EFFECTIVENESS OF VENO-OCCLUSION WITH LIGNOCAINE FOR PREVENTION OF PROPOFOL-INDUCED VASCULAR PAIN AT THE KENYATTA NATIONAL HOSPITAL

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H58/87342/2016

DISSERTATION SUBMITTED IN PART F ULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN ANAESTHESIA OF THE UNIVERSITY OF NAIROBI

STUDENT'S DECLARATION

I declare that this dissertation is my original work and has not been submitted for a degree award in this or any other university. All resources contained herein have been duly acknowledged.

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DEDICATION

To my parents and husband who have inspired and offered endless love and support.

ACKNOWLEDGEMENT

I wish to express my sincere gratitude to:

The Almighty God for giving me strength and perseverance

My supervisors, Dr. Patrick Olang' and Professor Thomas Chokwe for their continued support and guidance in the dissertation.

To my colleagues in the department of Anaesthesia for their constant encouragement.

EFFECTIVENESS OF VENO-OCCLUSION WITH LIGNOCAINE FOR PREVENTION OF PROPOFOL-INDUCED VASCULAR PAIN AT THE KENYATTA NATIONAL HOSPITAL

A COMPARATIVE STUDY BETWEEN LIGNOCAINE ALONE AND VENO-OCCLUSION WITH LIGNOCAINE FOR PREVENTION OF PROPOFOL-INDUCED VASCULAR PAIN AT THE KENYATTA NATIONAL HOSPITAL

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LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologist
GABA	G-Aminobutyric Acid
KNH	Kenyatta National Hospital
LCT	Long-Chain Triglycerides
MCT	Medium-Chain Triglycerides
NMDA	N-Methyl-D-Aspartate
NSAID	Non-Steroidal Anti-Inflammatory Drug
PVP	Propofol vascular pain
SD	Standard Deviation
VAS	Visual Analogue Scale

ABSTRACT

Background

Propofol is an intravenous sedative hypnotic agent widely used for induction and maintenance of general anesthesia. Pain is an acknowledged reaction of propofol administration which can be very disquieting to the patient [1–3]. Identifying an ideal method to lower the pain levels precipitated by propofol on induction has been a challenge and thus several studies have been conducted in view of the same, one being the use of lignocaine with venous occlusion [4].

Study Objective

To compare the two methods used to reduce propofol-induced pain; one involving veno-occlusion with lignocaine and one using lignocaine without veno-occlusion during Propofol injection.

Study Design

This was a comparative observational study carried out at the KNH main theatre during induction of anesthesia. 78 adult patients aged between 18-85 years were included in this study. The study procedure was explained to eligible patients and a written informed consent obtained. The anesthetic choice and application was at the discretion of the attending anesthesiologist to whom information was made known that observation would be made using VAS scores on tolerability to pain with propofol administration.

Results

lidocaine is widely used for alleviating PVP and our findings showed that giving 40mg of 2% lidocaine for 60seconds with venous occlusion [4–6] has proven to be more superior and effective than giving lidocaine alone prior to propofol administration with no major correlation on age, gender or ASA status. This is confirmed from the lower mean pain scores in the veno occlusion group compared to the lidocaine alone group. (U=110, P= <0.001)

Conclusion

It is apparent that the strategy to preclude PVP should be multifaceted and that giving 40mg of 2% lidocaine for 60seconds with venous occlusion [4–6] has proven to be more superior and effective than giving lidocaine alone prior to propofol administration.

1.0 CHAPTER ONE: INTRODUCTION

Propofol (2,6 di-isopropyl phenol) belongs to a group of chemicals known as alkyl phenols. It is insoluble in aqueous media, but highly lipid soluble and is either available as 1% or 2% formulations. The 1% formulation of propofol has purified egg phosphatide, soybean oil and glycerol. Disodium edetate is usually affixed as a bacterial growth inhibitor due to its high nutrient component formulation.

Propofol has been conventionally utilized for inducing and maintaining general anesthesia due to its ease of titration, predictability and rapid onset of action [7]. Its mechanism of action is via activation of G-Aminobutyric Acid GABA(A), inhibition of NMDA(N-Methyl-D-aspartate) receptors as well as modulation of calcium ion influx via slow calcium ion channels.

Pain is an acknowledged reaction of propofol administration [1–3] . Pain post propofol administration can be disquieting and is known to affect between 28% and 90% of patients [6]. Propofol can directly inflame the skin, mucous membranes and venous intima and can instantly lead to nociceptor and free nerve ending stimulation [8].

Injection pain is associated with the concentration of the aqueous free propofol [9]. PVP has been mainly attributed to the contact between the aqueous phase and the venous intima.

It has been advocated that propofol causes release of bradykinin via activation of the kallikrein-kinin system [1], leading to venous dilation and hyper-permeability, enhancing the contact between aqueous phase of propofol and free nerve endings, resulting in deferred pain within 10-20 seconds [10].

Several other factors attributed to pain on injection can be assessed, and these include the intrinsic drug properties defined by emulsion composition, pH, temperature, injection volume and osmolarity; as well as the injection technique [11], [12], drug concentration in the aqueous phase, rate of IV carrier fluid, use of local anesthetics, and the buffering effect of blood [11], [13], [14].

Many pre-treatment agents and techniques have been analyzed for alleviation of the pain associated with propofol injection [15]. Veno-occlusion with lignocaine administration prior to propofol injection is one such application that has been studied and shown to be an effective mode of preventing propofol-induced injection pain [4]. Though these techniques are part of routine clinical practice locally, no objective evaluation has been carried out on its effectiveness in comparison to other modalities of maintaining pain free anesthetic

administration (research gap) and this study therefore seeks to prove that veno-occlusion with lignocaine is more effectual than administration of lignocaine alone in assuaging propofol induced vascular pain and should be adopted by anesthesiologist for better anesthetic outcomes.

The 2 studies that were done by Dae Hee Kim et al and Massad et al on the use of veno-occlusion with lignocaine both demonstrated that veno-occlusion with lignocaine is more superior than the other applications.

2.0 CHAPTER TWO: LITERATURE REVIEW

Propofol (2,6 diisopropylphenol) is classified as an alkylphenol and is used as an intravenous sedative hypnotic agent [16]. It is considered to be more potent than inhaled agents and boasts an ephemeral activity, hence the favored agent for inducing and maintaining general anesthesia [17].

2.1 Physical and Biochemical Properties of Propofol

In its adulterated form, it exists as a colorless to pale straw-colored liquid at ambient temperature. It freezes at 19^0 C. The molecular formula of propofol is $C_{12}H_{18}O$. It is a simple phenol substituted with 2 isopropyl groups in the Ortho positions abutting to the hydroxyl group. The hydroxyl group serves as the only ionizable functional group, thus propofol is a highly lipophilic weak acid with a pKa of 11 [18]. The high lipophilicity associated with Propofol means that it can only be administered as an emulsion [19].

2.2 Formulations

Propofol was originally formulated in Cremophar El. However, it was associated with frequent anaphylactoid reactions and injection pain, and was discontinued from use [20]. Lipid emulsions were then developed with the most common formulation being 1% propofol in an emulsion equivalent to 10% Intralipid which contains Soybean oil, purified egg lecithin and glycerol. Each component within the emulsion serves to ensure maximum efficacy of the drug. The Glycerol maintains the isotonicity of the formulation with blood, the soybean oil serves as the stabilizing agent and the egg lecithin serves to emulsify the formulation [21].The pH of the suspension is then maintained at 7.5-8.0 by a sodium hydroxide base in order to maintain the stability of the formulation.

Lipid emulsions impact on onset time, potency, and awakening time compared to the initial formulation in Cremophar EL [20], however, newer formulations continue to be developed in order to increase the efficacy of the drug as well as minimize the side effects. Some of these new formulations include the introduction of medium chain triglycerides into the formulation which initially contained only long chain triglycerides (LCT vs MCT/LCT formulations) whereby the MCT/LCT formulations have shown less pain on injection [22]. In addition, introduction of Nano emulsion techniques have helped to improve the stability of propofol and useful life of the drug as well as reducing the pain associated with injecting the drug [23].

Lipid formulations have been shown to support microbial growth. Bacteria such as Staphylococcus aureus, Esherichia coli, Pseudomonas aeruginosa, Klebsiella Pneumonae and Candida albicans have been cultured from Propofol [24]. Various measures have been taken to try and suppress the growth of these microorganisms. These include use of Ethylene diaminetetraacetic acid (EDTA), sodium metabisulfite or the use of benzyl alcohol [7].

2.3 Pharmacokinetics

Propofol is normally administered through the intravenous route and has limited effect either per rectally or orally [25]. It has been shown to have limited bioavailability through these two routes due to extensive first pass metabolism in the intestinal wall.

Once propofol has been administered intravenously, the distribution through the body compartments is explained by a three-compartment linear model. This model proposes that once the drug is administered it enters the first central compartment (V_1) which is usually plasma, the second compartment which equilibrates rapidly (well perfused tissues e.g. the brain, V_2) and the third compartment which equilibrate slowly (Poorly perfused tissues e.g. fatty tissue). These models allow for the calculation of the volumes of distribution as well as rate constants for transfer of drugs across these compartments. Based on this model following administration of Propofol as a bolus, the concentration of the drug rapidly equilibrates between the brain and plasma, hence the rapid onset of anesthesia. The distribution is not constant over time, but decreases as the drug equilibrates between plasma and the tissues. This distribution is a product of infusion rate and duration.

2.4 Pharmacodynamics

The operating principles of propofol is not very well understood. However, it is postulated that its action involves activation of the inhibitory function of the neurotransmitter g-aminobutyric acid (GABA) [26]. The specific receptor it works on is $GABA_A$ [27]. Its mechanism of action maybe via a decrease in dissociation from GABA receptors in the brain and enhancing the inhibitory effects of the neurotransmitter. This, in turn increases the duration of opening of the chloride channels resulting in hyperpolarization of the cell membrane. Through its actions on $GABA_A$ receptors in the hippocampus and prefrontal cortex, propofol inhibits acetylcholine release [17]. This action appears to be important for the sedative effects of propofol.

It has been postulated that propofol also acts through the α adrenergic system whereby it may act on adrenergic receptors as part of its mechanism for sleep induction [28]. The

neuroprotective effects exhibited by propofol in high concentration is as a result of calcium surges secondary to NMDA receptor inhibition [29].

2.5 Mechanisms of Pain Induced by Propofol

70% of patients experience vascular pain if no pretreatment is administered at induction if propofol is used [2]. The American society of Anesthesiologists rank this pain as the 7th most significant drawback as it is sharp, excruciating, aching, burning and sometimes unbearable [2].

Propofol vascular pain can be either immediate or delayed. The immediate effect is most likely attributable to the direct effect of the drug on the vascular intima via nociceptive receptors/free nerve endings (A-delta fibres) while the delayed effects are most probably due to the activation of the Kallikrein-kinin cascade [1] with a 10-20 seconds latency period [30]. The free concentration within the 10% of propofol is thought to be associated with this pain at the site of injection [9].

A study that was conducted in rats by Ando et al in 2005 suggested that there was release of prostanoids particularly prostaglandin E2 may be a contributor to the pain of propofol injection [31].

This theory/study was further strengthened by the fact that pre-medicating with prostaglandin inhibitors-NSAIDS (flurbiprofen) accompanied by veno-occlusion reportedly minimized pain on propofol injection [30].

Other factors that are thought to contribute to the occurrence and severity of pain include temperature in pH of formula, age of patient, mixing formula with blood, size of vein, plastic syringes, carrier fluid infusion, filtration of formulae and celerity of injection.

2.5.1 Modification of Drug Composition

Modification of the lipid composition of propofol was thought to be one of the methods used to reduce PVP, though other formulations introduced into the market still under study, have been attempted to be used. Amphastor Pharmaceuticals & Company in USA introduced Ampofol® with a lower lipid emulsion containing 50% less soya bean oil, which is equipotent to propofol but was seen to induce more pain compared to the LCT formulas. Cleofol®, another clear solution of propofol with a lower lipid load was also reported to be associated with double incidence of pain than the LCT formulas. A new pro-drug of propofol, GPI 15715, water

soluble, is thought to induce less pain, however it is still under study. Currently MCT/LCT (Lipuro®) are being introduced are thought to have lower incidences of PVP compared to LCT alone preparations (Diprivan ^{TM}). This is attributed to elevated levels of free propofol within the aqueous phase in emulsions containing LCT compared to MCT/LCT formulations.

2.5.2 Cooling and Warming of Formula

In a study conducted by Mc Crirrick in 2005, concluded that the occurrence and severity of pain at the injection site was markedly diminished when propofol was infused at 4^0C .This was attributed to the cooling effect of the drug on the free nerve endings and inhibition of Kallikrein-kinin system leading to reduction in pain transmission [32].

Warming of the formulae to body temperature was thought to decrease the free concentration of propofol which is responsible for the pain. This may promote bacterial contamination especially in MCT/LCT formulations. Picard et al, in his meta- analysis, concluded that neither cooling nor warming had any effect on PVP [6].

2.5.3 Acidification of Propofol Formulae

Acidification of propofol is thought to reduce free propofol concentration hence reduction of pain at injection site while maintaining its potency [33].

2.5.4 Dilution of Formula / Infusion of Carrier Fluid

Clement et al concluded dilution of propofol with 5% dextrose reduces the free concentration of propofol, which is responsible for PVP, hence reduction in incidence of pain [34].

Huang et al demonstrated that infusion of propofol with a carrier fluid worsened PVP because of disruption of the lamina flow and enhancement of turbulent flow, which exposes the vascular endothelium to the free propofol, worsening pain [35].

2.5.5 Filtration Formula

It has been postulated that the use of micro-filters of approximately 0.2 micro-meters reduced both intensity and incidence of PVP due to reduction in contaminants of silicon lubricants released by the disposable plastic syringes when in contact with propofol [36].

2.5.6 Caliber of Vein

The severity and incidence of PVP is inversely proportional to the size of the vein, explaining more pain on propofol administration in pediatrics.

In adults, pain intensity ranges from 25% - 90% on the veins at the dorsum of the hand, 3% - 36% in the large veins (anti-cubital fossa). Injecting propofol in large veins is associated with less pain because less of the aqueous propofol interacts with the vascular intima as most remains mid-stream secondary to a higher blood flow [37].

2.5.7 Infusion Rate

Rapid infusion rate of propofol is associated with less pain as compared to pushing it slowly over a period of time, this is most probably due to loss of consciousness (rapid induction) achieved when a rapid bolus is administered [38].

2.5.8 Age and Gender

Hye-joo Kang et al, demonstrated females felt more pain than males, however it was inconclusive [39].

Older patients experienced less pain thus their lignocaine requirements are also less. This is as a result of Aging on pain thresholds [40].

2.6 Methods Proposed to Reduce Propofol-Vascular Pain

2.6.1 Adjuvant Drugs

Numerous clinical methods have been proposed to alleviate Propofol vascular pain with most recent studies done on anti-inflammatory, analgesic, hypnotics and local analgesics.

2.6.2 Ketamine

It is a non-competitive NMDA receptor antagonist and is thought to reduce Propofol Vascular Pain at less than a third of sub-anesthetic doses of 5-10mgs [41].

2.6.3 Opioids

Opioids are centrally acting and analgesics and confirmation of opioids receptors within the PNS has been thought to be the contributory factor to regional analgesia [32]. More side effects have been reported with pethidine. Alfentanil and fentanyl did not show much effect in peripheral pain alleviation [42].

2.6.4 Thiopental

Thiopental is thought to reduce pain at the site of injection via 3 major mechanisms. Its alkalinity and lipid solubility reduces the concentration of free propofol which is responsible

for PVP [11]. According to Scott et al, he concluded that it blocks the release of bradykinin which causes hyper-permeability and venous dilatation thus exposing free nerve endings to the free propofol [13]. It was then concluded by Agrawal et al that thiopental at doses of 0.5mg/kg may be as effective as lidocaine in alleviating PVP.

2.6.5 NSAIDS

NSAIDS are thought to reduce pain via inhibition of prostaglandin synthesis and the kinin cascade as well. The common NSAID that was studied was fluribrofen which is a prodrug and was noted to completely abolish PVP when administered prior [30].

2.6.6 Local Anesthetics

Lignocaine is the commonest local anesthetic used to alleviate PVP [6]. Another local anesthetic for example prilocaine has also been used. Lignocaine can be premixed with propofol in a syringe or it can be given prior to propofol infusion. Massad et al concluded the efficacy of the two techniques were indistinguishable; though it is postulated that pre-mixing lignocaine with propofol in a syringe might alter the PH and osmolarity of propofol therefore reducing pain at the site of injection [43]. Lignocaine, a weak base, releases hydrogen ions into the propofol mixture thereby eventually reducing its PH (reduces the amount of free propofol). It was then concluded by Erikson et al that acidification of propofol solely reduces PVP but addition of lignocaine in the propofol mixture reduces its anesthetic potency by destabilizing the emulsion [18]. Long acting local anesthetics such as bupivacaine are toxic hence not useful.

The other mechanism of action of lignocaine is via direct local anesthetic effect on the blood vessel/vascular smooth muscle [44].

2.6.7 Other Drugs

Other drugs like ephedrine at low doses of 30-70micrograms/kg given at induction has shown to be as effective as lignocaine with no hemodynamic effects [45]. Magnesium sulphate via NMDA receptors and interference with calcium channels was shown to be effective [46]. metoclopramide used with veno-occlusion has also proven to have the same efficacy as lignocaine in preventing PVP [47].

Neostigmine used with veno-occlusion has also shown to reduce PVP but has not been used in clinical practice because of its associated cardiac adverse effects [48].

Steroidal anti-inflammatory drugs e.g. dexamethasone given 60seconds prior to propofol infusion was shown to effectively reduce PVP though was also shown to cause itching and pain in some patients [49].

Nitrous oxide has also proven to reduce PVP via its analgesic effects [50].

2.6.8 Veno-Occlusion

Veno-occlusion also commonly known as modified bier's block is a technique that has been studied before but failed to gain popularity because of its cumbersome nature (set-up, timing and technique). It is commonly used with lignocaine and other drugs as well to help alleviate pain at injection site. It is the most effective in alleviating PVP [4]. In a randomized controlled trial of 200 patients by Massad et al assessing effectiveness of veno occlusion with lignocaine in alleviating propofol vascular pain he compared 4 groups; 1 group receiving propofol alone, 2 groups receiving lignocaine without veno occlusion and 1 group with veno occlusion and lignocaine. he concluded that the pain reduction in the veno occlusion and lignocaine group was statistically significant compared with the control groups ($p< 0.005$).

In another study that was done by Dae Hee et al where he standardized the veno-occlusion as a technique and used different doses of lignocaine and he concluded that Pretreatment with intravenous 40 mg or 0.5 mg/kg lidocaine with venous occlusion is recommended to prevent pain following injection of lipid emulsion propofol.

The functional principle of this technique is alluded to two main ways, direct effect of lignocaine on the nerve endings blocking pain transmission (action potential) and this is best attained by granting adequate time for the drug to take effect.

Secondly, lignocaine is thought to block the Kallikrein-kinin system and eventually blocking the release of bradykinin which is responsible for the pain. Massad et al conducted a study where he had 5 arms and he compared the pain scales in each. He concluded that the best technique out of the 5 groups that experienced the least pain was the arm with lignocaine and veno-occlusion [4].

Physically, venous occlusion may cause venous diameter distension mimicking a larger vein. The increased blood volume related to venous occlusion may provide a better buffer system in contact with propofol. Subsequently, the ischemic /reperfusion conditioning by occluding and removing a rubber tourniquet in the forearm may increase expression and activation of transient receptor potential Vanilloid 4 (TRPV4) channels to induced endothelial relaxation [51]. Rath

et al. demonstrated the hypoxic preconditioning in restoring Nitric oxide and further improving endothelium-derived hyperpolarization (EDH)-mediated relaxation and vasodilatation through TRPV4. Thus, the ischemic/reperfusion of venous may maintain venous distention even after the remove of the tourniquet and reduce the concerned injection pain efficiently combined with lidocaine.

Veno-occlusion techniques include application of a tourniquet which may cause pain. Tourniquet pain is narrated as a diffuse, bland, sheath like, achy sensation at the tourniquet application site. It may be betokened as a rise in heart rate and mean arterial pressure intra – operatively. The etiology is unclear, but has been postulated to a cutaneous neural mechanism, slow conducting C fibers. Prostaglandins release secondary to cell injury due to tourniquet compressions sensitizes pain receptors leading to increased pain perception. Continuous nociceptive afferent due to limb ischemia causes central sensitization via NMDA receptors [52], [53]. Tourniquet pain has important impacts on anesthesia. Many techniques like application of EMLA cream, infiltration with local anesthetics, use of wider cuff with lower inflation pressure, addition of opioids, clonidine, epinephrine along with local anesthetics in spinal block have been sought to affect the occurrence or magnitude of this pain, however, none has attained complete success. Wide cuffs exert low pressure occlusion by dispersing the pressure hence minimizing risk of underlying tissue damage.in adults and children [54]. In our study the amount of pressure required to occlude the intended vessel is very minimal (a small press even by the finger is adequate to veno-occlude) and very minimal pain is expected to be perceived by the patient as compared to tourniquet pain perceived during orthopedic surgeries.

3.0 CHAPTER THREE: METHODOLOGY

Study Justification

70% of patients experience vascular pain if no pretreatment is administered at induction if propofol is used [40]. The American society of Anesthesiologists rank this pain as the 7th most significant drawback to the use of propofol. The pain is sharp, excruciating, aching and burning at the same time. Because of this, pain can be an added stressor to the patient already distressed by anesthesia and surgery. Pain alleviation is thus paramount to try and prevent this situation.

No data has actually been generated and no study has been conducted in our set-up (paucity of data) A similar study was conducted by Massad et al in Jordan university. Veno-occlusion was the best intervention in alleviating propofol-induced vascular pain as compared to those used currently. This intervention, if proved to be effective, could be recommended for better anesthetic experience for our patients.

3.1 Study Objectives

3.1.1 Broad Objectives

To determine whether veno-occlusion with lignocaine minimizes propofol-induced vascular pain compared to lignocaine injection without veno-occlusion.

3.1.2 Specific Objectives

a) To determine the mean pain score when veno-occlusion is used with lignocaine versus when no veno-occlusion is used with lignocaine to alleviate propofol-induced vascular pain.

b) To determine the difference in the mean pain score when veno-occlusion is used with lignocaine verses when no veno-occlusion is used with lignocaine to alleviate propofol-induced vascular pain.

3.2 Research Question:

Does veno-occlusion with lignocaine effectively alleviate propofol-induced vascular pain?

3.3 Research Methodology

3.3.1 Study Design

Comparative observational study

3.3.2 Study Site

The Kenyatta National Hospital main theatre.

3.3.3 Study Population

Adult patients undergoing elective surgery at the KNH fulfilling the following criteria:

3.3.4 Inclusion Criteria

a) All Consenting adult patients slated for elective surgical procedures under general anesthesia with propofol as the induction agent.
b) ASA I and ASA II patients.
c) If the primary anesthesia provider was willing to have the patient included in the study.

3.3.5 Exclusion Criteria

a) Patients who declined to give consent for the study.
b) Patients with allergies to soya/proteins (ingredients of propofol) or previous adverse events to propofol anesthesia
c) Pediatric patients
d) Patients with contra-indications to propofol use (e.g. hypotensive patients)
e) Patients who lost verbal contact with the investigator before assessment of pain
f) Difficulty in communication or patient not being co-operative.
g) If the primary anesthesia provider was unwilling to have the patient included in the study.

3.4 Sampling Method

Consecutive/enumerative sampling method was used and convenience sampling applied as well.

3.4.1 Sample Size Determination

Sample size was calculated using the (Daniel, 1999) formula;

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at 5.8%, from a study conducted by Endale et al (2015) found 5.8% of the patients experienced pain.)

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.058(1-0.058)}{0.05^2} = 78$$

3.4.2 Patient Selection

The principal investigator looked at the elective lists for patient selection a day prior to the surgery to have an idea of the patients who will undergo general anesthesia. Consent was then sort from patients after the nature and the benefits of the study was explained into detail and thereafter a meticulous preoperative assessment of the patients was conducted the day before the surgery. Patients were then identified based on the inclusion and exclusion criteria.

Patient's weight and baseline vital signs (blood pressure, pulse rate) were taken by the principal investigator the day before the surgery. Using the data collection tool, data was collected and filled by the principal investigator or the trained research assistant.

Convenience sampling was used to recruit patients into the study until the required sample size is achieved.

3.4.3 Data Collection

A comparative observational study which intended to come up with a recommendation at analysis as to which method was suitable to minimize propofol vascular pain and eventually improve anesthetic outcomes. After consent was sort, patients who were to undergo general anesthesia for elective surgery at the Kenyatta National Hospital depending on the anesthetist's choice of method for alleviating propofol vascular pain i.e. lignocaine with or without veno-occlusion were observed during induction of anesthesia and a pain assessment was made. These two methods were already in existence and the principal investigator or her research assistant would purely observe and see how the patients tolerated propofol and then compared pain scales at analysis. The method chosen was as per the anesthetist's discretion and there was no interference or intervening in any way whatsoever at any point during the procedure. A verbal pain assessment using a visual analogue scale (VAS) was utilized to determine the pain intensity. This scale was already clarified to the patient during consent explanation.

3.4.4 Data Analysis

Data was checked for completeness prior to entry into **SPSPC^{+TM}** 22. It was then checked for errors and cleaned prior to analysis. Demographic characteristics and clinical characteristics were analyzed and presented as frequencies and proportions for categorical data, while continuous data was analyzed and presented as means with standard deviations or as medians with interquartile range. The mean pain scores when veno-occlusion was used and when it was not used with lignocaine to alleviate propofol vascular pain was analyzed and presented as means with standard deviations and if applicable the student's t-test was used to determine their differences. Statistical significance was considered at $p<0.05$.

3.4.5 Data Protection

All data collected was kept locked and confidential at all times. Electronic forms of data were protected with confidential passwords at all times. Data was accessible to the principal investigator and the data manager and it was well preserved until analysis, presentation and archival were done.

3.4.6 Study Limitations

a) Pain is subjective and everyone has his/her own pain threshold. Therefore, assessing the exact pain scores may have been exaggerated.

b) Loss of verbal contact was not encountered in any of the patients.

c) Time taken to apply the tourniquet with a rubber tubbing.

3.4.7 Bias Minimization

Selection bias was minimized, as patients meeting the inclusion criteria were sampled into either of the two groups at the discretion of the attending Anesthetist without any influence.

Information / observation bias was minimized by use of the VAS Scale, a universal pain scale, already explained to the patient prior to drug administration.

Confounding bias was minimized by the use of a standard vein at the dorsum of the hand, standard temperature of propofol (room temperature), standard dose of lignocaine, standard duration of veno-occlusion and standard use of a specified formulation of propofol (Lipuro by B-Braun).

3.4.8 Ethical Considerations

Ethical approval was sought from the Kenyatta National Hospital/ University of Nairobi – Ethics and Research Committee before embarking on the study(p855/10/2019). Participants in the study were enrolled after the nature of the study was explained to them and informed consent obtained. Confidentiality was maintained at all stages of the study. Study participants who had declined inclusion and/or left the study at any point were allowed to do so without victimization or compromise to their management.

No complications were observed in any patients during the study. No additional costs were incurred by the study participants or those who declined participation. Study findings were availed to the University of Nairobi and Kenyatta National Hospital ERC.

4.0 CHAPTER 4: RESULTS

In this study we enrolled a total of 80 adults slated for general anesthesia in KNH during the period of January 2020 to March 2020.Out of the 80 patients, females were 47(58.8%) and males were 33(41. 3%). In regards to age, patients were between 18-85 years' majority lying between 46-55 years (25%). Table 1 below illustrates this.

Table 1: Sociodemographic characteristics

Characteristics	Frequency (N)	Percent (%)
Age in years		
18-25	11	13.8
26-35	17	21.3
36-45	15	18.8
46-55	20	25.0
56-65	11	13.8
Above 65	6	7.5
Gender		
Male	33	41.3
Female	47	58.8

In regards to adjuvants,71 patients (88.8%) received fentanyl 100micrograms prior to administration of propofol,1 patient (1.3%) received fentanyl with ketamine 50mg as an adjuvant and 8 patients (10%) did not receive any adjuvants prior to propofol administration as shown in table 2 below.

Table 2: Adjuvants

	Frequency (N)	Percent (%)
Fentanyl	71	88.8
Fentanyl + Ketamine	1	1.3
None	8	10.0

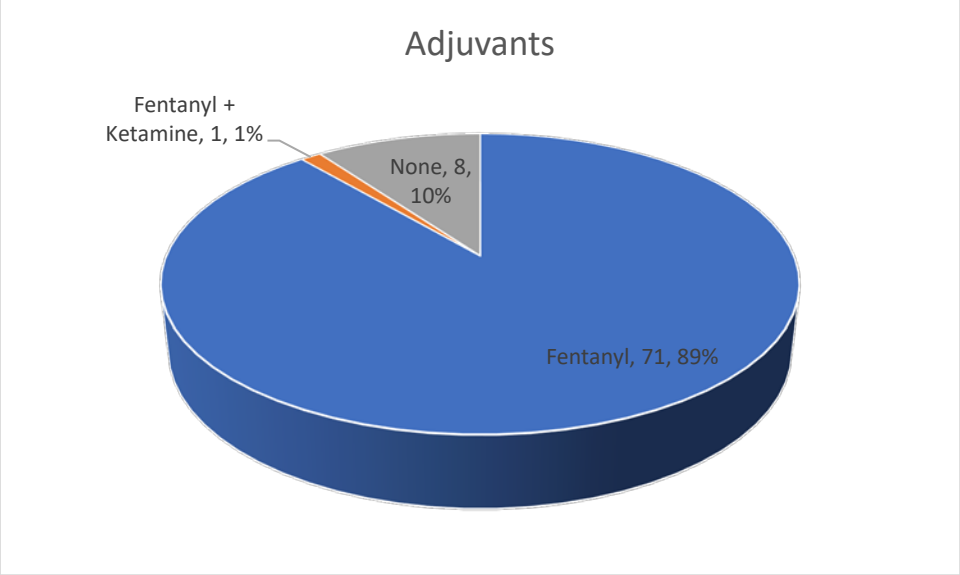

Figure 1: Adjuvants

Out of the 80 patients that were studied,49 0f them (61.3%) had veno-occlusion done as a technique with lidocaine while 31 of the patients (38.8%) received lidocaine alone 60 seconds prior to propofol administration as illustrated in table 3 below.

Table 3: Veno-occlusion

Veno-occlusion	Frequency (N)	Percent (%)
Yes	49	61.3
No	31	38.8

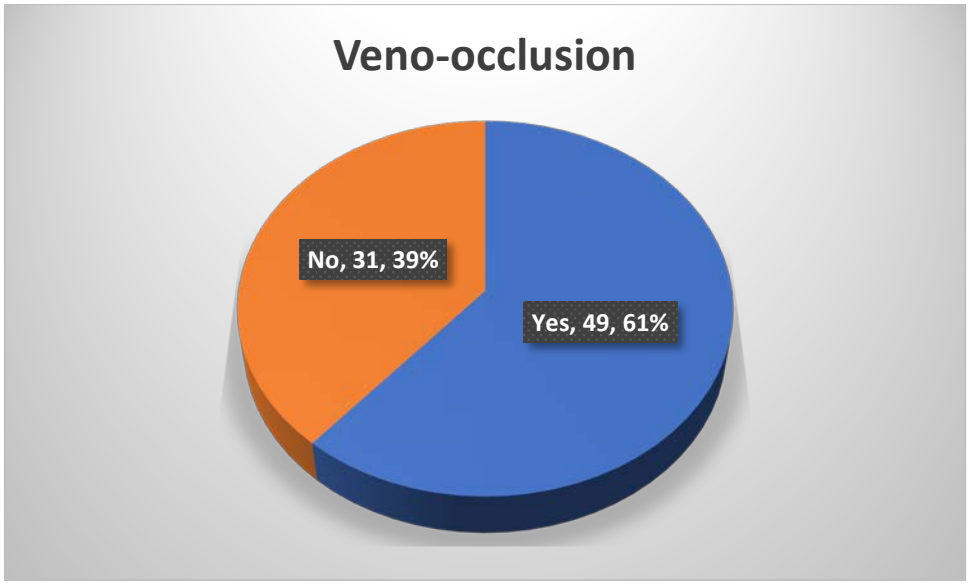

Figure 2: Veno-occlusion

Pain scores were assessed among patients as the first 3mls propofol was being infused using the visual analogue scale. It was noted that out of the 80 patients,36(45%) experienced no pain at all, 33(41.3%) experienced mild pain and 11(13.8%) experienced moderate pain. This is illustrated in table 4 below.

Table 4: VAS Scores

VAS scores	Frequency (N)	Percent (%)
None (0)	36	45.0
Mild (1-3)	33	41.3
Moderate (4-6)	11	13.8

	Yes n (%)	No n (%)	Total n (%)	p-value
None (0)	30 (83)	6 (17)	36 (45)	<0.001
Mild (1-3)	17 (51.5)	16 (48.5)	33 (41.3)	0.134
Moderate (4-6)	2 (18)	9 (82)	11 (13.8)	0.002

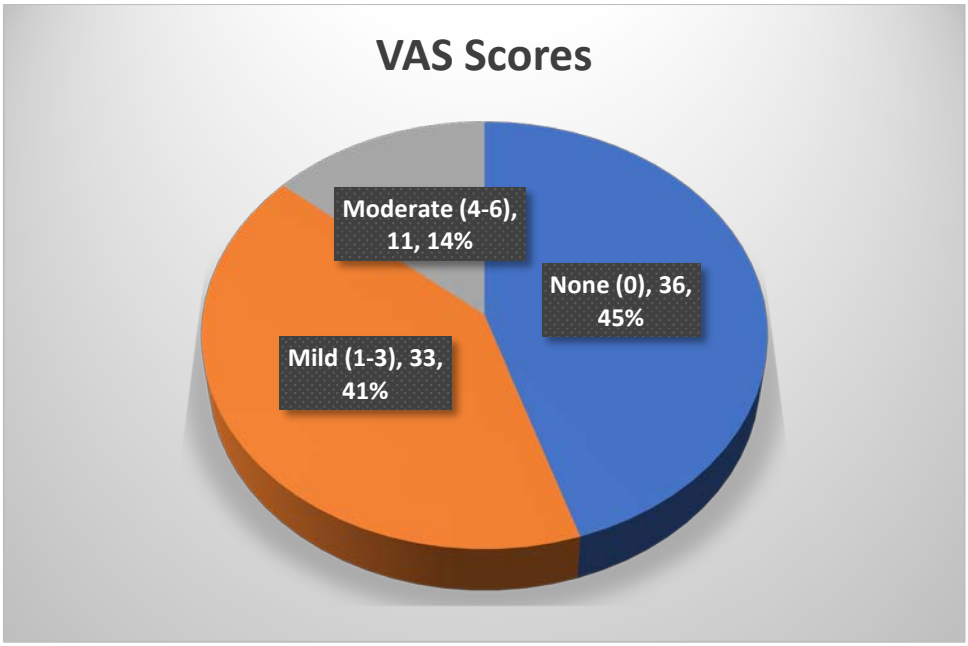

Figure 3: VAS Scores

Table 5: Ranks Table

	Tourniquet	N	Mean Rank	Sum of Ranks
VAS score	Yes	49	32.37	1586.00
	No	31	53.35	1654.00

A Mann-Whitney U test was used to determine the differences in the pain scores for the patients

The Ranks table above provides information regarding the output of Mann-Whitney U test. It shows mean rank and sum of ranks for the two groups tested (i.e., with tourniquet and without tourniquet groups).

The table below shows us the actual significance value of the test. Specifically, the Test Statistic table provides the test statistic, U statistic, as well as the asymptotic significance (2-tailed) p-value as shown below.

Table 6: Test Statistic

	VAS Score
Mann-Whitney U	361.000
Z	-4.168
p-value	<0.001

We studied which factors (age, weight, sex, ASA classification and therapy modality) had a statistically significant effect on pain in univariate analysis using the Chi square test, and then we tested for significant interactions between the factors.

The only factor that was found statistically significant was the veno-occlusion therapy modality (age p=0.125, ASA p=0.840, gender p=0.193). This is illustrated in table 7 below. Both the 2 groups were comparable with respect to age, weight, gender and ASA status

Table 7: Univariate Analysis for factors

	Total	Pain	No pain	p-value
Age in years *(Mean ± SD)*		41.1 ± 16.2	46.3 ± 13.3	0.125
Gender				
Male	33	21	12	0.193
Female	47	23	24	
Weight in Kgs. *(Mean ± SD)*				
ASA status		68.6 ± 8.6	69.0 ± 12.2	0.842
1	39	21	18	0.840
2	41	23	18	
Tourniquet				
Yes	49	19	30	<0.001
No	31	25	6	

Table 8: Demographic distribution of patients in the two groups according to age, weight, ASA and gender

Group (veno-occlusion)	Age	Weight	ASA (1/2)	Gender (M/F)
Yes	44.4 ± 15.5	68.8 ± 10.7	(23/26)	(19/30)
No	41.9 ± 14.6	68.7 ± 9.9	(16/15)	(14/17)

From this data, it can be concluded that pain score in the without veno-occlusion was statistically significantly higher than the with veno-occlusion group (U = 110, p = <0.001).

5.0 CHAPTER 5: DISCUSSION

Propofol is an immensely popular drug among anaesthesia providers. It is used for induction of anaesthesia because of its excellent pharmacokinetic and pharmacodynamics profiles [17]. Although recovery is smooth, induction might be stormy because of the pain on injection [1]–[3]. Different methods have been instituted to try and alleviate the incidence and severity of this pain. These include the use of large calibre veins [37], diluting propofol with 5% or 10% dextrose prior to injection [34], cooling of the formulation to 4 degrees Celsius prior to administration [32], giving adjuvant drugs e.g. NSAIDS [30], opioids, or Ketamine [41] prior to administration among other methods.

It was noted that out of the 78 patients who were enrolled in this study, the majority (48) were females. This may be attributed to the better health seeking behavior among females than males. Similar incidences were noted in other studies done by Massad et al and Walker et al [4], [5].

Regarding the sociodemographic pattern of the patients and what their pain scores were like we studied which factors age weight sex and ASA classification had a statistically significant effect on pain in the univariate analysis with the use of the chi -square test and then examined the significant interactions between the factors. It was observed that none of the demographic factors was statistically significant (age p= 0.125, ASA p = 0.840, sex p=0.193). This could mean that these factors do not have a direct correlation with pain induced by intravenous propofol injection. Our findings are like those observed in the studies by Massad et al and Walker et al [4], [5].

We compared two active treatment strategies used to attenuate propofol related injection pain and found a statistically significant difference in pain intensity experienced with tourniquet-controlled lidocaine pretreatment versus lidocaine alone. Therefore, we argue that this method allows us to make the following comparisons with existing data and provide additional insights First according to Massey et al. and Walker et al. in their quantitative reviews' tourniquet-controlled lidocaine pretreatment is statistically superior to lidocaine alone to eliminate propofol induced injection pain. PRE administration of lidocaine 60 seconds prior to propofol administration remained effective but not as effective as when veno occlusion was used. Lidocaine is a local anesthetic that acts through a direct local anesthetic effect on the blood vessels and vascular smooth muscles. The probable reason why it might not be as effective when used alone as it is with venous occlusion may be due to the fact that once it is administered

into the bloodstream most of it is washed out leaving a contact time minimum between the drug and the vascular bed.

On the other hand, veno-occlusion appears to be superior as shown in our study and this could be due to the blockage of the nerve fibers responsible for the transmission of pain secondary to the irritant effect of propofol and the direct anesthetic effect of lidocaine is achieved only when we allow enough time for the medicine to work. These factors could have decreased the incidence and severity of pain in our study but did not completely abolish it due to other mechanisms e g enough time for vein occlusion or inadequate inhibition of the kinin cascade which may have come into play.

In the study by Massad et al pain was assessed using the point scale (no pain, discomfort, pain). This may have limited their quantification of pain intensity between groups.

Walker et al reached the same conclusion with us although they used a lidocaine propofol mixture rather than lidocaine alone before propofol injection. The difference between their study design and ours was the decision to mix only 50 mg of propofol with 50 mg of lidocaine whereas most clinicians usually mix a similar amount of lidocaine with 200 mg of propofol.

Scott et al [13] also conducted a similar study but found that there was no difference between the two groups that he had (propofol admixture and pre-treatment with lignocaine) This could be explained by the small sample size as well as the lower dose of lidocaine used (10mg).

Current practice of alleviating pain in our set up includes propofol-lidocaine admixture in one syringe. Worldwide this is the most popular method because it is easy and fast. The downside of this method is that the physicochemical properties of propofol are slightly affected by the pH of lidocaine when these two drugs are mixed [18]. Some patients do not respond well to the current technique and a decent range still complain of pain or exhibit behavioral changes secondary to the pain.

6.0 CHAPTER 6: CONCLUSION

In conclusion, this study shows that veno-occlusion with lidocaine minimizes propofol-induced vascular pain compared to lidocaine injection without veno-occlusion. The mean pain score in the veno-occlusion group was lower (32.37) than that in the “lidocaine only” group (53.35). There was additionally a statistically vital distinction within the mean pain scores (U=110, P= <0.001) of the two groups.

6.1 RECOMMENDATION

A randomized controlled trial with more methods of preventing propofol injection pain would be recommended for better results.

We recommend the use of veno-occlusion with lidocaine as an effective method of alleviating propofol vascular pain (P=<0.001).

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APPENDICES

Appendix I: Explanation and Consent for the Patient/Next of Kin (English)

A COMPARATIVE OBSERVATIONAL STUDY ON THE EFFECTIVENESS OF VENO-OCCULUSION WITH LIGNOCAINE TO ELIMINATE PROPOFOL-INDUCED VASCULAR PAIN.

Study site

Kenyatta National Hospital

Introduction

My name is Sameera Ramzan Mohammed, a postgraduate student perusing a Masters' degree in Anesthesia at the University of Nairobi. I am conducting a comparative study on the effectiveness of veno-occlusion with lignocaine in alleviating propofol-induced vascular pain. Pain following propofol infusion is seen in approximately 70% of patients if other modes of pre-treatments are not initiated.

Procedures to be followed in the study

- A comparative observational study which intends to come up with a recommendation at analysis as to which method is suitable to minimize propofol vascular pain and eventually improve anesthetic outcomes.
- After seeking consent, patients undergoing general anesthesia for elective surgery at the Kenyatta National Hospital depending on the anesthetist's choice of method for alleviating propofol vascular pain i.e. lignocaine with or without veno-occlusion will be observed during induction of anesthesia and a pain assessment made.
- These two methods are already in existence and I or my research assistant will purely observe and see how the patients tolerate propofol and then compare pain scales at analysis.
- The method chosen will be as per the anesthetist's discretion and there will be no interference or intervening in anyway whatsoever at any point during the procedure.
- A verbal pain assessment using a visual analogue scale (VAS) will be utilized to determine the pain intensity. This scale will have been elaborated to the patient during consent explanation.

Purpose

The purpose of this study is to assess the effectiveness of veno-occlusion with lignocaine in minimizing pain induced by propofol, since the pain can be distressing to patients who are already undergoing a lot of stress related to the planned surgery. Pain following propofol infusion is seen in approximately 70% of patients if other modes of pre-treatments are not initiated. As per the current practice of clinical anesthesia by American Society of Anesthesiologists, it is ranked as the 7^{th} most significant drawback to the use of propofol. The pain is sharp, excruciating, aching and burning at the same time. Because of this, pain can be an added stressor to the patient already undergoing stress from anesthesia and surgery and this memory may be persistent even in the recovery room. Alleviation of this pain is, therefore, necessary to try and prevent this situation which is the main purpose of this study; a painless stress-free anesthesia.

Participation

Participation is voluntary and you are free to withdraw from the study at any point in time. You will not incur any extra cost due to this study other than the usual cost of care at Kenyatta National Hospital. There will be no financial benefits from participation, and participation will not affect or delay your planned treatment.

Risks of participation

The risks associated with participating in this study are minimal and will not alter your planned treatment. The 2 main drugs (propofol and lignocaine) used have minimal side effects and appropriate dose ranges will be used to prevent any of these side effects.

Confidentiality

All the information obtained will be handled with utmost confidentiality. The patients name will not appear in any document

Sharing of results

The results obtained from this study will be shared with other experts through formal platforms.

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Tel:2726300 Ext:44102

Consent form

I……of……
OR I …… next of kin to…… of …… hereby give written consent for the participation in the prospective comparative observational study assessing the pain scores when veno-occlusion is used with lignocaine to alleviate propofol vascular pain.

I have understood the information regarding the study. I have had my questions addressed.

I have the right to withdraw at any point

Signed……. Date…….

INVESTIGATOR'S DECLARATION:

I have explained to the patient/ next of kin about the study. I have addressed all their questions and concerns to the best of my knowledge.

Signed……. Date…….

Appendix II: Explanation and Consent for the Patient/Next of Kin (Swahili)

Fomu ya Makubaliano ya Kujiunga Na Utafiti

Fomu hii ya utafiti ni ya wale wagonjwa ambao wanahudumiwa katika hospitali kuu ya

A COMPARATIVE STUDY BETWEEN LIGNOCAINE ALONE AND VENO- OCCLUSION WITH LIGNOCAINE FOR PREVENTION OF PROPOFOL-INDUCED VASCULAR PAIN AT THE KENYATTA NATIONAL HOSPITAL

Kenyatta na wamealikwa kujiunga na utafiti

Kielezo

Jina langu ni Sameera Ramzan Mohamed, ninafanya utafiti wa shahada ya juu katika anaesthesia kwenye Chuo Kikuu cha Nairobi.

Utafiti huu unalenga kuchunguza mbinu bora Zaidi ya kuweza kupunguza au kuondoa uchungu unaosababishwa na dawa ya kulala kabla ya kufanyiwa upasuaji(propofol) ambayo inatumika sana na inajulikana kusababisha uchungu huu kama moja ya madhara yake. uchungu wa dawa hii unaweza kusababisha matekeo mabaya kwa mgojwa na hata kuchelewa kupoa haraka.

Utafiti huu utaweza kuboresha matokeo ya wagonjwa. Kusajiliwa kwa utafiti huu ni kwa hiari yako. Hakuna malipo utakayo lipa zaidi ya malipo ya hospitali. Hakuna pesa utakayo pewa kwa kushiriki. Hakuna hatari inayotokana na kushiriki katika utafiti huu. Uko na ruhusa kujiondoa kwa utafiti wakati wowote. Majina yako hayatatumika katika utafiti na usiri mkubwa utatumiwa katika utafiti. Kama jamaa/mgonjwa utahitajika kuelewa kuhusu utafiti na kutia sahihi kubalio ili jamaa/ wewe asajiliwe katika utafiti

Baada ya utafiti, uchambuzi wa takwimu utafanywa. Habari itachapishwa katika kitabu kitkachowekwa kwa maktaba ya Chuo Kikuu Cha Nairobi. Usiri mkubwa utatumika kwa kuziweka taarifa hizi. Sasa nitakupa nafasi ya kuuliza masawali yoyote uliyo nayo kuhusu utafiti huu. Ikiwa umekubali kushiriki katika utafiti huu, tia sahihi yako kwenye nafasi iliyotolewa. Maswali yoyote kuhusu utafiti huu yanaweza kuelekezwa kwa KNH-ERC, Hospitali ya Rufaa ya Kenyatta, Sanduku la Posta20723, Nairobi. Simu: 2726300-9

Fomu ya Idhini

Nambari ya Usajili…….

Mimi ni……. Kutoka…….

Ama mimi ni jamaa wa karibu wa…….

Kutoka…….

Nimekubali kushiriki katika utafiti wa

A COMPARATIVE STUDY BETWEEN LIGNOCAINE ALONE AND VENO-OCCLUSION WITH LIGNOCAINE FOR PREVENTION OF PROPOFOL-INDUCED VASCULAR PAIN AT THE KENYATTA NATIONAL HOSPITAL

Ninaelewa ya kwamba uchunguzi utafanyika bila madhara yoyote kwa mgonjwa.

Nina uhuru wa kujiuzulu kutoka kwa utafiti huu wakati wowote.

Sahihi……. Tarehe…….

Tamko la Mtafiti

Nina thibitisha kwamba nimemwelezea mgonjwa kwa ukamilifu kuhusu utafiti huu na amekubali bila kushurutiushwa

Sahihi……... Tarehe……Mawasiliano

Mawasiliano

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The Secretary: KNH/UON Ethics and Review committee
Tel:2726300 Ext:44102

Consent Form for The Anesthetic Care Provider

I DR./RCO……have agreed to take part in this study so as to improve patient outcomes.

Appendix III: Data Collection Tool

1. Biodata

Date:

Patient Number:

Age: **Sex:** **M** **F**

Weight (kgs):

Operation/Procedure:

ASA Status:

2. Vitals pre-operative

Blood Pressure (mmHg): **Heart Rate (b/min):**

SpO2:

3. Tourniquet

With **Without**

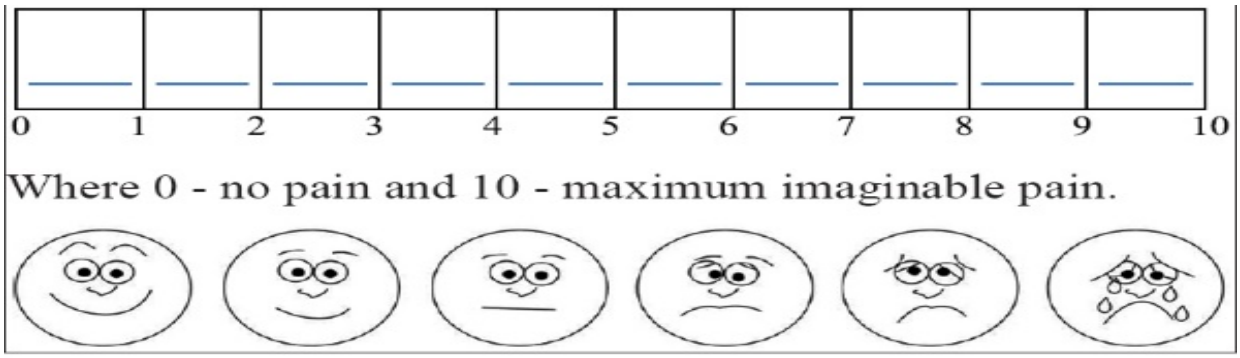
4. Adjuvants prior to propofol administration

Opioids (fentanyl)

Ketamine

Others

Appendix IV: Visual Analogue Scale



0	2	4	6	8	10
Very happy, no hurt	Hurts just a little bit	Hurts a little more	Hurts even more	Hurts a whole lot	Hurts as much as you can imagine

The VAS is a continuous unidimensional scale that measures pain intensity. It is most commonly anchored by “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 10). It is very simple to use and the patient is just required to give a number that corresponds to the pain intensity. The presence of pain and any behavioral changes or signs will be indicated. Behavioral signs will be considered when the patient had strong vocal responses, tears or arm withdrawal associated with facial grimacing.

Appendix V: Copy of KNH-UON ERC Approval