A COMPARATIVE EVALUATION OF THE USE OF INTRAVENOUS LIGNOCAINE VERSUS PLACEBO FOR THE SUPPRESSION OF COUGHING IN ADULT PATIENTS DURING EMERGENCE FROM ANAESTHESIA FOR HYSTERECTOMY AT DOCTOR GEORGE MUKHARI ACADEMIC HOSPITAL

Dissertation

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By

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DECLARATION

I, Dineo Carol Raesibe Moroasui, student number 210143123, declare that A COMPARATIVE EVALUATION OF THE USE OF INTRAVENOUS LIGNOCAINE VERSUS PLACEBO FOR THE SUPPRESSION OF COUGHING IN ADULT PATIENTS DURING EMERGENCE FROM ANAESTHESIA FOR HYSTERECTOMY AT DOCTOR GEORGE MUKHARI ACADEMIC HOSPITAL is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

........................................

Signature

........................................

Date
DEDICATION

In loving memory of Tate – Bauba a’ Ngwato a’ Bauba! You would have been proud.
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My sincere gratitude to the following people:

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when I couldn’t be there. I can never thank you enough.
ABBREVIATIONS AND ACRONYMS

DGMAH: Dr George Mukhari Academic Hospital
SMU: Sefako Makgatho Health Sciences University
IV: intravenous
IT: intratracheal
BP: blood pressure
MAP: mean arterial pressure
HR: heart rate
CVS: cardio-vascular system
CNS: central nervous system
SL: suspension laryngoscopy
ASA: American Society of Anaesthesiologists
GA: general anaesthesia
ETT: endotracheal tube
SREC: School’s Research Ethics Committee
SMUREC: Sefako Makgatho Health Sciences University Research and Ethics Committee
MAC: Minimum Alveolar Concentration
pH: A numeric scale used to specify the acidity or basicity of an aqueous solution
pKa: The negative base-10 logarithm of the acid dissociation constant of a solution expressed by this formula: pKa = - log_{10} Ka
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ABSTRACT

BACKGROUND
Emergence from anaesthesia and tracheal extubation can stimulate cardiovascular and airway reflexes such as coughing and laryngospasm. Suppressing these reflexes is important in order to prevent complications including death. Intravenous lignocaine is reported to suppress cough but the effects are temporary. The aim of the study was to evaluate its effectiveness when given during emergence.

METHODS
The study was conducted as a prospective, randomized, double-blinded, placebo-controlled study. Seventy-eight women scheduled for hysterectomy under general anaesthesia were randomized into two groups. Participants received either 1mg/kg of 2% lignocaine or placebo (normal saline) during emergence from anaesthesia. The effectiveness of lignocaine in suppressing cough during emergence from anaesthesia and extubation was compared to placebo over a period of twenty minutes post administration of study drugs.

RESULTS
The mean age of participants was 47.5 years in the lignocaine group and 48.6 in the placebo group. The differences in the mean for age for the two groups was not statistically significant (p = 0.44). In the study sample, coughing occurred in 13/39 and 15/39 (33.3% and 38.5%) patients in lignocaine and placebo groups respectively, which was statistically nonsignificant (p = 0.47). The frequency of cough during the twenty-minute assessment period was not statistically significant.
between the two groups. Blood pressure, heart rate and oxygen saturation values recorded during the observation period between the two groups did not show any statistically significant differences, with p values more than 0.05.

CONCLUSION

2% lignocaine 1mg/kg intravenously was not effective in suppressing cough during emergence from anaesthesia in women who underwent hysterectomy at Dr George Mukhari Academic Hospital (DGMAH)
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CHAPTER 1

1.1 BACKGROUND OF THE STUDY

The process of tracheal extubation under light planes of anaesthesia can stimulate cardiovascular and airway reflexes. The cardiovascular reflexes are characterised by tachycardia and hypertension which can be exaggerated in hypertensive patients, increasing the risk of complications like stroke and myocardial infarction\(^1\). Airway reflexes that can occur during emergence include coughing and bucking against the endotracheal tube and laryngospasm. Coughing against the endotracheal tube is undesirable as it leads to an increase in intracranial, intraocular and middle ear pressures\(^2\).

From observation alone at DGMAH, a significant number of patients cough during emergence from anaesthesia, although there are no formal studies to confirm this observation. There are strategies that can be used to manage these reflexes including the use of opioids, deep extubation and the use of lignocaine.

Currently none of these strategies have been adopted as part of protocol for prophylaxis against coughing during emergence from anaesthesia at DGMAH. It is therefore critical to investigate the benefits of lignocaine in the current study in order to see if the risks associated with emergence can be minimized.
1.2 RATIONALE FOR AND SIGNIFICANCE OF PROPOSED RESEARCH

The purpose of the study was to evaluate the effectiveness of lignocaine in suppressing airway reflexes and coughing during extubation. The aim was to inform protocol at DGMAH on prevention of excessive airway reflexes during emergence from anaesthesia. In the current study 2% lignocaine 1mg/kg was investigated on patients undergoing hysterectomy with the aim that results could be extrapolated to other surgical procedures in which active airway reflexes are potentially harmful, for example post ophthalmic surgery with fear of extrusion of eye contents or in patients with raised intracranial pressure, in which case cerebral perfusion will be further compromised.

1.3 RESEARCH QUESTION

The current study endeavours to answer the following question: Does IV administration of lignocaine effectively suppress airway reflexes in patients undergoing hysterectomy during light planes of anaesthesia if given during emergence?

1.4 AIM

The aim of the current study was to investigate the effectiveness of using intravenous lignocaine in suppressing airway reflexes during emergence from anaesthesia and tracheal extubation.

1.5 OBJECTIVES

The objectives of this study were:
• To investigate the incidence of cough in both arms (experimental and control arms) of the study
• To compare the superiority of using 2% lignocaine 1mg/kg IV versus the use of placebo between the two groups of patients
• To advocate that IV lignocaine should be used as prophylaxis for the management of the airway during extubation if this study can prove that lignocaine is superior to placebo

1.6 DEFINITION OF TERMS

**Cough**: a protective reflex serving a normal physiologic function of clearing excessive secretions and debris from the pulmonary tract

**Emergence**: the point in the process of recovery from general anaesthesia at which a return of spontaneous respiration, protective airway reflexes and consciousness occur

**Hysterectomy**: surgical removal of the uterus

**Tracheal intubation**: insertion of a tube into the trachea for the purpose of securing the airway

**Tracheal extubation**: removal of an endotracheal tube when it is no longer needed

**Placebo**: a substance having no pharmacological effect but administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation

**Lignocaine**: a local anaesthetic agent belonging to the amino amide group of local anaesthetics
CHAPTER 2: LITERATURE REVIEW

2.1 ANAESTHESIA AND AIRWAY MANAGEMENT

Undergoing anaesthesia for certain life-threatening conditions is meant to save life and or to improve the quality of life of patients. Most surgical procedures that are not possible to perform under regional anaesthesia with a conscious patient are carried out under general anaesthesia, and airway management forms an important aspect of anaesthesia care. Airway management entails both tracheal intubation and extubation, and all tracheal intubations are done with the intention of subsequent extubation at the end of the procedure. Tracheal intubation may be done for different reasons, but in anaesthesia the aim is to protect the airway in a patient who is unconscious, to provide a route for continued ventilation of the lungs, and as a conduit to provide drugs that keep the patient under anaesthesia.

2.2 SEQUELAE OF AIRWAY MANIPULATION

Tracheal intubation and extubation are accompanied by physiological changes, namely: increase in arterial blood pressure (BP), increase in heart rate (HR), stimulation of airway reflexes like coughing, breath holding, and laryngospasm. Asai et al. reported a high incidence of respiratory complications during extubation when compared to intubation and, according to Swati et al., this observation may reflect widespread adoption of difficult airway guidelines which predominately address induction of anaesthesia.

Coughing and sore throat produced by irritation by the endotracheal tube are common with an incidence ranging from 38 to 96%. Pandey et al. reported that
fentanyl used during induction of anaesthesia and intubation induces cough and that the cough is not always brief and benign. The same authors further explain that this coughing is associated with undesirable increases in intracranial, intraocular, and intra-abdominal pressures and that it may require immediate intervention.

Suppressing these haemodynamic and airway reflexes is desirable to facilitate smooth emergence from anaesthesia. There are strategies that can be used to manage these reflexes including the use of opioids, calcium channel blockers, beta blockers, deep extubation and lignocaine. There are advantages and disadvantages to choosing a particular strategy of managing these reflexes during extubation.

2.3 DEEP EXTUBATION

According to Valley et al., deep extubation refers to the removal of the tracheal tube in a spontaneously breathing patient who is sufficiently anaesthetized to obtund laryngeal reflexes. Fan et al. state that deep extubation offers the advantage of a smooth extubation thereby reducing coughing, cardiovascular stimulation and intraocular, intracranial and middle ear pressure changes. In a review article by Haddad et al., morphine, fentanyl and remifentanil were recommended as first line therapy in the management of pain in patients with severe traumatic brain injury since they provided analgesia, mild sedation and depression of airway reflexes.

In a randomized control trial, Fan et al. compared dexmedetomidine and remifentanil for tracheal extubation in deeply anaesthetized adult patients after otologic surgery. In that study, patients were assessed for quality of extubation, and
smooth extubation was defined as no gross purposeful movement such as coughing within one minute of extubation. The researchers found that dexmedetomidine administration at the end of surgery produced a dose-dependent effect in providing smooth extubation without significantly prolonging recovery from anaesthesia. When dexmedetomidine was compared to remifentanil, the benefits of dexmedetomidine included hemodynamic stability, opioid sparing and a lower incidence of post-operative nausea and vomiting (PONV). It was also reported that respiratory rate during extubation was lower in the remifentanil group than in the dexmedetomidine groups. These results are consistent with the respiratory depressant effect of opioids. Harvey et al. further state that both morphine and codeine have antitussive properties. The authors further explain that the receptors involved in the antitussive action appear to be different from those involved in analgesia, but respiratory depression is undesirable.

In a systematic review of studies previously conducted in which issues around the period of extubation were addressed, in particular level of consciousness, Jubb et al. had a grade D recommendation (evidence level 3 which is non analytic studies: case reports, case series or expert opinion or extrapolated evidence from well conducted case control or cohort studies with a low risk of confounding bias or chance and a moderate probability that the relationship is causal) for deep extubation in adults, but with regard to extubation following paediatric surgeries, they state that the incidence of cough and laryngospasm were similar whether using deep or awake extubation – grade C recommendation (a body of evidence including studies rated as $2^+$ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as $2^{++}$). In a published article on tracheal extubation, Swati and Seema disagree, stating that
the incidence of respiratory complications has been found to be greater after extubations under deep anaesthesia regardless of the type of surgery. Deep extubations come with the risk of aspiration of gastric contents and loss of airway and are not recommended in patients with a full stomach or those who had a difficult intubation⁷.

2.4 PHARMACOLOGY OF LIGNOCAINE
Lignocaine is a local anaesthetic (LA) drug belonging to the amide group of local anaesthetics. It is an amino alkyl xylidide. Lignocaine has found many uses in anaesthesiology, with different modes of administration as described in Milner et al.¹¹:

- Topicalization of mucous membranes, for example in the mouth prior to awake instrumentation of the airway
- Topical infiltration, skin infiltration with lignocaine and adrenaline
- Skin patches, topical patches useful in the management of local chronic pain
- Oral lignocaine used in the management of chronic pain
- Neuraxial administration, for regional anaesthesia both intrathecally and epidurally
- Intravenous administration: for systemic analgesia, blunting the intubation response, treatment of ventricular dysrhythmias and for intravenous regional anaesthesia.

According to Milner et al. 11, IV lignocaine is effective as a systemic analgesic for both acute and chronic post-operative pain and that it appears to exert its analgesic effect on the dorsal root ganglia as well as via central inhibition at the hypothalamus and thalamus. The authors further explain that a single dose of lignocaine can block the peripheral nerves in chronic neuropathic pain for weeks.
2mg/kg IV lignocaine is recommended for management of intubation response \textsuperscript{11}. Different researchers have investigated different doses of lignocaine with different modes of administration and obtained different outcomes \textsuperscript{12,14}. In a study conducted to evaluate the effectiveness of IV lignocaine in suppressing fentanyl induced cough in children \textsuperscript{12}, 1mg/kg and 0.5mg/kg of IV lignocaine were compared to placebo. This study concluded that IV lignocaine can markedly suppress fentanyl-induced cough in children even in doses as low as 0.5mg/kg. Lignocaine serum levels correlating to suppression of airway reflexes have also been investigated and reported to be between 2.3 and 3mcg/ml \textsuperscript{13,14}.

LA are weak bases that exist in equilibrium between the lipid-soluble non-ionised form and the ionised hydrophilic form. When these fractions are present in equivalent concentrations, the pH is known as the dissociative constant, or the pKa of the drug. Environmental pH and the pKa of a drug determines the amount of LA that exists in either the ionised or non-ionised form. The closer the pKa of a specific drug is to serum pH, the larger the non-ionised fraction available for crossing biological membranes for interaction with intracellular Na\textsuperscript{+} channels and as a result faster onset of action \textsuperscript{11}. The authors further explain that lipid solubility confers a higher potency and this is because of a higher concentration gradient across the membrane driving more of the drug intracellularly; the increased affinity of the more lipid-soluble drug for the Na\textsuperscript{+} channel and due to the ability to alter the conformation of the Na\textsuperscript{+} channel by direct effects on the lipid membrane.

At physiological pH, local anaesthetic agents are ionised and it is the ionised form that interacts with protein receptors of the Na\textsuperscript{+} channel to inhibit its function \textsuperscript{10}. 
Increased plasma-protein binding is associated with increased duration of action \(^\text{11}\). Lignocaine has 64% protein binding compared to bupivacaine with 95% protein binding. As a result lignocaine has a shorter duration of action as compared to bupivacaine. This characteristic has clinical implications when it comes to toxicity from LA. Milner et.al \(^\text{11}\) states that the most common cause of complications of LA is overdose and that LA may also cause complications as a result of direct effects on nerves, muscles and systemic targets. Anaphylactic reactions also occur and are known to be precipitated by para-amino benzoic acid which is a breakdown product of ester local anaesthetics. Systemic adverse effects affect mainly cardiovascular system and the central nervous system \(^\text{11}\). In the heart it can cause delayed conduction in the His-Purkinje system, myocardial depression, hypotension, bradycardia, prolonged P-R interval and widened QRS complexes, while CNS side effects include: tinnitus, circumoral numbness, confusion, and convulsions in a dose-related manner. Toxicity presents with CNS symptoms followed by CNS signs including ventricular fibrillation and cardiac arrest. The cardiac-to-central nervous system toxicity of LA is quoted using the CC: CN dose ratio and this is the ratio of the dose causing cardiac collapse (CC) to the dose causing seizures or convulsions (CN). Increased cardiotoxicity is indicated by a lower number for example, CC: CN for bupivacaine is 3 and for lignocaine is 7.

2.5 EVIDENCE FOR USE OF LIGNOCAINE FOR BLUNTING AIRWAY AND HAEMODYNAMIC RESPONSES TO EXTUBATION

In a study by D' Aragon et al.\(^\text{15}\), the effects of lignocaine spray and intracuff alkalinated lignocaine on the occurrence of cough at extubation were investigated. In this randomized double blind placebo controlled prospective study, 120 women
undergoing gynaecological surgery were enrolled. Prior to intubation 4% lignocaine or 0.9% saline was sprayed onto the patient’s supra and subglottic areas. After intubation a tracheal tube cuff was filled with either an alkalinized 2% lignocaine or 0.9% saline. In this study there were four groups of intervention. The primary outcome was the incidence of cough at extubation and the secondary outcome was the incidence of sore throat post extubation. The highest incidence of cough was in the saline-saline group 20/29 (69%) compared to 12/28 (42%) in the spray-cuff; 7/29 (24%) in the spray-saline and 19/30 (63%) in the saline-cuff groups. The same report showed that the use of lignocaine spray reduced the incidence of cough at extubation while the use of intracuff alkalinized lignocaine had no impact on the occurrence of cough.

In another study by Wetzel et al.\textsuperscript{16}, 4% intracuff lignocaine was not found to be effective in reducing the incidence of cough during emergence from general anaesthesia in smokers undergoing procedures lasting less than 1.5 hours. In the same study, one group of 18 patients received 5ml of intracuff lignocaine while the other group received saline intracuff. The incidence and frequency of cough was investigated. 25% of patients in the saline group had a cough as compared to 16% of patients who had a cough in the lignocaine group. It was also reported that patients with the highest number of coughs were from the lignocaine group. The conclusion was that lignocaine did not significantly decrease the incidence of coughing at emergence. The lack of effect in the use of lignocaine to reduce the incidence of cough was attributed to a number of factors: smaller sample size, a shorter duration of time for lignocaine to diffuse across the cuff membrane and the effect of dose – a smaller dose used to avoid side effects.
In a contradicting report by Navarro et al.\textsuperscript{17}, endotracheal tube cuff filled with alkalinized lignocaine was shown to be able to prevent emergence phenomena. From the three studies described above, it is evident that there are conflicting views regarding the use of intracuff lignocaine in the prevention of cough during emergence from anaesthesia\textsuperscript{15-17}.

In another study conducted in Korea by Lee et al.\textsuperscript{18}, preoperative laryngeal and intratracheal spraying with 1.5mg/kg of 10\% lignocaine was found to be effective in attenuating arterial pressure increases to suspension laryngoscopy (SL) and in suppressing cough during extubation. Two groups of 30 patients each were randomly assigned to receive either 10\% lignocaine or saline intratracheally. Half the dose was sprayed on the larynx and epiglottic area and the remainder was sprayed in the trachea. It was observed that in both the lignocaine and saline groups there was an increase in mean arterial pressures (MAP) and HR with SL but that these parameters were significantly higher in the saline group as compared to the lignocaine group. The incidence of cough was also significantly higher in the control group before and after extubation. The conclusion was that preoperative laryngeal and intratracheal spraying with 1.5mg/kg of 10\% lignocaine was effective in attenuating increases in BP due to SL and also in suppressing cough during extubation. Findings from the study by Lee et al.\textsuperscript{18} are in keeping with findings from D’ Aragon et al.\textsuperscript{15} with regard to spraying the airway with lignocaine. D’ Aragon et al. had a 24\% incidence of cough in the spray-saline group compared to 69\% incidence of cough in the saline-saline group.
George et al.\textsuperscript{19} did not get the same findings as Lee et al.\textsuperscript{18}. In this study, which was conducted in India, 2% lignocaine instilled through the trachea did not prevent cough at extubation when given 20-30 minutes before extubation. It was found that intratracheal (IT) lignocaine was not superior to IV lignocaine or placebo in attenuating cough or haemodynamic response to extubation when given 20-30 minutes before extubation, and these results were attributed to the low serum levels of lignocaine obtained 10 minutes after injection and at extubation. The mean serum concentrations in the same study were 0.84mcg/ml and 0.88mcg/ml for IV and IT groups respectively at 10 minutes post injection, and 0.63 and 0.79mcg/ml for IV and IT groups respectively at extubation. According to Nishino et al.\textsuperscript{13} and Lee et al.\textsuperscript{18}, the levels for attenuation of the extubation response are between 2.3 and 3mcg/ml. George et al\textsuperscript{19} highlighted a time delay between drug administration and extubation, with extubation occurring after 20 to 25 minutes as opposed to the 10 minutes post drug administration initially planned. With these findings the authors suggested a weak or short duration of action of lignocaine.

According to a study conducted by Takekawa et al.\textsuperscript{20}, IV lignocaine prior to intubation decreases the incidence of post-operative sore throat and cough. In another study by Erb et al.\textsuperscript{14}, the effects of intravenous lignocaine on laryngeal and respiratory reflex responses in anaesthetized children were evaluated. They tested whether the incidence of laryngospasm evoked by laryngeal stimulation is temporarily diminished after the administration of intravenous lignocaine, and it was concluded that IV lignocaine 2mg/kg significantly reduced the incidence of laryngospasm, but that the effects were short-lived.
In a study by Sanikop et al.\textsuperscript{21}, 1.5 mg/kg of IV lignocaine was compared to placebo in prevention of post extubation laryngospasm in children. In this study, IV lignocaine given two minutes before extubation was also found to be effective in preventing post extubation laryngospasm in children undergoing cleft palate repair. From the literature discussed, it seems that the different modes of administering lignocaine for prevention of airway-related complications during emergence from anaesthesia may be dependent on: route of administration; dose used and timing of administration, however there is no consensus thus far\textsuperscript{18-21}. 
CHAPTER 3: METHODOLOGY

3.1 STUDY SETTING

The study was conducted in the operating theatre at DGMAH, a tertiary health institution situated approximately 32 km north of the city of Pretoria.

3.2 STUDY DESIGN

The study was conducted as a double-blind, randomized, placebo-controlled study in which patients who underwent hysterectomy were assigned to receive either lignocaine (study group) or normal saline (placebo group). The occurrence of cough during emergence from anaesthesia was recorded.

3.3 STUDY POPULATION AND SAMPLING METHOD

The study population consisted of adult female patients scheduled for elective hysterectomy under general anaesthesia with tracheal intubation at DGMAH.

Prior to conducting the study, ethical clearance was obtained from Sefako Makgatho Health Sciences University Research and Ethics Committee (SMUREC appendix 6). Written informed consent (appendix 1) was also obtained prior to inclusion in the study.

3.3.1 INCLUSION CRITERIA

The following patients were included in the sample:
• Adult patients aged 18 to 70 years who gave informed consent to participate in the study
• Patients classified as American Society of Anaesthesiology (ASA) I and II
• Patients undergoing hysterectomy under general anaesthesia (GA) with tracheal intubation
• All the patients were well conversant in either English or Setswana

3.3.2 EXCLUSION CRITERIA

The following patients were not included in the sample group:

• Patients who were not willing to give informed consent for participation in the study
• Patients who had not reached age of maturity and were unable to give consent
• Patients with anticipated difficult intubation
• Patients with contra-indication to lignocaine
• Patients with a history of bronchospasm, upper or lower respiratory tract infection
• Patients with a history of ischaemic heart disease or arrhythmias

3.4 SAMPLE SIZE

A nominal sample size of seventy-eight (78) patients consisting of 39 patients – study group and 39 patients – control group were enrolled for the study. The study group received 1mg/kg IV 2% lignocaine and the control group received placebo (normal saline). This sample size was calculated based on a two-sided 95%
confidence interval and an allowable alpha error of 0.05. The calculation was also based on 90% power of the study to detect significant difference in the occurrence of coughing between the study arm (lignocaine) and the placebo arm (normal saline). The calculation of the sample size was derived using Statistical Package for Social Sciences (SPSS®) version 21.0.

3.5 PROCEDURES

Informed consent (appendix 1) was obtained prior to administration of anaesthesia and taking part in the study.

Eligible patients were randomly assigned to group A or group B and given the blinded study drug, which gave every patient an equal chance of receiving either the placebo (normal saline) or the study drug (lignocaine). All patients in the study received standard anaesthesia consisting of:

- IV induction agent: propofol
- Neuromuscular blocking agent: vecuronium
- Intra-operative opioids: fentanyl
- prophylaxis for nausea and vomiting: dexamethasone
- Maintenance with Isoflurane, oxygen and medical air
- Reversal with neostigmine and atropine

Instead of morphine, adequate doses of Tramadol and Nonsteroidal anti-inflammatory drugs (sodium diclofenac) were given for post-operative pain management. The following monitors were used throughout the procedure: non-invasive blood pressure monitor (NIBP), continuous electrocardiogram (ECG), pulse
oximeter and capnography. Both the patients and the anaesthetist were blinded to the study. The researcher prepared the drugs and labelled them as drug A or drug B and their identity was not revealed to the administering doctor. The drugs were administered by the anaesthetist allocated to the theatre for that day. Drug A or B was randomly chosen by the anaesthetist prior to IV administration. The drug was given after the volatile anaesthetic agents were stopped and reversal for neuromuscular blocking agents had been given. The study drugs were administered at the end of the procedure owing to the short duration of action of intravenous lignocaine \(^{19, 22}\). Patients were assessed for the presence of cough against the endotracheal tube from the time the study drug was given until a point when the tube was completely removed from the trachea. Patients were extubated when they were able to obey commands. The code for the investigational drugs was broken by the researcher after the data was analysed by the statistician.

### 3.6 ETHICAL CONSIDERATIONS

This study involved human participants and issues of research ethics were accordingly taken into consideration. The following ethical principles were taken into consideration when conducting this study.

- Ethical clearance (appendix 5) was obtained from both SREC and SMUREC prior to the conduct of the study; the ethics reference number is SMUREC/M/61/2015: PG (appendix 5).
- Permission to include patients of DGMAH was also obtained from the Chief Executive Officer of the hospital. The clinical manager responsible for theatre and the head of the department of Obstetrics and Gynaecology also approved of the study (appendix 2).
• Written consent (appendix 1) was obtained from all patients taking part in the study.

• Patient information was kept confidential. No reference was made to the patient’s names or their hospital numbers.

• Participation was completely voluntary, and refusal to take part did not affect the quality of care for the patient.

Patient comfort was not compromised: As already stated, morphine was seen as a confounding variable as its actions were anticipated to have antitussive effects on patients\(^{10}\) and therefore it was withheld; however, adequate doses of an alternative analgesic in the form of Tramadol and sodium diclofenac were provided.

### 3.7 OUTCOME VARIABLES

• Assigned group: A (lignocaine 1mg/kg) or B (normal saline)

• Incidence of cough from injection of study drugs to extubation or up to 20 minutes

• Time interval between administration of study drugs and extubation.

• Frequency of coughing

• Vital data: blood pressure (BP), heart rate (HR), oxygen saturation (SPO2) at 0, 3, 10 and 20 minutes following administration of study agents

• Complications: laryngospasm, hypotension, bradycardia, seizures

### 3.8 DATA COLLECTION METHOD

Data was prospectively collected by an anaesthetist during the patients’ emergence from anaesthesia, using a data collection form (appendix 4). All anaesthetists
involved in the collection of data were trained on how to record data on the data collection form.

3.9 DATA ANALYSIS

The data generated from this study (information recorded on data collection form – appendix 4) was transcribed into Microsoft Excel® Spread sheet and imported into a Statistical Programme for Social Sciences® (SPSS®) version 21.0 for analysis. Demographic characteristics of patients were summarized by descriptive statistics for range, mean, standard deviation (SD), proportions and percentages. Differences between the two arms of the study were statistically analysed by using Student t-test, and this was converted to p-values, based on a two-tailed test of significance. Statistically significant differences in variables between the two arms were established if p-value is ≤ 0.05

3.10 RELIABILITY AND VALIDITY

Reliability in quantitative research refers to a measurement’s repeatedly giving the same result or to a research instrument’s being internally consistent 23.

1. Selection of patients for each of the two arms of the study was based on randomisation
2. Statistical derivation of sample size was applied so as to ensure appropriate power of the study and provided the required measure of reliability of the findings
3. Data was collected prospectively on to the data collection form (appendix 4) which contained all variables analysed for the study
4. The statistician was blinded to data generated from the study until all analyses were done
Validity refers to the extent to which research instruments are measuring what they set out to measure.  
1. Training was provided to all the anaesthetists who were involved in data collection  
2. The same data collection form (appendix 4) was used throughout the study although different anaesthetists were collecting data hence ensuring consistency.

3.11 RESEARCH BIAS

According to Ogunbanjo, bias can be defined as any effect at any stage of a research process, or inference that tends to produce results that depart systematically from the true values. Someck et al. also describe bias as an in-built tendency to see the world and hence interpret data in a particular way.

The following biases were anticipated and measures put in place to eliminate or minimize them.

- **Researcher bias**: minimized by employing an independent anaesthetist who had no interest in the study for observing and recording of the findings. This was further controlled by the use of a statistician and statistical data analysis software to analyse the data.

- **Sampling bias**: eliminated by randomization of patients and by the double blinded design. The anaesthetist chose drug A or B and injected it into the patient with both the patient and the anaesthetist not aware of the identity of the drug.

- **Reporting bias**: eliminated by providing the statistician with data recorded on the data collection form designed for this study, with only the results obtained
from this study being reported and the code for the study drugs broken after all analyses were done.
78 patients were enrolled for the two arms of the study through a randomization process. 39 patients (50%) were in the study group (Group A) and received lignocaine, while the remaining 39 (50%) formed a control group (Group B) who received normal saline (placebo). Table 4.1 below shows the ages of the patients, which ranged between 21 and 70 years in the lignocaine group compared with an age range of 29 – 69 years in the placebo group; B. The difference in the mean (± Standard Deviation) of 47.5 years (± 10.0) for the group which received lignocaine (study group) compared with 48.6 years (± 10.7) for the placebo group (control) was not statistically significant with p-value = 0.64.

Table 4.1: Age distribution of the patients in the study
[Group A = Lignocaine; Group B = Placebo]

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range (yrs.)</strong></td>
<td>21 – 70</td>
<td>29 – 69</td>
<td></td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>47.5</td>
<td>48.6</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Standard Deviation</strong></td>
<td>10.0</td>
<td>10.7</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.1 below illustrates the type of surgery that the women underwent for hysterectomy. Hysterectomy was either by transvaginal approach or by the
abdominal route. Very few patients underwent transvaginal hysterectomy 8/39 (20.5%) for the lignocaine group compared with 6/39 (15.4%) for the placebo group. Hence, the majority of the women in the two groups had abdominal hysterectomy: 31/39 (79.5%) for the lignocaine group as against 32/39 (84.6%) in the placebo group. The differences in the type of surgery performed for hysterectomy between the two groups did not show any statistically significant value with p = 0.92

Figure 4.1: Type of Hysterectomy performed
[Group A = Lignocaine; Group B = Placebo]
The occurrence of coughing was determined among the women in the two arms of the study (Figure 4.2) and shows that coughing occurred among 13/39 (33.3%) of the women in the lignocaine study group (Group A) and among 15/39 (38.5%) women in the placebo group (Group B). The comparison of occurrence of coughing between the two groups did not yield any statistically significant difference (p-value = 0.47).

Similarly, the frequency of coughing was noted to range between 1 and 7 occurrences over a 20-minute assessment period, in all the women in the two arms of the study (Figure 4.3). Differences in frequency of coughing were not statistically significant between the two groups either at baseline (0 minute, p = 0.40); or at 5 minutes (p = 0.50); 10 minutes (p = 0.30) or 20 minutes (p = 0.62) following the administration of lignocaine (study group A) or normal saline (control group B).
Table 4.2 below shows the time interval (in minutes) between administration of study medications: lignocaine (study group); or normal saline (control group) and extubation. Time to extubation ranged from 5 to 18 minutes in the lignocaine Group and ranged from 0.5 to 18 minutes in the control group. The difference in mean (± Standard Deviation) of the time interval to extubation, which was 11.5 minutes (± 3.0) for the study group A, was not statistically different from the mean (± SD) of 10.3 minutes (± 3.6) for the control group B (p = 0.12).
Table 4.2: Time interval between administration of medications and extubation
[Group A = Lignocaine; Group B = Placebo]

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (minutes)</td>
<td>5 – 18</td>
<td>0.5 – 18</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.5</td>
<td>10.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>3.0</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Extreme outlier</td>
<td>1 (100 minutes)</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

One of the patients in the group of women who received lignocaine was adjudged to have an extreme outlier value of time interval to extubation and was excluded from the overall analysis for the group. The reason for this extreme value will be a subject for discussion in the later part of this dissertation.

The effects of the study medications (lignocaine or normal saline) on haemodynamic parameters (blood pressure, heart rate and oxygen saturation) were evaluated and compared for the two groups of patients. Table 4.3 shows the effects on blood pressure as assessed over a 20-minute period following administration of study medication. There was no noticeable change in blood pressure over the assessment period of 20 minutes among women in each of the two groups. There were no statistically significant differences in either systolic or diastolic blood pressure when
the two groups were compared immediately after administration of study medication and over the entire 20-minute post-administration assessments (Table 4.3).
Table 4.3: Comparison of changes in Blood Pressure between the two arms of the study [Group A vs Group B]

<table>
<thead>
<tr>
<th></th>
<th>Group A (Mean ± SD)</th>
<th>Group B (Mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>Systolic BP</td>
<td>125 ± 20</td>
<td>125 ± 21</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>76 ± 16</td>
<td>75 ± 15</td>
</tr>
<tr>
<td>3 min</td>
<td>Systolic BP</td>
<td>126 ± 22</td>
<td>133 ± 22</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>78 ± 17</td>
<td>80 ± 13</td>
</tr>
<tr>
<td>10 min</td>
<td>Systolic BP</td>
<td>129 ± 26</td>
<td>139 ± 20</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>77 ± 17</td>
<td>84 ± 14</td>
</tr>
<tr>
<td>20 min</td>
<td>Systolic BP</td>
<td>128 ± 21</td>
<td>127 ± 17</td>
</tr>
<tr>
<td></td>
<td>Diastolic BP</td>
<td>77 ± 14</td>
<td>76 ± 11</td>
</tr>
</tbody>
</table>

Key: Group A = Lignocaine; Group B = Placebo; SD = Standard Deviation;
P-value = Level of statistical significant difference between the two arms of the study.

A similar comparison was made for changes in heart rates following the administration of study medications (Table 4.4). The heart rates (bpm) ranged between 57 and 120 (0 minute); 62 – 144 bpm (3 minutes); 62 – 139 bpm (10 minutes) and 64 – 136 bpm (20 minutes) for women who received lignocaine. These
heart rates were 64 – 128 bpm (0 minute); 60 – 130 bpm (3 minutes); 65 – 136 (10 minutes) and 50 – 122 bpm (20 minutes) for women who received normal saline.

The comparison of the mean heart rates (± SD) between the two groups of women over the entire time of assessment (Table 4.4) did not yield any statistically significant differences. The p-values at various times of assessment after administration of medications were: 0 minute (p = 0.50); at 3 minutes (p = 0.40); 10 minutes (p = 0.70) and at 20 minutes (p = 0.70).
Table 4.4: Comparison of changes in Heart Rate between the two groups of Patients [Lignocaine = Group A vs Placebo Group B]

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start (0 min)</td>
<td>Range [Mean ± SD]</td>
<td>57 – 120 90 ± 18</td>
<td>64 – 128 91 ± 16</td>
</tr>
<tr>
<td></td>
<td>3 min</td>
<td>Range [Mean ± SD]</td>
<td>62 – 144 89 ± 17</td>
</tr>
<tr>
<td></td>
<td>10 min</td>
<td>Range [Mean ± SD]</td>
<td>62 – 139 91 ± 20</td>
</tr>
<tr>
<td></td>
<td>20 min</td>
<td>Range [Mean ± SD]</td>
<td>64 – 136 87 ± 17</td>
</tr>
</tbody>
</table>

**KEY:**  
*Group A = Lignocaine; Group B = Placebo; SD = Standard Deviation*  
*P-value = Level of statistical significant difference between the two arms of the study.*

Table 4.5 below shows the values of oxygen saturation as determined over 20 minutes of assessment following the administration of either lignocaine (study group) or normal saline (placebo group). At all times during the assessment of this variable, oxygen saturation ranged from 89% to 100% (lignocaine group) and from 90% to 100% for women in the placebo arm of the study. At all times during the evaluation of oxygen saturation, there were no statistically significant differences between the two groups of women either at baseline, at 3, 10 or 20 minutes following administration of study medications.
Table 4.5: Differences in Oxygen Saturation between patients in the Lignocaine (Group A) and those in the Placebo arm (Group B)

<table>
<thead>
<tr>
<th></th>
<th>Group A [% saturation]</th>
<th>Group B [% saturation]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start (0 min)</td>
<td>94 – 100 (98 ± 1.3)</td>
<td>93 – 100 (98 ± 1.5)</td>
<td>NSS</td>
</tr>
<tr>
<td>3 min</td>
<td>90 – 100 (98 ± 1.9)</td>
<td>90 – 100 (98 ± 2.1)</td>
<td>NSS</td>
</tr>
<tr>
<td>10 min</td>
<td>89 – 100 (97 ± 2.4)</td>
<td>90 – 100 (97 ± 2.6)</td>
<td>NSS</td>
</tr>
<tr>
<td>20 min</td>
<td>94 – 100 (97 ± 1.7)</td>
<td>92 – 99 (97 ± 1.8)</td>
<td>NSS</td>
</tr>
</tbody>
</table>

Key: SD = Standard Deviation; NSS = Not Statistically Significant [Actual p-value cannot be calculated because the difference between mean values at each assessment time = 0]

Figure 4.4: Incidence of complications [Lignocaine (A) vs Placebo (B)]
The incidence of complications in this study was low and Figure 4.4 illustrates the few cases of complications. There were 3 cases (7.7%) of hypotension among women who received lignocaine compared with 2 cases (5.1%) of hypotension among women who received normal saline. In addition, there was also one case (2.6%) of laryngospasm among the women who received lignocaine medication. The majority of the women, 35/39 (89.7%) for the lignocaine group and 36/39 (92.3%) for the normal saline group, went through the study without any complications and the comparison of these was not statistically significant (p = 0.23).
CHAPTER 5 DISCUSSION

5.1 DISCUSSION OF RESULTS

In this study, the effectiveness of 2% lignocaine 1mg/kg IV was compared to placebo (normal saline) in blunting airway reflexes during light planes of anaesthesia post hysterectomy. Following statistical analysis it was evident that 2% lignocaine 1mg/kg IV was not superior to placebo in blunting airway reflexes as evidenced by the incidence of cough in both groups, the difference between which was not statistically significant ($p = 0.47$). The incidence of cough in the placebo group (38.5%) is comparable to earlier findings by Swati and Seema, where an incidence of cough ranging from 38 to 96% was reported, although there were no formal studies that determined the incidence of cough at DGMAH. In the current study the incidence of cough and the frequency of coughing between the two groups was not found to be statistically different during the period of observation post injection of study drugs. Serum lignocaine levels were not measured in the current study and this is noted to be a limitation. If serum levels had been measured during the observation period, perhaps clinical correlation could have been made and possibly have provided an explanation for the results obtained.

Although doses as low as 0.5mg/kg were found to be effective in blunting respiratory reflexes, the timing of observations become important. Of note in the study by Gecaj-Gashi et al., the period of observation was one minute following injection of lignocaine in anaesthetised children. Again in the study by Nishino et al., the period during which lignocaine was found to be most effective was two minutes post injection. The issue of timing of administration of lignocaine is further corroborated
by findings from the work of George et al. 19. The authors found that 2% lignocaine given intratracheally or intravenously at a dose of 1mg/kg was not superior to placebo in attenuating cough or haemodynamic responses when given 20 – 30 minutes before extubation. They further attribute their observations to low lignocaine serum levels measured at 10 minutes post administration and at extubation. Serum levels at which lignocaine was found to be effective are said to be between 2.3 and 3 mcg/ml 13, 14. It is important to note that most of the studies described as evidence on the use of lignocaine used doses more than 1mg/kg 14, 18-21.

Intubations are done with the intention of extubating when the endotracheal tube is no longer necessary. Timing and technique for extubation are influenced by the balance between the residual effect of anaesthetic drugs and recovery of airway and other reflexes, with significant number of complications including death occurring around the time of extubation 3. According to Peterson et al. 3, “coughing may be particularly troublesome during light anaesthesia extubation and cannot be entirely prevented”. Time interval to extubation in the current study was 11.5 minutes in the lignocaine group compared to 10.3 minutes in the placebo group. Although there is a slight difference in the time to extubation, it was not found to be statistically significant (p = 0.12). In both groups, time to extubation was slightly more than 10 minutes, probably outside of the period of effectiveness for suppression of airway reflexes.

Statistical analysis of the haemodynamic parameters during the period of observation between the two groups revealed no differences, in keeping with the study by George et al. 19. The same observation was made for oxygen saturation between the two groups.
Complications encountered during the study were laryngospasm and hypotension. One of the patients in the lignocaine group was considered to be an extreme outlier with time to extubation taking longer than the calculated average for that group. The said patient was reported to have laryngospasm following extubation, severe enough to necessitate deepening of anaesthesia and re-intubation according to the algorithm for management of laryngospasm \(^{24}\). The patient did not suffer any injury following laryngospasm and was subsequently extubated and discharged to the ward after a period of observation in recovery. The patient who developed laryngospasm provides further evidence that probably the dose of lignocaine was inadequate to blunt the airway reflexes.

Three patients in the lignocaine group (7.7\%) and two patients in the placebo group (5.1\%) developed transient hypotension. Hypotension in the lignocaine group could be explained as one of the recognized side effects of lignocaine \(^{11}\). The occurrence of hypotension in the placebo group could have a number of causes for example: hypovolaemia secondary to significant blood loss intraoperatively; residual effect of volatile anaesthetic agents; BP measuring instrument malfunction. It is difficult to explain the occurrence of hypotension in this group because estimated intraoperative blood loss and minimum alveolar concentration (MAC) of isoflurane were not recorded on the data collection form. Although hypotension in the lignocaine group could be a side effect of lignocaine, other factors like residual effect of volatile anaesthetic agents, hypovolaemia from significant blood loss and possible BP measuring instrument malfunction cannot be ruled out. All the patients in the study who developed transient hypotension were not treated with vasogenic drugs as subsequent BP readings were normal and were later discharged to the ward after a
period of observation in the recovery area. Conducting a pilot study could have possibly revealed this limitation from the data collection form.

5.2 STUDY STRENGTHS
The following were noted to be the strengths of the conducted study:

- Data was collected prospectively
- Randomization of the sample
- Double blinding design of the study
- Data analysis done by statistician and code for the study drugs revealed after the data was analysed

5.3 STUDY LIMITATIONS

- Lack of prior piloting of the study which would possibly have revealed the shortfalls of the data collection form in recording all the necessary information required to draw conclusions from the results obtained.
- The following were not included on the data collection form:
  - Duration of procedure
  - Estimated blood loss
  - A column indicating absence of complications
  - MAC value for Isoflurane at extubation
  - Patient weight
  - Ease of intubation
  - Cigarette smoking not part of exclusion criteria and acknowledged as a possible confounding factor due its effect on airway hyperreactivity
Omission of laboratory tests to correlate with clinical findings – lignocaine serum levels during the period of observation

5.4 CONCLUSION

In the current study, 2% lignocaine 1mg/kg IV was not found to be effective in suppressing cough during emergence from anaesthesia when compared to placebo in adult patients undergoing hysterectomy at DGMAH.
5.5 RECOMMENDATIONS

It is highly recommended that future studies should

- consider conducting a pilot study to assess the reliability of the data collection form in providing all the necessary information needed to draw conclusions from the study

- consider different doses of lignocaine for investigation and further correlate the clinical findings with laboratory tests, in this case to determine serum lignocaine levels at different observation periods;

- consider larger sample size, because for the current study it is difficult to make any generalization about the effect or lack of effect of lignocaine.
REFERENCES


Coughing and straining against the endotracheal tube are common during emergence from anaesthesia and this is associated with an increase in complications, some of which pose a threat to life, for example laryngospasm.

Attempts are made to minimize these airway reflexes during emergence in order to reduce the incidence of airway complications.

I herewith invite you to participate in my research study: **A Comparative evaluation of intravenous lignocaine versus placebo for the suppression of coughing in adult patients during emergence from anaesthesia for hysterectomy at Dr George Mukhari Academic Hospital.**

In this study I investigate whether IV lignocaine has an effect on the occurrence of coughing and straining and whether it is superior to placebo.

To participate in the study you will be given the study medication, IV lignocaine or placebo, at the end of your operation during awakening. The anaesthetist will record on the data form the occurrence and frequency of any coughing. If you do not understand, feel free to ask and your questions will be answered.

Participation is totally voluntary; you are under no obligation to participate in the study. You have the right to opt not to take part in the study without any penalties.

............................................................................................................................

Researcher                                      Date
I confirm that I have received and understand all the information regarding this study. It was also explained to me that my participation in this study is completely voluntary and that I may withdraw from it at any time without supplying reasons and will not suffer any penalty.

I hereby freely agree to participate in this study.

.................................................................................................
Signature of participant/volunteer                      Place                      Date

.................................................................................................
Witness
Statement concerning participation in a Research Project

Name of Project/Study: A Comparative evaluation of intravenous lignocaine versus placebo for the suppression of coughing in adult patients during emergence from anaesthesia for hysterectomy at Dr George Mukhari Academic Hospital

I have been informed of the aims and objectives of the proposed study and have been given the opportunity to ask questions and adequate time to consider the matter. The aim and objectives of the study are sufficiently clear to me. I have not been pressurized to participate in any way.

I understand that participation in this study is completely voluntary and that I may withdraw from it at any time and without supplying reasons. This will have no influence on the regular treatment that holds for my condition, nor will it influence the care that I receive from my regular doctor.

I know that this study has been approved by the SREC and SMUREC. I am fully aware that the results of this study will be used for scientific purposes and may be published. I agree to this, provided my privacy is guaranteed.

I hereby agree to participate in this study.

........................................................... ...........................................................
Name of participant /volunteer Signature of participant/volunteer

........................................... ........................................... ...........................................
Place Date Witness
Statement by the Researcher

I provided verbal and written information regarding this study.
I agree to answer any future questions concerning the study as well as I am able.
I will adhere to the approved protocol.

................................................................. .................................................................
Name of Researcher Signature

................................................................. .................................................................
Date Place
Dear Prof/Dr/Sir/Madam

RE: APPLICATION FOR PERMISSION TO CONDUCT A STUDY AT YOUR HOSPITAL

I am Dineo Carol Raesibe Moroasui, a Master's student in the Department of Anaesthesiology at Sefako Makgatho Health Sciences University. I am requesting permission to conduct a research project towards fulfilment of the MMed Anaesthesiology degree.

Title of study: A COMPARATIVE EVALUATION OF THE USE OF INTRAVENOUS LIGNOCaine VERSUS PLACEBO FOR THE SUPPRESSION OF COUGHING IN ADULT PATIENTS DURING EMERGENCE FROM ANAESTHESIA FOR HYSTERECTOMY AT DR GEORGE MUKHARI ACADEMIC HOSPITAL

Aim of the study: The aim of the current study is to investigate the effectiveness of using intravenous lignocaine in suppressing airway reflexes during emergence from anaesthesia and tracheal extubation.

Methods: A randomized double blinded placebo controlled study. Data will be collected by an independent anaesthetist using a data sheet to record the observations following the patient’s procedure during emergence from anaesthesia. On completion of the surgical procedure, during emergence from anaesthesia after
the reversal of neuromuscular blockade, the study drug will be given and observations made of the presence or absence of cough and its frequency until the patient is extubated. I am hoping to enrol 78 patients into the study from Dr George Mukhari Academic Hospital.

Ethical clearance will first be obtained from both SREC and SMUREC. Please find attached a copy of the study protocol.

Kind regards,

Researcher:
Dr DCR Moroasui
Tel: 072 403 7455
Email: deecrt@gmail.com
DEAR PROF

RE: APPLICATION FOR PERMISSION TO CONDUCT A STUDY WITH PATIENTS ADMITTED TO OBSTETRICS AND GYNAECOLOGY UNDERGOING HYSTERECTOMY AT DR GEORGE MUKHARI HOSPITAL

I am Dineo Carol Raesibe Moroasui, a Master’s student in the Department of Anaesthesiology at Sefako Makgatho Health Sciences University. I am requesting permission to conduct a research project towards fulfilment of the MMed Anaesthesiology degree.

Title of study: A COMPARATIVE EVALUATION OF THE USE OF INTRAVENOUS LIGNOCAINE VERSUS PLACEBO FOR THE SUPPRESSION OF COUGHING IN ADULT PATIENTS DURING EMERGENCE FROM ANAESTHESIA FOR HYSTERECTOMY AT DR GEORGE MUKHARI ACADEMIC HOSPITAL

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patient is extubated. I am hoping to enrol 78 patients into the study from Dr George Mukhari Academic Hospital.

Ethical clearance will first be obtained from the SREC and SMUREC. Please find attached a copy of the study protocol.

Kind regards,

Researcher:
Dr DCR Moroasui
Tel: 072 403 7455
Email: deecrt@gmail.com
APPENDIX 3

STATISTICAL ANALYSES

The Chairperson,
Medunsa Campus Research and Ethics Committee (MCREC),
Box
UNIVERSITY OF LIMPOPO
Medunsa Campus

Dear Sir/Madam

STATISTICAL ANALYSES

I have studied the research protocol of Dr. Dineo Carol Raesibe Moroussai

Titled: A Comparative evaluation of intravenous Lignocaine versus placebo for the suppression of coughing in adult patients during emergence from anaesthesia for Hysterectomy at Doctor George Mukhari Academic Hospital.

And I agree/do not agree * to assist with the statistical analyses.

Yours sincerely,
Prof O.A Towobola

Signature: Statistician

23/10/2014
Date

* If you do not agree to assist with the statistical analyses, please provide reasons on a separate sheet.
**APPENDIX 4**

**DATA COLLECTION FORM**

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Age</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Type of surgery (Hysterectomy)</strong></th>
<th><strong>Randomisation (Assigned Group)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans-Vaginal</td>
<td>Abdominal</td>
</tr>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presence of cough from injection of study drugs to extubation (incidence)</th>
<th>Frequency of coughing</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

**Vital DATA**

<table>
<thead>
<tr>
<th>Time between injection of study drug to extubation (min)</th>
<th>Blood Pressure</th>
<th>0 min</th>
<th>3 min</th>
<th>10 min</th>
<th>20 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Heart Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Saturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Complications (Mark with x)**

<table>
<thead>
<tr>
<th>Laryngospasm</th>
<th>Hypotension</th>
<th>Bradycardia</th>
<th>Seizures</th>
</tr>
</thead>
</table>
APPENDIX 5

Dr. George Mukhari Academic Hospital
Office of the Acting Director Clinical Services
Enquiries: Dr. PMT, Shembe
Tel: (012) 529 3800
Fax: (012) 560 0099
Philmy.mabusela@gauteng.gov.za
kedibone.matsimela@gauteng.gov.za

To: Dr. Dineo Carol Raesibe Moroasui
    Department of Anaesthesia
    PO Box 273
    University of Limpopo
    MEDUNSA
    0204

Date: 05 November 2014

PERMISSION TO CONDUCT RESEARCH

The Dr. George Mukhari Hospital hereby grants you permission to conduct research on
"A comparative evaluation of the use of Intravenous Lignocaine versus Placebo for the
suppression of coughing in adult patients during Emergence from Anaesthesia for
Hysterectomy at Dr. George Mukhari Academic Hospital."

This permission is granted subject to the following conditions:

☐ That you obtain Ethical Clearance from the Human Research Ethics Committee of the
   relevant University

☐ That the Hospital incurs no cost in the course of your research

☐ That access to the staff and patients at the Dr George Mukhari Hospital will not
   interrupt the daily provision of services.

☐ That prior to conducting the research you will liaise with the supervisors of the
   relevant sections to introduce yourself (with this letter) and to make arrangements
   with them in a manner that is convenient to the sections.

Yours sincerely

DR. MNE. SITHOLE
ACTING DIRECTOR CLINICAL SERVICES
Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)
Motletlegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5617/3698 | fax: (012) 521 3749
Email: lorato.phiri@smu.ac.za
P.O. Box 163 Meduns 0204

APPROVAL NOTICE - NEW APPLICATION

09 April 2015

Dr DCR Morausui
Department of Anaesthesiology
P.O Box 205
MEDUNSA, 0204

MEETING: 03/2015

SMUREC Ethics Reference Number: SMUREC/M/61/2015: PG

The New Application received on 16 March 2015, was reviewed by members of Sefako Makgatho University Research Ethics Committee on 09 April 2015 and was approved on 09 April 2015.

Title: A comparative evaluation of the use of intravenous lignocaine versus placebo for the suppression of coughing in adult patients during emergence from anaesthesia for hysterectomy at Dr George Mukhari Academic Hospital

Researcher: Dr DCR Morausui
Supervisor: Dr RD Khobo-Mpe
Co-supervisor: Dr JLY Bitumula
Hospital Superintendent: Dr Shambe (DGMAH)
Other Involved HOD: Prof Monokoane
Department: Anaesthesiology
School: Medicine
Degree: MMed Anaesthesiology

Please note the following information about your approved research protocol:


Please remember to use your protocol number (SMUREC/M/61/2015: PG) on any documents or correspondence with the REC concerning your research protocol. Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.

International Organisation (ORG0004319), Institutional Review Board (IRB00005122), Federal Wide Assurance (FWA00009419)

Expiry date: 11 October 2016 and NHREC No: REC/PH08/003

Sincerely,

DR C BAKER
DEPUTY CHAIRPERSON SMUREC

Members of the Interim Council:
Prof O Shisana (Chairperson), Ms SA Michunu, Mr P Slack, Dr N Simelela, Prof AM Segone, Dr E van Staden

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