EFFECT OF INTRAVENOUS LIGNOCAINE INFUSION ON INTRAOPERATIVE END TIDAL DESFLURANE CONCENTRATION REQUIREMENTS: A RANDOMISED DOUBLE-BLINDED CONTROLLED STUDY

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INTRODUCTION

Lignocaine is an amide local anaesthetic and class 1B antiarrhythmic that is widely used in all medical and surgical fields. It also contains analgesic, antinociceptive, immune-modulating and anti-inflammatory actions.[1] There are many clinical studies demonstrating lignocaine's many perioperative benefits. Yang et al (2020) in a systemic and meta-analysis review showed that giving IV lignocaine in the perioperative period was safe, reduced airway complications, obtunds cough reflex and reduce sore throat.[2] Other reported advantages of systemic lignocaine administration include pain reduction, reduced opioid consumption, nausea, ileus duration and length of hospital stay.[3-6] These benefits has been shown to persist from the onset of its effects up to 36 hours after infusion has been terminated.[5, 7]

In addition to its analgesic properties, systemic lignocaine has a minimum alveolar concentration (MAC) sparring effect on volatile anaesthetics which has been proved in multiple animal studies.[8-11] The mechanism for lignocaine's MAC sparring effect is likely due to blockage of sodium channels.[8] Recently, Omar et al (2019) and Weinberg et al (2017) demonstrated in their clinical studies that parenteral lignocaine reduced Bispectral index (BIS) guided sevoflurane requirements.[12, 13] Weinberg et al (2017) also tabulated data from numerous trials which detailed the effects of parenteral lignocaine in reducing volatile agent requirements.[13] Cardiovascular depression and risk of post-operative nausea and vomiting are related to volatile agents in a dose dependent manner.[14, 15] Lower volatile agents requirement should result in a more favourable cardiovascular profile which would be beneficial in hypovolemic patients and those with low cardiac reserves. Furthermore, coupled with opioid reduction, incidence of post-operative nausea and vomiting could be reduced. Awakening from volatile agent anaesthesia is dependent on its washout from alveolar ventilation and its dose at end of surgery.[16] Therefore, it is postulated that emergence and extubation time might be faster resulting in more efficient utilisation of the operation theatre.

Clinical effects of IV lignocaine infusion are widely reported to be seen at 1-2 mg kg^{-1} h^{-1} which results in plasma levels below 5 mcg ml^{-1}.[3-5, 7, 17] Context sensitive halftime after a 3-day infusion is about 20-40 min and there is no accumulation in healthy individuals.[5] However, its clinical effectiveness differs between types of surgery, possibly due to sample size and design of the studies.[3] Patient safety is of paramount importance hence it should be noted that measurement of plasma levels of lignocaine is not widely available in Malaysia and

there is limited data regarding its optimal dosing and duration. Lignocaine has a narrow therapeutic index whereby CNS toxicity (numbness of tongue, metallic taste, light headedness and tinnitus) will begin to manifest when plasma concentration exceeds 5 mcg ml^{-1} and if left untreated, will progress to visual disturbances, muscle twitching, unconsciousness, seizure, respiratory arrest and cardiovascular collapse.[5] Cardiovascular toxicity is a rare and late complication as it usually occurs at plasma levels exceeding 10 mcg ml^{-1} which is well above that is required for neurological toxicity.[5] In the event of severe toxicity, intralipid can be given as per the guideline provided by the Association of Anaesthetists for Great Britain and Ireland.

Desflurane is an inhalational anaesthetic agent with a low blood: gas coefficient (0.42) which allows for more precise control of the level of anaesthesia, rapid induction and rapid emergence resulting in shorter recovery when compared to other inhalational agents like sevoflurane.[18, 14, 19] Therefore, it is preferably used for long surgery, bariatric surgery, obese patients or elderly patients as the faster offset leads to early wake up which minimises the risk of respiratory depression that is commonly associated with these cases.[14, 18, 19] These characteristics also makes it suitable for ambulatory and day-care surgery.[14] As little as 0.02% are metabolised in vivo, hence no dose adjustment is needed for patients with renal or hepatic dysfunction while the rest are vented to the environment without much or any degradation.[14, 18, 19] However, due to its high cost, it is not widely used for all cases.

To the best of our knowledge, there is no research on the effects of IV lignocaine infusion on intraoperative desflurane requirements in human population. Reduction of desflurane requirements when coupled with the reported benefits of IV lignocaine, will contribute to a high quality, cost effective, optimal, balanced and safe provision of anaesthesia.

OBJECTIVE

1. To investigate the effect of IV lignocaine on the end tidal desflurane concentration required to maintain BIS values between 40-60.
2. To compare intraoperative haemodynamic changes in patient with intravenous lignocaine vs normal saline.

MATERIALS AND METHODS

This prospective, double-blinded, randomised controlled study will be submitted for the approval of the Research Committee of Department of Anaesthesiology & Intensive Care, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Research & Ethics Committee, UKMMC and will be registered at ClinicalTrials.gov.

Written informed consent will be obtained from selected patients recruited into the study, which will be conducted by a single operator who is the principal investigator of this study. The study will be conducted in Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur.

Inclusion Criteria:

1. American Society of Anaesthesiology (ASA) I or II patients.
2. Patients aged between 18-75 years of age.
3. Patients scheduled for elective laparoscopic cholecystectomy.
4. Patients scheduled for laparoscopic hernioplasty.
5. Patients scheduled for emergency laparoscopic appendicectomy.
6. Patients scheduled for emergency laparoscopic cystectomy.
7. Patient weight ranging from 50 – 100 kg.
8. Surgery lasting at least one hour.

Exclusion Criteria:

1. Patients with a known allergy to study drug.
2. Patients with body mass index (BMI) more than 35 kg m^{-2}.
3. Patients who are taking sedatives.

4. Patients with chronic substance abuse.
5. Patients with history of seizures, psychiatric disorders, cardiac failure, arrythmias, hepatic or renal dysfunction.
6. Patients who are taking class IB antiarrhythmics or amiodarone.
7. Surgery lasting more than 3 hours.

Methodology:

Patient will be reviewed and recruited during premedication round, written consent will be explained and obtained. Patients will be fasted for at least six hours before their surgery. Tablet paracetamol 1g will be given to patients once they are called to operation theatre.

Patients will be randomly assigned into two groups based on computer generated randomisation tables. Group A will receive intraoperative lignocaine while Group B will receive normal saline. The study drugs will be prepared by an anaesthetist registrar who is not involved in the study. Each drug syringe will be coded and given to the primary investigator who will be blinded.

In the operation theatre, intravenous access will be obtained using an 18 G cannula in all patients and infusion of crystalloid will be started. Standard monitoring will then be applied using continuous electrocardiography (ECG), non-invasive blood pressure (NIBP) monitoring, pulse oximetry and capnography. BIS (BIS Quatro™, USA) will be used to assess the depth of anaesthesia for all patients and baseline values for BIS shall be obtained prior to induction. Pre induction blood pressure (BP) and heart rate (HR) will also be recorded. The study drugs will be given 5 min before induction of anaesthesia and two syringe pumps will be used to deliver the study drugs. First, a bolus of the study drug prepared in a 10 ml syringe will be given to the patient over a period of 3 min via the syringe pump. The time of initiation of the bolus will be taken. After bolus, the BP and HR will be recorded. Subsequently, infusion of the study drug prepared in a 20 ml syringe will be started and continued until the end of surgery using the other syringe pump. The time at the start of infusion will be taken.

Group A will receive an IV bolus dose of 1.5 mg kg^{-1} of 2% lignocaine HCL diluted up to 10 ml with normal saline in a 10 ml syringe which will be delivered via a syringe pump over a period of 3 min. This is then followed by an IV infusion at the rate of 1 mg kg^{-1} h^{-1} of 2%

lignocaine HCL in a 20 ml syringe which will be administered by another syringe pump. Patients in Group B will receive an IV bolus of 10 ml of normal saline over a period of 3 min followed by an IV infusion of an equal volume of normal saline, both of which will be delivered by separate syringe pumps.

Anaesthesia will be induced with IV fentanyl 2 mcg kg^{-1} followed by IV propofol 2-3 mg kg^{-1} and IV rocuronium 0.6 mg kg^{-1}. After 3 minutes of mask ventilation with only 100% oxygen, tracheal intubation using an appropriately sized endotracheal tube (ETT) will be performed to secure patient's airway. The patient will then be connected to Aisys CS^2 anaesthesia machine and the lungs will be ventilated with desflurane in 50% oxygen-air balance at a tidal volume of 6-8 ml kg^{-1}. End tidal CO_2 ($EtCO_2$) level will be maintained between 35-45 by adjusting the respiratory rate. The time of induction and intubation will be documented.

Anaesthesia shall be maintained with desflurane, in 50% oxygen-air balance with a total flow of 1.0 L min^{-1}. The end tidal desflurane (Et-Des) concentration will be adjusted to maintain a target BIS of between 40-60. BIS, MAC values, Et-Des concentration, BP and HR will be recorded every 10 min from the time of induction until the end of surgery. IV parecoxib 40 mg will be given to all patients. Boluses of IV fentanyl 50 mcg will also be given to maintain blood pressures within 20% of pre-operative levels. Dosage of fentanyl given post induction will be recorded. Bolus of IV ephedrine 6 mg will be given during hypotensive episodes with HR less than 60 beat per min while those with normal HR will be given a bolus of IV phenylephrine 100 mcg. Patients will also be given IV dexamethasone 8 mg post induction and IV granisetron 1 mg 30 mins before end of surgery to reduce the risk of post-operative nausea and vomiting. Core temperatures will be maintained above 35 °C with fluid warmer and warming blanket. If surgery lasts more than 3 hours, patient will be excluded from the study and infusion of the study drug will be stopped.

Desflurane and study infusions will be discontinued and estimation of desflurane cost will be estimated at the end of surgery. Neuromuscular block will be reversed with a combination of IV atropine 1 mg and IV neostigmine 2.5 mg. When the patient meets all criteria for extubation, the ETT will be removed. Time to extubation (defined as time from desflurane discontinuation to tracheal extubation) will be recorded. Pain score will be assessed in recovery bay and if required, patient will be given patient-controlled analgesia morphine.

Signs of lignocaine toxicity will be monitored in all patients beginning from the time of bolus of the study drug until one-hour post operatively in the recovery bay. During general anaesthesia, signs of lignocaine toxicity that will be looked out for include an initial tachycardia and hypertension followed by prolonged PR interval, widened QRS, sinus bradycardia, ventricular arrhythmias, hypotension and cardiac arrest. When the patient is awake in recovery bay, along with late signs of lignocaine toxicity as mentioned above, patient will be observed for one hour for early signs and symptoms characterised by perioral numbness, tinnitus, light headedness, visual disturbances, muscle twitching, seizure, altered mental state and respiratory arrest. If any of these were to occur, then infusion of the study drug will be stopped and these patients will be excluded from the study and managed according to hospital protocol.

STATISCAL ANALYSIS

a) Sample size calculation:

The α value is set at 0.01 and power of study at 90%. The sample size is calculated using t- test. Calculation as derived from a study by Kuo et al (2006) and Omar et al (2019).[6, 12]

The sample size is calculated using the "Power and Sample Size Calculations" program.
Sample size was calculated using t-test.
Requested output: Sample size
Design: Independent
Input: $\alpha = 0.01$; power = 0.9; $\delta = 0.5$; $\sigma = 0.4$; M = 1
Case sample size: 21 x 2 plus 10% drop out rate = 48
Sample = 24 per study group

b) Statistical test:

Analysis will be analysed using SPSS software for windows. The Kolmogorov-Smirnov test will be used to assess variable normality distribution. Categorical variables will be analysed by chi square test. Continuous variables will be compared using student's t -test. p value less than 0.05 will be regarded as statistically significant.

FLOW CHART

Patients for scheduled for laparoscopic cholecystectomy/appendicectomy/cystectomy/hernioplasty

- ASA I or II patients
- Age 18-60 years old
- Weight 50 – 100 kg
- Surgery lasting more than one hour

Written informed consent explained and obtained

- Patients with a known allergy to study drug
- Patients with BMI > 35 kg m^{-2}
- Patients who are taking sedatives
- Patients with chronic substance abuse
- Patients with history of seizures, psychiatric disorders, cardiac failure, arrythmias, hepatic or renal dysfunction
- Patients who are taking class IB antiarrhythmics or amiodarone.
- Surgery lasting more than 3 hours

Excluded

Random allocation into Group A (lignocaine) or Group B (normal saline)

Group A
IV bolus of 1.5 mg kg^{-1} of lignocaine 2% diluted in 10 ml syringe over 3 mins followed by infusion at 1 mg kg^{-1} h^{-1} of lignocaine 2% in 20 ml syringe

Group B
Bolus followed by infusion of equal value of normal saline

In OT

- Monitor: ECG, NIBP, HR, Pulse oximetry, capnography, temperature probe, BIS
- Record Baseline BIS values, pre induction BP/HR
- Study drug given 5 min prior to induction
- Induction of anaesthesia with fentanyl 2 mcg kg^{-1} and propofol 2-3 mg kg^{-1}
- Intubation with appropriate size ETT to secure airway
- Tidal volume 6-8 ml kg^{-1}, maintain Et-CO_2 between 35-45
- Anaesthesia maintained with desflurane in 50% oxygen-air balance
- Adjust Et-Des to maintain BIS values at 40-60
- Stop study drug and desflurane at end of surgery
- Extubate patient when all criteria met

- Et-Des, MAC, BIS, BP and HR values are recorded at 10 mins interval from time of induction
- Record time of bolus and infusion of study drug
- Record total amount of IV fentanyl given
- Document time to extubation
- Estimation of desflurane cost at end of surgery

- Multimodal analgesia with IV PCM 1g and IV parecoxib 40 mg
- IV dexamethasone 8 mg post induction
- IV granisetron 1 mg 30 min before end of surgery
- IV ephedrine 6 mg for IV phenylephrine 100 mcg for hypotensive episodes

- Monitor for lignocaine toxicity all throughout surgery from time of bolus of study drug
- Look for CVS signs when patient intubated: initial tachycardia and hypertension followed by prolonged PR interval, widened QRS, sinus bradycardia, ventricular arrhythmias and cardiac arrest
- Stop infusion of study drugs in case of toxicity
- Monitor for 1 hour in recovery and observe for early signs and symptoms of lignocaine toxicity

AAGBI Safety Guidelines

Management of Severe Local Anaesthetic Toxicity

1 Recognition

Signs of severe toxicity:

- Sudden alteration in mental state, severe agitation or loss of consciousness, with or without tonic-clonic convulsions
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may occur
- Local anaesthetic (LA) toxicity may occur some time after an initial injection

2 Immediate management

- Stop injecting the LA
- Call for help
- Maintain the airway and, if necessary, secure it with a tracheal tube
- Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)
- Confirm or establish intravenous access
- Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
- Consider drawing blood for analysis, but do not delay definitive treatment to do this

3 Treatment

IN CIRCULATORY ARREST

- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that arrhythmias may be very refractory to treatment
- Consider the use of cardiopulmonary bypass if available

GIVE INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Continue CPR throughout treatment with lipid emulsion
- Recovery from LA-induced cardiac arrest may take >1h
- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

WITHOUT CIRCULATORY ARREST
Use conventional therapist to treat:

- hypotension,
- bradycardia,
- tachyarrhythmia

CONSIDER INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Propofol is not suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

4 Follow-up

- Arrange safe transfer to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved
- Exclude pancreatitis by regular clinical review, including daily amylase or lipase assays for two days
- Report cases as follows:
  In the United Kingdom to the National Patient Safety Agency (via **www.npsa.nhs.uk**).
  In the republic of Ireland to the Irish Medicines Board (via **www.imb.ie**).
- If Lipid has been given, please also report its use to the International registry at **www.lipidregistry.org**. Details may also be posted at **www.lipidrescue.org**

Your nearest bag of Lipid Emulsion is kept .....

This guideline is not a standard of medical care. The ultimate judgement with regard to a particular clinical procedure or treatment plan must be made by the clinician in light of the clinical data presented and the diagnoses and treatment options available.

Figure 1A. *Reproduced by kind permission of the Association of Anaesthetists of Great Britain and Ireland and available for download at:* www.aagbi.org/publications/guidelines/docs/la_toxicity_2010.pdf

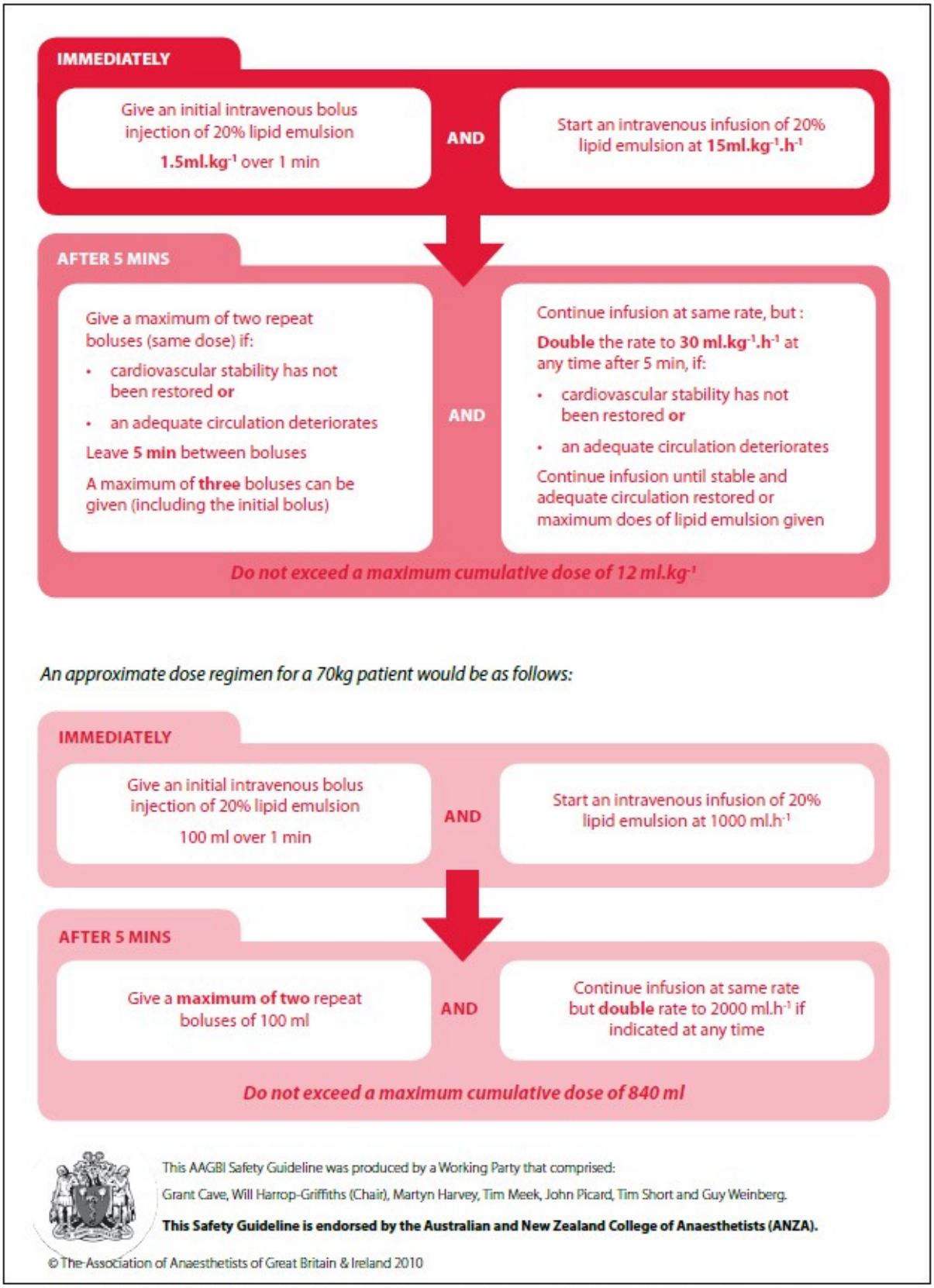

Figure 1B. *Reproduced by kind permission of the Association of Anaesthetists of Great Britain and Ireland and available for download at:* www.aagbi.org/publications/guidelines/docs/la_toxicity_2010.pdf

GANTT CHART

	March 2020	April - October 2020	Dec 2020- May 2021	June 2021	July 2021	August 2021	Sept 2021	October 2021
Proposal Presentation to Research Committee, Dept of Anaesthesiology, UKMMC	****							
Proposal submission to Research & Ethics Committee, UKMMC		****						
Data collection			****					
Data analysis				****				
Project write- up					****			
Presentation on preliminary report						****		
Presentation on final report							****	
Submission to SPS								****

DATA COLLECTION SHEET

Study Number:_____

1. DEMOGRAPHIC DATA

Age	
Gender	Male/ Female
ASA	I/ II
Weight (kg)	
Height (m)	
Past medical illness (if any state current medications)	
Diagnosis	
Surgical Procedure	

2. INTRAOPERATIVE DATA

Pre-indcution : BP___/___mm Hg ; HR___bpm
Baseline BIS :_____
Time of study drug bolus :_____
Time of study drug infusion :_____
Post bolus : BP___/___mm Hg ; HR___bpm
Time of induction :_____
Time of intubation :_____

Time (min)	0*	10	20	30	40	50	60	70	80	90
BP (mm Hg)										
HR (bpm)										
Et-Des										
MAC										
BIS										

Time (min)	100	110	120	130	140	150	160	170	180	190
BP (mm Hg)										
HR (bpm)										
Et-Des										
MAC										
BIS										

*Pre induction

IV Paracetamol 1g : ☐
IV Paracoxib 40 mg : ☐
Total bolus of fentanyl given (mcg) :_____
Time to extubation (min) :_____
Amount of agent used (ml) :_____
Agent cost (RM) :_____

3. Lignocaine side effects/toxicity

Signs and symptoms of toxicity	
Intraoperatively after bolus of study medication CVS signs:	
• Initial hypertension and tachycardia	• YES/NO
• Sinus bradycardia	• YES/NO
• Conduction blocks (prolonged PR/QRS complex)	• YES/NO
• Ventricula arryhtmias (VT, VF, Torsade de Pointes)	• YES/NO
• Hypotension	• YES/NO
• Asystole	• YES/NO
In recovery (observe for 1 hour) Neurological symptoms:	
• Circumoral and/or tongue numbness	• YES/NO
• Metallic taste	• YES/NO
• Drowsiness/ light-headedness	• YES/NO
• Tinnitus	• YES/NO
• Blurring of vision	• YES/NO
• Agitation/ confusion	• YES/NO
• Loss of consciousness	• YES/NO
• Tonic-clonic convulsion	• YES/NO
CVS signs:	
• Initial hypertension and tachycardia	• YES/NO
• Sinus bradycardia	• YES/NO
• Conduction blocks (prolonged PR/QRS complex)	• YES/NO
• Ventricula arryhtmias (VT, VF, Torsade de Pointes)	• YES/NO
• Hypotension	• YES/NO
• Asystole	• YES/NO

BUDGET PROPOSAL

No.	Item	Price Per Unit (RM)	Quantity	Total (RM)
2.	BIS strip	125	46	5750
3.	IV Paracetamol	10	46	460
4.	IV Parecoxib	30	46	1380
5.	Desflurane	500	8	4000
Total				11590

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PATIENT INFORMATION SHEET

AND

CONSENT FORM

(FOR ADULT PATIENTS)

INFORMATION SHEET FOR PATIENT

Research Title
Effect of intravenous lignocaine infusion on intraoperative desflurane requirements.

Introduction
Lignocaine is a widely used medication which is used to prevent pain to a specific area of the body for surgery. It is also used to control severe and fast abnormal heart rate, reducing pain, nausea, cough and sore throat after surgery. Desflurane is a gas that is commonly used for general anaesthesia whereby a patient is rendered unconscious, thus unaware of events and does not feel pain. It can be used safely for all patients but more suitable for obese patients with breathing problems and long surgery as awakening from general anaesthesia is quicker with less drowsiness. Bispectral index (BIS) is a strip of sensor placed on patient's forehead to assess the patient's level of unconsciousness during general anaesthesia and to guide dosing of desflurane. The aim of this study is to investigate the effect of lignocaine in reducing desflurane requirement as guided by BIS during the surgery under general anaesthesia.

What would this involve?
Patients who participate in this study will receive one of two injections (lignocaine or normal saline) through the vein. The injections will be given before general anaesthesia and continued through infusion until the operation ends. The concentration of desflurane used as guided by BIS will be recorded.

The Benefits
The researched performed will help to reduce the requirement of desflurane which will in turn reduce its cost and side effects. Together with the added benefits of lignocaine, this will lead to a safer and better provision of anaesthesia in the future.

The risks
Uncommon mild side effects of lignocaine include light-headedness, anxiety, numbness in the mouth, blurring of vision, metallic taste, ringing in the ears and nausea or vomiting. Severe and rare complications include fits, trouble breathing, unconsciousness, abnormal heart rate, complete stoppage of heart and severe allergy to lignocaine. However, these are unlikely to occur in our study because only a small dose of lignocaine is used. Your vital signs will be constantly monitored throughout the operation and post operatively and should any side effects developed; the study medications will be stopped immediately. In the event of severe side effects, an antidote and appropriate rescue medications will be administered immediately and you will be transferred to ICU for advanced care.

Desflurane can cause nausea and vomiting which can be minimised with medication given during and after operation. Other side effects include increased salivation, coughing, airway blockade, low blood pressure and increased heart rate which depends on the dose delivered and usually reversible. Hence, should such side effects occur, it will be adjusted to its appropriate dose and suitable medications may be given to counter such side effects.

Confidentiality
The result of data obtained will be reported in a collective manner with no reference to a specific individual. Hence data from each individual will remain confidential.

Do I have to take part?
The participation into this study is voluntary. If you prefer not to take part, you do not have to give reason and your decision will not affect the treatment given.

The right to withdraw
Patient has the right to withdraw from study at any time without affecting future treatment.

Payment and compensation
You do not have to pay for participating in this study. Similarly, no payment is available to you for participating in this study.

If I have any questions, whom can I ask at any point of this study?

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INFORMED CONSENT FORM

Research Title: ……

Researcher's Name: ……

I, ……, IC No: …….....

- have read the information in the Patient Information Sheet **including information regarding the risk in this study.**
- have been given time to think about it and all of my questions have been answered to my satisfaction.
- understand that I may freely choose to withdraw from this study at anytime without reason and without repercussion.
- understand that my anonymity will be ensured in the write-up.

I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.

……. ……..
(Signature) (Date)

…….	…….
Witness (if any)	Researcher
…….	…….
(Signature)	(Signature)
…….	…….
(IC Number)	(IC Number)
……..…	…….
(Date)	(Date)