been found in a study done by Behdad S et al (6).

Hallucination is known as one of the emergence phenomena associated with ketamine use.5(7.8%) patients in group II only developed postoperative hallucination, which can be due to

higher ketamine use in the group. However the difference was not statistically significant between the groups (p=0.058). In contrast to our finding, a study done by Ayatollahi V et al to compare two different concentration of ketofol in 1:1 and 1:3 ratios for PSA, there was higher proportion of vomitting and hallucination in ketofol 1:1 which was statistically significant . The researcher concluded that higher and significantly different concentration of propofol used in ketofol 1:3 group can be attributed for the fewer side effects (28). The reason for insignificant result in our study might have been due to the similar mean doses of propofol use between the two groups.

No patients in both groups has developed respiratory depression in the recovery period . A similar pattern of results was obtained in other studies implying that small dose of ketamine use in ketofol combination minimizes post procedural adverse events (7,29,30,31).

6.1 Strength and Limitations of the study

Strength

- The strength of this study is the fact that the study participants were homogeneous between the two groups and the study subjects were representative.

Limitations

- The main limitation in this study is the inability to conduct double blind control study.
- Another limitations of this study were, lack of separate recovery room for the participants after the procedure and the presence of patients treated in out patient basis, which attributed to the limited time for post operative follow up which was on average 20-30 minutes.
- Most studies used for comparison were randomized control trial.

CHAPTER SEVEN

7. CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

The result of this study showed that the level of sedation assessed by Ramsay sedation score was comparable between the two groups. Additional study drug use was similar between groups unlike intraoperative analgesia consumption, which was higher in ketofol 1:3 groups. There was a comparable HR, MAP and oxygen saturation profile in both groups. Although 5 patients in group II developed post procedural hallucination, both combinations had a general favorable outcome in postoperative adverse events profile. We conclude, by this study that ketofol (1:2) compared with ketofol (1:3) generally provide equivalent sedative effect, hemodynamic and respiratory stability and over all safety of postoperative adverse events, while minimizing the need for additional intraoperative analgesia.

7.2 Recommendations

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

- When parameters such as hemodynamic and respiratory profile, intraoperative analgesia requirement and post procedural adverse events is considered, ketofol 1:2 combination for pediatrics undergoing BMA and Biopsy can be used as an alternative to ketofol 1:3 combination .
- Further randomized control trial to avoid bias in finding the optimal ketofol combination for pediatrics undergoing BMA and Biopsy.

REFERENCES

1. Abla O , JFriedman , JDoyle . Performing bone marrow aspiration and biopsy in children: Recommended guidelines. Paediatr child Health 2008 Jul/Aug;13(6):499-501.

2. Sethi DS, Smith J.Pediatric sedation. Anaesthesia Tutorial of the week 105(2008)

3. Habibi MR, kiabi FH, soleimani A, Zedi AE.**S**edation and analgesia during bone marrow. Indian journal of medical and paediatric oncology. 2013Oct-Dec; 34(4): 337-339.

4. Sedationsolutions. [Online] [Cited: 9 19, 2019.] http://www.sedationsolutions.co.uk.

5. Oyebola O, Temiye EO, Asiyanbi G K, Akanmu N O, Desalu I. Ketamine–propofol versus ketamine–midazolam for procedural. Research and Opinion in Anesthesia & Intensive Care. 2018 Oct; 5(3): 198-204.

6. Behdad S, Karimi N, Fallah R, Yazdi AG, Vaziribozorg S, Haddad F. Two different concentrations of propofol and ketamine combinations in pediatric patients under intrathecal injection of chemotherapy drugs Int J Res Med Sci 2015 Dec ;3:3677-80. .

7. Hashemi A, Ayatolahi V, Ghilian R, Yazdi G. Ketofol for bone marrow aspiration and lumbar puncture in. Iranian Journal of Pediatric Hematology Oncology. 2011 Nov; 1(4): 126-132.

8. Masoud N, Shafa A, Golparvar M, Godarzi K. Comparison of Analgesic and Sedative Effects of Ketamine-Propofol. 2017, Vol. 22(5): 1-7.

9. Gohil M, Rathod K. Bone Marrow Aspiration Cytology Study in a Tertiary Care Center,Gujarat, India. Int J Sci Stud 2018 Jan;5(10):11-14.

10. Ghasemi A, Gharavi F M, Sabzevari A R. General Anesthesia for Lumbar Puncture and Bone Marrow Aspiration. Iranian Journal of Pediatric Hematology Oncology. 2013Mar; 3(2): 54-58.

11. Amornyotin S . Ketofol: A Combination of Ketamine and Propofol. Journal of Anesthesia & Critical Care. 2014 Nov 18; 1(5): 1-3.

12. Maala B, David W, Johnson,J Chan,M Taljaard, N Barrowman, Farion J, Ali S, Beno S Dixon A,.M M Timoney. Risk Factors for Adverse Events in Emergency Department. JAMAPediatrics. 2017 Aug 21; 17(10): 957-964.

13. Joseph P, Cravero, George T. Blike, Michael Beach, Susan M. Gallagher, James H, Hertzog, Jeana E. Havidich and Barry Gelman. Incidence and Nature of Adverse Events During. PEDIATRICS. 2006 Nov; 118(3): 1087-1096.

14. Michelle J, Alletag, Marc A, Awerbach, Carl R, Baum. Ketamine, Propofol, and Ketofol Use for Pediatric Sedation. Pediatric Emergency Care. 2012 Dec; 28(12): 1391-1395.
15. Gamal A, Ejaimil, Ali A, Salama. A Prospective Evaluation of "Ketofol"(Ketamine/Propofol. Annals of International Medical and Dental Research. 2016 Mar; 2(2): 341-349.
16. Elizabeth J, Beckman. Analgesia and Sedation. PedSAP. 2017, 3: 7-30.
17. Mittal N, Goyal A, Gauba K, Kapur A. Jain A Double Blind Randomized Trial of Ketofol Versus Propofol for. The Journal of Clinical Pediatric Dentistry. 2013 Jul; 37(4): 415-420.
18. Gokcinar D, Ergin V, Cumaoglu A, Menevse A, Aricioglu A. Effects of ketamine, propofol, and ketofol on proinflammatory cytokines and markers of oxidative stress in a rat model of endotoxemia-induced acute lung injury. Acta Biochim Pol. 2013, 60(3): 451-456.
19. James R, Johanna C, Erin J, Plummer D, Hubbard L, Richard O. Randomized, Double-Blinded, Clinical Trial of Propofol, 1:1 Propofol/Ketamine, and 4:1 Propofol/Ketamine for Deep. Annals of Emergency Medicine. 2014 May; 1-9.
20. Finn L, Jacqueline A H, Brian J A. Ketofol Dosing Simulations for Procedural Sedation. Pediatric Emergency Care. 2014 Sep; 30(9): 621-630.
21. Amit S, Mosdossy G, Mcleol S, Lehnhardt K, Peddle M, Rieder M. A Blinded, Randomized Controlled Trial to Evaluate Ketamine/Propofol Versus Ketamine Alone for Procedural Sedation in Children. Annals of Emergency Medicine. 2011 May; 57(5): 425-433.
22. Mohammad J, Bahreni M, Ieani A D, Masoomi R, Arbab M, Mirfazaelian H. Ketamine-propofol combination (ketofol) vs propofol for procedural sedation and analgesia: systematic review and meta-analysis. American Journal of Emergency Medicine. 2016 Dec; 36: 558-569.
23. Maurizi P, Russo I, Riccardi R. Safe lumbar puncture under analgo-sedation in children with acute lymphoblastic leukemia. Int J Clin Oncol. 2013, 1-5.
24. Khutia S K, Mandal M C, Das S. Intravenous infusion of ketamine–propofol can be an alternative to intravenous infusion of fentanyl–propofol for deep sedation and analgesia in paediatric patients undergoing emergency short surgical procedures. Indian Journal of Anaesthesia. 2012, 56(2): 145-151.
25. Nejati A, Shariat R, Harari, Ashraf H, Lalaf A, Golshani K. Ketamine⁄Propofol Versus Midazolam⁄Fentanyl for Procedural Sedation and Analgesia in the Emergency Department: A

Randomized, Prospective, Double-Blind Trial. Society for Academic Emergency Medicine. 2011Mar 8; 18(8): 800-806.

26. Hazwani TR, Al-Alem H. Procedural moderate sedation with ketamine in pediatric critical care unit. Avicenna J Med 2017 Jan‐ Mar;7:7‐ 11.
27. Bacha A, Aregawi A, Teklay G, Tasew H. Effect of ketofol versus propofol as an induction agent on ease of laryngeal mask airway insertion conditions and hemodynamic stability in pediatrics. BMC Anesthesiology. 2019 Mar;19(41): 1-8.
28. Vida A. Two Different Concentrations of Ketofol for Procedural Sedation and Analgesia in Closed Reduction of Nasal Fracture. The Journal of Craniofacial Surgery. 2016 Jun; 24(4): 996-1000.
29. Yazdi AG, Ayatollahi V, Hashemi A, Behdad S H, Yazdi. Effect of two Different Concentrations of Propofol and Ketamine Combinations (Ketofol) in Pediatric Patients under Lumbar Puncture or Bone Marrow Aspiration. Iranian Journal of Pediatric Hematology Oncology. 2013 Mar; 3(1): 187-192.
30. Kip G, Atabek D, Bani M. comparision of three different ketofol proportions in children undergoing dental treatment. Niger J clin pract. 2018 Nov; 21: 1501-7.
31. Daabiss M, Elsherbiny M, Otaibi R A. Assessment of different concentrations of ketofol in procedural operations. Saudi Journal of Anesthesia. 2009 Apr; 3(1):15-19.

Annex I

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 and propofol (ketofol)in 1:2 versus 1:3combinations for procedural sedation and analgesia in pediatric patients undergoing Bone marrow aspiration and Biopsy in Tikur Anbessa Specialized Hospital

Hello, my name is _____ and I'm a data collector for the study entitled Effect of ketamine and propofol (ketofol)combination for PSA in pediatric patients undergoing Bone marrow aspiration and Biopsy at Tikur Anbessa Specialized Hospital. It is a study aimed to assess the effect of using the two combination of ketofol during the procedure in this hospital.

Being a part of this study will not affect your child in any way the service He/She are getting in this hospital. Your child is selected randomly to participate in the study just because He / She undergoes a procedure in this hospital no other special criteria. You are free to withdraw your child from the study and you can stop answering to any questions that are forwarded to you at any time you want. In the study any answer you gave will be confidential and in addition your child's name, address or any information that identifies your child will not be used.

Do you give permission to have your child included in the study?

A. Agree ☐ B. disagree ☐

Annex II

Amharic version of verbal consent form

ከቃለ መጠይቅ በፊት ፈቃደኝነት መጠየቂያ ቅጽ፡

ሰላምታ ጤና ይስጥላኝ
እኔ _____እባላለሁ፡፡ በአዲስ አበባ ዩንቨርስቲ አንስትዚያ ት/ቤት የጥናት ቡድን አባል ነኝ፡፡ የጥናቱ ዋና አላማ በሆስፒታሉ ውስጥ የመቅኔ ምርመራ የተደረገላቸውን ህፃናት ህመማን የሚሰጣቸውን ሁለት የሰመመን መድሀኒት ቅልቅል ውጤት መገምገም ነው፡፡ ይህንን በተመለከተ ስለ ልጆ የተወሰኑ ጥያቄዎችን ልጠይቆት እፈልጋለሁ፡፡ መጠይቁ 2-5 ደቂቃ ብቻ የሚፈጅ ሲሆን ተሳትፎዎት ሙሉ በሙሉ በዕርሶ ፈቃደኝነት ላይ የተመሰረተ ነው፡፡
በዚህ ጥናት ልጆ መሳተፉም ሆነ አለመሳተፉ በሆስፒታሉ ውስጥ በሚያገኘው/በምታገኘው አገልግሎት ላይ ምንም አይነት ለውጥ አያመጣም፡፡ ልጆ የተመረጠው/ችው በዚህ ሆስፒታል ህክምና ስለተደረገለት/ላታ ብቻ ነው፡፡

ቃለ መጠይቁን በማንኛውም ሰአት ማቋረጥ ወይም ጥያቄዎችን አለመመለስ ይችላሉ፡፡ ለጥያቄዎች የሚሰጧቸዉ መልሶች በሚስጥር የሚጠበቁ ሲሆን የልጆ ስም ወይንም ልጆን የሚለይ ማንኛውም መረጃ አይገለጽም፡፡ እንዲሁም የሚሰጡት ምላሽ ከልጆ ማንነት ጋር በማንኛውም መልኩ አይያያዝም፡፡
ልጆ በጥናቱ እንዲካተት ፈቃደኛ ኖት?

ሀ. ፈቃደኛ ሆኛለሁ ☐ **ለ . ፈቃደኛ አይደለሁም** ☐

Annexe III

Questioner

Section I: Socio Demographic Data (chart review) and preoperative Data

Card number:		**Bed no:**	**Code**
Ser. no	**Question**	**Response**	
101	Age	1.< 1 3. 5-8 2. 1-4 4.> 9	
102	Sex (M/F)	1. Male 2. Female	
103	Weight(kg)		
104	Height(cm)		
105	BMI	1.≥24kg/m2 2.≥30kg/m2 3.≥35kg/m2 4.other value_____	
106	ASA physical status	1. ASAI 2. ASA II	
107	Does the patient have any Coexisting disease?	1.Yes 2.No	
108	If yes specify	1.Cardiac 2.Respiratory 3.Renal 4.other	
109	Preoperative Diagnosis		
110	Planed procedure		

Section II: Question related to anesthesia management

S.no	Question	Response	Code
201	Did the patient receive any analgesia before induction?	1. YES 2. 2. NO	
202	If yes specify type and dose	1.Fentanyl____(mg) 2.Tramadol ____(mg) 3.Paracitamol___(mg) 4.Ketamine____(mg) 5.Other____(mg)	
203	Did the patient receive any anti emetic agent before induction?	1. Yes 2. 2. NO	
204	If yes specify type and dose	1 .Metochlopromide___mg 2. ondasetrone ___mg) 3. other	
205	Did the patient receive any premedication, anticholinergic.	1. YES 2. NO	
206	If yes specify type and dose	1.Atropine___mg 2.Glycopyrulate__mg 3.Other _____ mg	
207	Type of Induction agent	1. IV 2. Inhalational	
208	Induction drug and dose given	1. Thiopental ____mg 2. Propofol ____mg 3. Ketamine____ mg 4. Halothane ____MAC	

209	Ketofol combination Ratio used for induction	1. 1:2 2. 1:3 3.Other combination	
210	Additional bolus drug given for maintainance?	1. YES 2. NO	
211	If yes specify type and dose	1.Ketamine ____mg 2.Propofol ____mg 3.Ketofol ____mg	
212	Was intraoperative analgesia given?	1. YES 2. 2. NO	
213	If yes specify type and dose of the drug given	1. Fentanyl ____mg 2. Tramadol ____mg 3. Paracetamol __mg 4. Ketamine ____mg 5. Other ____mg	
214	Total sedation agents used intraoperatively (mg)	1 2	
215	Duration of procedure(min)		

Section III: Hemodynamic changes (HR and MAP) and respiratory profile (spo2) in the intraoperative period

TIME(min)	Hemodynamic change		Spo2(%)
	HR(beats/min)	MAP(mmhg)	
Before induction			
After induction			
After 10 min			
After 20 min			
After 30 min			

Section IV: Intraoperative Ramsay Sedation score (RSS)

Time	Ramsay Sedation score (RSS)
After induction	
10 min	
20 min	
30 min	

Section V: Post operative adverse events profile

s.no	Question	Response	code
501	Did the patient show signs of nausea during recovery period?	1. YES 2. NO	
502	If yes specify any interventions given	1. Reassurance 2. Antiemetics 3. Other	
503	Did the patient develop vomiting during recovery period	1. YES 2. NO	
504	If yes specify any interventions given	1. Reassurance 2. Antiemetics 3. Other	
505	Did the patient show signs of hallucination during recovery period?	1. YES 2. NO	
506	If yes any interventions given	1. Reassurance 2. Anxiolitics 3. other	
507	Did the patient show sign of respiratory depression?	1. YES 2. NO	
508	If yes any interventions done/given	1. Reposition airway alignment 2. 100 % oxygen 3. Other	
509	Was post-operative analgesia given?	1. YES 2. NO	
510	If yes specify type and dose of the drug given	1. Fentanyl___mg 2. Tramadol ___ mg 3. Paracetamol __mg 4. Other __mg	

Ramsay Sedation Score(RSS)

Score	Definition
1	Patient is anxious and agitated, restless
2	Patient is cooperative, oriented and quite
3	Patient responds to commands only
4	Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient exhibits no response