THE EFFECTS OF TOPICAL LIGNOCAINE SPRAY ON INTUBATING CONDITIONS DURING INDUCTION OF ANAESTHESIA WITH TARGET CONTROLLED INFUSION (TCI) REMIFENTANIL AND PROPOFOL – RANDOMISED CLINICAL TRIAL

HOSPITAL UNIVERSITI SAINS MALAYSIA

Dr. Sadia Naim Khan

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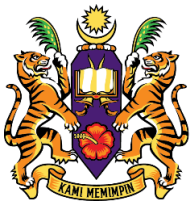

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LIST OF SYMBOLS, ABBREVIATIONS & NOMENCLATURE

%	Percent
<	Less than
Ce	Target effect-site concentration
DBP	Diastolic blood pressure
ETI	Endotracheal intubation
GA	General anaesthesia
HR	Heart rate
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
IV	Intravenous
LA	Local anaesthetic
LOC	Loss of consciousness
MAP	Mean arterial pressure
MO	Medical officer
NMBAs	Neuromuscular Blocking agents
NMBDs	Neuromuscular blocking drugs
NMRT	Non-muscle relaxant anaesthetic technique
NS	Normal saline
OT	Operation theatre
P	P-value
PONV	Postoperative nausea and vomiting
SBP	Systolic blood pressure
SD	Standard deviation
TCI	Target controlled infusion
TIVA	Total intravenous anaesthesia
USM	Universiti Sains Malaysia

ABSTRAK

Latar belakang: Agen penyekat neuromuskular (NMBA) masih dianggap penting untuk menghasilkan keadaan intubasi yang optimum. Walau bagaimanapun, terdapat minat berterusan untuk teknik intubasi alternatif tanpa NMBA menggunakan remifentanil infusi terkawal sasaran (TCI) dengan ubat tambahan lain. Matlamat kajian ini adalah untuk menilai kesan gabungan semburan lignocaine topikal dan TCI remifentanil dan propofol pada keadaan intubasi endotrakeal tanpa NMBA.

Metodologi: 60 pesakit dewasa ASA I dan II, berumur 18 hingga 65 tahun, yang dijadualkan secara elektif untuk anestesia am (GA) menjalani induksi dengan TCI remifentanil 4 ng/ml dan propofol 4 µg/ml, secara rawak kepada dua kumpulan; Kumpulan TL (n=30) menerima 10 sedutan (0.1ml setiap semburan) 10% semburan lignocaine dalam rongga mulut, manakala Kumpulan NS (n=30) menerima jumlah garam biasa yang sama, 3 minit sebelum induksi. Keadaan intubasi dinilai semasa laringoskopi menggunakan laringoskop video C-Mac. Perubahan hemodinamik selepas intubasi dan peratusan pesakit yang memerlukan penyelamatan NMBA telah direkodkan.

Keputusan: Kumpulan TL menunjukkan peratusan yang lebih tinggi daripada prosedur laringoskopi mudah [96.7% berbanding 56.7%; $p<0.01$] dan kedudukan pita suara terbuka [86.7% vs. 56.7%; $p=0.028$] daripada Kumpulan NS. Walau bagaimanapun, tidak terdapat perbezaan yang ketara dalam keadaan intubasi keseluruhan, keperluan penyelamatan NMBA dan perubahan hemodinamik antara kedua-dua kumpulan.

Kesimpulan: Semburan lignocaine topikal meningkatkan prosedur laringoskopik dan kedudukan pita suara terbuka semasa intubasi menggunakan TCI remifentanil dan propofol

tanpa NMBA.

Kata kunci: agen penyekat neuromuskular, infusi terkawal sasaran - tci, remifentanil, propofol, semburan lignocaine topikal, keadaan intubasi, tindak balas pressor.

ABSTRACT

Background: Neuromuscular blocking agents (NMBAs) are still considered crucial in order to produce optimal intubating conditions. However, there is an ongoing interest for alternative intubation techniques without NMBAs using target-controlled infusion (TCI) remifentanil with other adjunct drugs. The aim of this study was to evaluate the effect of combination of topical lignocaine spray and TCI remifentanil and propofol on endotracheal intubating conditions without NMBAs.

Methodology: 60 adult patients of ASA I and II, aged 18 to 65 years, who were electively scheduled for general anaesthesia (GA) underwent induction with TCI remifentanil 4 ng/ml and propofol 4 µg/ml, were randomised into two groups; Group TL (n=30) received 10 puffs (0.1ml per spray) of 10% lignocaine spray in the oral cavity, whereas Group NS (n=30) received the same amount of normal saline, 3 minutes prior to induction. The intubating conditions were assessed upon laryngoscopy using C-Mac video-laryngoscope. Post intubation haemodynamic changes and percentage of patients required rescue NMBAs were recorded.

Results: Group TL showed significant higher percentage of easy laryngoscopic procedure [96.7% vs. 56.7%; $p<0.01$] and open vocal cord position [86.7% vs. 56.7%; $p=0.028$] than Group NS. However, there were no significant differences in overall intubating condition, requirement of rescue NMBAs and haemodynamic changes between the two groups.

Conclusion: Topical lignocaine spray improved laryngoscopic procedure and open vocal cord position during intubation using TCI remifentanil and propofol without NMBAs.

Keywords: neuromuscular blocking agents, target-controlled infusion – tci, remifentanil, propofol, topical lignocaine spray, intubating conditions, pressor response.

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

1.1.1 Intubation without neuromuscular blocking agents

One of the leading causes of injuries associated with general anaesthesia (GA) is damage to the airway. Therefore, excellent intubating conditions are essential to abate the occurrence of above.[1] The use of neuromuscular blocking drugs (NMBAs) at induction has been advocated prior to tracheal intubation in order to provide better intubating condition and subsequently less vocal-cord sequelae.[2,3]

However certain contraindications and complications, including anaphylactic reactions, residual curarisation and awareness during GA associated with NMBAs may limit their usage in all cases.[4,5] Other important reasons to reconsider the use of muscle relaxants are haemodynamic changes associated with depolarizing muscle relaxants and potential effects specific to the use of suxamethonium like hyperkalemia, suxamethonium apnea, malignant hyperthermia amongst others. The use of reversal drugs for nondepolarizing muscle relaxants, for example neostigmine is additionally associated with an increase in salivation and postoperative nausea and vomiting (PONV).

Short procedures performed by a skilled surgeon may be significantly quicker than the duration of action of the NMBAs, leading to unnecessary delay in recovery while awaiting reversal from neuromuscular blockade. For procedures where neuromuscular monitoring is required e.g., thyroid surgery, ENT or neurosurgery; and where the neuromuscular junction must be functional, the options include either giving a short acting agent and allowing it to wear off or avoiding neuromuscular blocking agents altogether.[6]

Although with the introduction of sugammadex, both rocuronium and vecuronium can be reversed completely and considerably more rapidly than with traditional reversal agents, this technique may have financial implications for routine practice.[7]

Thus, there is an ongoing interest to explore options whereby endotracheal intubation (ETI) may be performed in the absence of NMBAs without causing harm e.g., for awake intubation for expected difficult airway management, airway obstruction in children, or certain neuromuscular disorders (e.g., myasthenia gravis).

1.1.2 Target Controlled Infusion (TCI) Remifentanil & Propofol

By 1960s, pharmacokinetic models for intravenous (IV) infusions began to be outlined and by 1980s, computer controlled IV infusion systems were introduced. TCI is such a method that attempts to achieve a user defined drug concentration in a body compartment or tissue of interest. This concept was first suggested by Kruger Thiemer in 1968. The first TCI system – the 'Diprifusor' was introduced in the year 1996.[8]

The modality of TCI is the computer-assisted IV administration of drugs such as propofol and remifentanil for induction and maintenance of GA. The mathematical algorithm of a TCI device allows continuous automatic calculation of distribution and elimination of the intravenous anaesthetic drug, and successively adjusts the infusion rate to maintain a predicted plasma or effect site drug concentration. One of the major benefits of TCI over manually controlled infusion systems is, therefore, its greater and better control over the drug concentration and the depth of anaesthesia obtained.[9]

The combination of opioids with propofol, particularly remifentanil has shown promise in significantly improving the quality of tracheal intubation without muscle relaxant use.[10–16]

In addition to reducing the cardiovascular response and improving tolerance to the tracheal tube, remifentanil also provides a useful alternative to suxamethonium for short surgical procedures where an endotracheal tube is required.[17]

The use of total intravenous anaesthesia (TIVA) with propofol and remifentanil has shown significantly fewer episodes of postoperative nausea and vomiting (PONV) compared with sevoflurane, as demonstrated by Hong et al.,[18] with higher incidence of nausea (38.1% vs. 4.8%) and vomiting (19.2% vs. 0%) in sevoflurane-nitrous oxide group versus propofol-remifentanil group. TIVA is also associated with earlier awakening and earlier return to spontaneous ventilation.[11,18]

However, both drugs are associated with adverse effects, which are dose dependent. Both may well lead to respiratory depression, hypotension, and bradycardia. When administered rapidly or in high doses remifentanil can cause chest wall rigidity in addition to other side effects associated with opioid use.[19–21]

1.1.3 Lignocaine

The mechanism of action of lignocaine in blunting pressor response differs according to the method of administration.

The addition of IV lignocaine 1-3 min before the induction of anaesthesia blunts cough reflexes and dysrhythmias resulting from tracheal intubation.[22]

The combination of propofol and lignocaine is suggested to be synergistic for tracheal intubation. The anti-tussive action of lignocaine probably accounts for the improvement and a dose of IV 1.5 mg/kg given 3 min before intubation has been reported to be optimal.[22]

Although disputed, IV lignocaine has been shown to attenuate the increase in HR, arterial pressure, and intracranial pressure. However, in few studies, doses in excess of 1 mg/kg may lead to tinnitus and patient discomfort.[23]

Topical lidocaine acts by stabilizing the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses resulting in rapid onset of localized anaesthetic effect. Local administration like gargles and sprays may be effective for cough suppression due to the local anaesthetic action at the base of tongue and pharyngeal walls preventing the receptor stimulation and improving intubating conditions.[24] The inhibition of airway tactile stimulation could be mainly due to direct blockade of the mechanoreceptors of the airways and partly to its systemic effect.[25]

Use of oropharyngeal topical lignocaine spray (100mg)[26] has been shown to be effective in attenuating pressor response (in terms of HR, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP))[24] especially when intubation was performed more than 2 min after a tracheal spray in a study by Takita et al.[25] Incidence of postoperative hoarseness and vocal cord injuries has been reported to be lower with better intubating conditions.[1]

In this clinical trial our objective was to evaluate the effect of 10% topical lignocaine spray on endotracheal intubating conditions and hemodynamic stability during anesthesia induction with TCI remifentanil & TCI propofol without using any NMBA. We aimed to

compare the number of patients that will require rescue muscle relaxant in cases of unacceptable conditions.

1.2 LITERATURE REVIEW

The search for best combination of induction drugs that may produce excellent intubation conditions began well before 1980s. With the introduction of propofol and remifentanil, better and safer parameters were attained without using inhalational agents or neuromuscular relaxants. Subsequently there was further interest to explore the possibility of adding adjuvants that may potentially obtund the pressor response further and improve upon the intubating conditions – aiding to decrease the doses for both propofol and remifentanil in order to improve the side effects profile of each.

From our literature review, we observe that insufficient studies exist that have combined topical lignocaine, TCI remifentanil and propofol for induction.

Bolow et al.[24] conducted a double-blind randomized trail which was designed to evaluate intubating conditions after induction with propofol 2.5 mg/kg and alfentanil 30 μg/kg. The 60 adults recruited were then randomized to 2 groups receiving either topical 4% lignocaine or normal saline (NS) spray. Overall, they found significantly better acceptable conditions with 100% in test group versus 63% in control group, concluding that adding topical lignocaine offered consistent and satisfactory intubation conditions.[24]

Woods et al.[15] compared haemodynamic responses and intubating conditions in 60 patients in which three different drug regimens of remifentanil were used. All were induced with IV propofol 2mg/kg, one group receiving IV lignocaine 1mg/kg. Their results showed overall

intubating conditions were mostly unacceptable in group with low dose remifentanil and no lignocaine. 100% acceptable conditions in the group which received IV lignocaine and 85% in group that received a higher dose of remifentanil and no IV lignocaine. They concluded that remifentanil 1 μg/kg and IV lignocaine 1 mg/kg, or remifentanil 2 μg/kg can provide excellent intubating conditions, may provide the advantage of an early return to spontaneous breathing without major heamodynamic changes.[15]

Troy et al.[27] conducted a double-blind randomized trial recruiting 60 adults that were divided into 3 groups receiving different TCI of remifentanil (19, 15, and 11ng/ml reduced to 10, 8, and 6 ng/ml, respectively). They concluded that target effect-site concentration (Ce) of remifentanil 8 ng/ml along with an Ce of propofol 3 μg/ml provide satisfactory conditions for intubation, while avoiding major adverse hemodynamic effects. The higher dose of remifentanil provided more satisfactory intubating conditions (75% compared to 35%). Since no IV/topical lignocaine or any other adjunct was used, it is likely that higher doses of remifentanil were required to provide better intubating condition.[27]

Kim et al.[28] conducted a similar study to Troy[27] and colleagues with lower TCI propofol and remifentanil doses. They found that remifentanil Ce of 4 or 6 ng/ml combined with 5 μg/ml propofol provided good or excellent conditions for tracheal intubation and prevented cardiovascular and BIS response during induction without muscle relaxants. However, the use of 6 ng/ml dose was associated with frequent occurrence of hypotension and bradycardia that required treatment.[27,28]

These dissimilarities in doses among these and other similar studies may be explained by the different study designs, choice of premedication and/or different defined optimal intubation condition.

Kim et al.[29] aimed to evaluate the effects of tracheal lidocaine on tracheal intubating condition without NMBAs, and hemodynamics during anesthesia induction with TCI propofol and remifentanil. 50 patients, aged 18-60 years, scheduled for closed reduction of fractured nasal bone, were randomized to control group or topical lidocaine group. They observed a significant difference between the two groups, with 88% of those receiving topical lignocaine 1 min after induction having acceptable intubating condition compared to 52% in control group. They also noticed higher MAP values, thus lesser obtundation of pressor response in control group.[29]

Sun et al.[30] ran a metanalysis searching 3 databases for randomized controlled trials (RCTs) to observe the effects of IV lignocaine on cough induced by opioids during induction of GA. In total 6 RCTs, they observed that IV lignocaine, with the lowest effective dose of 1.5mg/kg, decreased the risk of opioid induced cough (confidence interval (CI) 0.355-0.625; P = 0.074) and its severity significantly (CI -0.480 to -0.151; P = 0.038).[30]

Pang et al.[31] performed suspension laryngoscopy successfully with propofol and remifentanil with and without cisatracurium (n = 80). They observed longer intubation time (P = 0.003) in group without NMBA, however the intubating conditions and heamodynamic changes were comparable.[31]

El-Tahan et al.[32] hypothesized that the use of a non-muscle relaxant anesthetic technique (NMRT) during thoracotomy would be associated with comparable surgical conditions with

the standard use of NMBAs. Their prospective, randomized controlled study showed that NMRT offered acceptable laryngoscopy and intubating condition; using propofol (1.5-3 mg/kg) and a TCI remifentanil with Ce of 4 - 6 ng/mL; with a good-to-excellent quality of intubating conditions (93.9% v 100%, NMRT v cisatracurium; $p > 0.09$).[32]

Ide et al.[33] defended the method of ETI without muscle relaxants using propofol and remifentanil. Their RCT included 44 patients who were divided in two groups, one that received IV 0.6 mg/kg rocuronium and the control group that received IV NS. Even though there were differences in subcategories of intubating conditions, over all conditions were comparable, and there was no postoperative hoarseness or pain reported by either group.[33]

Kumar et al.[34] evaluated pressor responses in 96 patients randomized into 3 groups: Group F: IV fentanyl 2 μg/kg, Group L: nebulization with 3 mg/kg of 4% lignocaine, and Group FL: both nebulization with 3 mg/kg of 4% lignocaine and IV fentanyl 2 μg/kg 5 min before intubation. They noted that fentanyl with or without lignocaine was superior to lignocaine alone in mitigating the heamodynamic response. However, groups with lignocaine fared far better than fentanyl alone. Vecuronium 0.1mg/kg was given therefore cough response was not observed.[34]

Another RCT performed by Jokar et al.[35] evaluated the effect of lignocaine spray on attenuating pressor responses to ETI in 192 patients admitted to intensive care unit (ICU). In Group 1, inhaled nebulized lignocaine 4% (75 mg/kg) around epiglottis and larynx. In Group 2, intravenous (IV) lignocaine 2% (75 mg/kg) and control group was given no lignocaine either spray or IV. They utilized atracurium for paralysis. Though not statistically significant their findings showed overall better heamodynamic stability in nebulized group compared to

IV lignocaine group. Statistical difference, however, was seen between lignocaine groups and control, with groups receiving lignocaine had improved pressor responses than control group.[35]

Clivio et al.[36] performed a systemic review and metanalysis that included 25 trials (n = 3507) where the effect of IV lignocaine on opioid induced cough was analyzed. They observed that IV lignocaine 0.5 to 2 mg/kg prevented cough (dose-dependent) at various stages of GA, i.e., at intubation (7 trials), at extubation and after opioid administration, in trials where NMBAs were not used.[36]

Dolsan et al.[37] studied the intubating conditions in 70 patients randomized to 2 groups who were induced with either propofol and sufentanil (0.3 μg/kg) or propofol and remifentanil (3 μg/kg) without muscle relaxants. They concluded that in situations where muscle relaxants are best avoided, induction with remifentanil provides superior intubating conditions and better heamodyamics in comparison to sufentanil (51.4% vs. 20%; P = 0.0064).[37]

Varshney et al.[38] observed the heamodynamic effects during ETI induced with 2 mg/kg of IV propofol, 1.5 mg/kg of IV suxamethonium and prior oropharyngeal spray with either nitroglycerin (NTG) or lignocaine spray. In comparison to the control group both agents were effective in decreasing the pressor responses in terms of blood pressure and HR (P <0.050), with nitroglycerin having better results than lignocaine. Their study however didn't included assessment of intubating conditions.[38]

Zou Y. et al.[39] investigated the hemodynamic responses of IV lignocaine to ETI. They randomized 90 patients into 3 groups all receiving sufentanil as induction agent: Group L1 – 1 mg/kg of lignocaine, Group L1.5 – 1.5 mg/kg of lignocaine, Group S – normal saline (NS);

given 2 min before ETI. They observed significantly lower systolic blood pressure (SBP) in group L1 whereas the diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were comparable in all groups. They concluded that IV lignocaine 2 min prior to ETI may have an attenuating effect on blood pressure.[39]

Table 1 shows summary of results of some relevant studies involving remifentanil, propofol and lignocaine and intubating conditions observed.

Study ID	Pre-medication	Total	Group/n	Incidence of intubation conditions (%)			Adverse effects
				Excellent	Acceptable	Poor	
Woods et al.[15]	temazepam 20 mg ranitidine 150 mg	60	Propofol 2 mg/kg with: G1(n= 20) 1 μg/kg remi G2(n= 20) 1 μg/kg remi & lignocaine 1 mg/kg G3(n= 20) 2 μg/kg remi		 7 (35%) 20 (**100%**) 17 (85%		
Alexander et al.[13]	IV midazolam 0.03 mg/kg	60	Propofol 2 mg/kg with: G1(n= 20) 3 μg/kg remi G2(n= 20) 4 μg/kg remi G3(n= 20) 5 μg/kg remi		12 (60% overall) 19 (**95%** overall) 19 (95% overall)	8 1 1	none
Troy et al.[27]	PO 20 mg temazepam	60 Effect site	TCI Propofol 6.5μg/ml G1(n= 20)TCI remi 19ng/ml to 10ng/ml G2(n= 20)TCI remi 15ng/ml to 8ng/ml G3(n= 20)TCI remi 11ng/ml to 6ng/ml		 15 (75%) 15 (75%) 7 (35%)		none
Kim et al.[40]	PO midazolam 0.1 mg/kg	64	TCI Propofol 5μg/ml (effect site) G1(n= 22)TCI remi 2ng/ml G2(n= 21)TCI remi 4ng/ml G2(n= 21)TCI remi 6ng/ml		 32% 91% 95%		Hypotension bradycardia
Ithnin et al.[41]	none	60 target plasma conc.	TCI remifentanil determined by response or decrements of 0.5 ng/ml of the prior patient, using increments or decrements of 0.5 ng/ml TCI Propofol 3μg/ml G1(n= 30) Macintosh G1(n= 30) Glidescope		IQR score for all patients 7 8		none
Kwak et al.[42]	none	47 Effect site	IV 30 mg Lignocaine TCI Propofol 5μg/ml (effect site) TCI remifentanil determined by response or decrements of 0.5 ng/ml of the prior patient, using increments or decrements of 0.5 ng/ml G1(n= 24) orotracheal G1(n= 23) nasotracheal	 4 4	 8(12/24) 7(11/23)	 12 12	hypotension
Kim et al.[29]	IV 0.2 mg glycopyrrolate	50 effect-site conc.	TCI: propofol at 5.0 μg/ml and remi at 5.0 ng/ml G1 (n= 25) topical 4% 3ml lignocaine Control group (n= 25) topical normal saline	 14 6	 8 (**88%** overall) 7 (52% overall)	 3 12	hypotension 1 1

Table 1. Summary of studies evaluating the intubating conditions utilizing various induction agents and adjuncts

1.3 STUDY RATIONALE

Avoiding NMBAs may be beneficial, or necessary, in some patients, especially if surgery does not require muscle relaxation for facilitation.

TCI remifentanil & propofol can provide satisfactory conditions for intubation, without the use of muscle relaxants. TCI allows for easy adjustment of anaesthetic depth and can attenuate the haemodynamic response to laryngoscopy. Optimal Ce of remifentanil ranging from 4 to 8 ng/ml and propofol 3 to 4µg/ml are required to provide satisfactory conditions for intubation. [27,43] As discussed earlier however, higher doses of remifentanil are associated with adverse effects such as bradycardia, muscle rigidity and hypotension.[20,21]

In our facility, the algorithm recommended by the College of Anaesthesiologists, Academy of Medicine of Malaysia is followed as induction technique for NMRT using TIVA/TCI technique; and it was implemented for our study as well.

Combination with topical lignocaine spray prior to induction, to improve intubating conditions and heamodynamic stability can potentially decrease the requirements of remifentanil, and therefore provide insight for application of this technique in the future in more sensitive patient groups such as elderly and those undergoing certain ENT, gynaecological, neurosurgical, and emergency surgeries. This combination may additionally be beneficial in surgeries where inhalational agents are contraindicated.

To the best of our knowledge, no study has been conducted in adult Malaysian population undergoing elective surgery under GA, which compared the effects of topical lignocaine with TCI remifentanil & TCI propofol on induction condition for ETI without muscle relaxants.

1.4 OBJECTIVES OF STUDY

1.4.1 General

To evaluate the effect of topical lignocaine spray on endotracheal intubating conditions and haemodynamics during anaesthesia induction with TCI remifentanil & propofol without neuromuscular blocking agent.

1.4.2 Specific

1. To compare the intubating conditions (acceptable – excellent & good or unacceptable – poor) provided by topical lignocaine with TCI remifentanil and propofol versus Control (TCI remifentanil and propofol with placebo).

2. To compare the proportion of patients requiring rescue muscle relaxant for intubation.

3. To compare the effects of topical lignocaine on haemodynamics – HR and MAP during anaesthesia induction with TCI remifentanil and propofol versus Control (TCI remifentanil and propofol with placebo).

1.4.3 Null Hypothesis

H0: Addition of topical lignocaine does not allow a higher percentage of acceptable intubating conditions or aid in suppressing pressor response to ETI during anesthesia induction with target-controlled infusion TCI remifentanil & TCI propofol without NMBA.

H1: Addition of topical lignocaine allows a higher percentage of acceptable intubating conditions as well as aids in suppressing pressor response to ETI during anesthesia induction with TCI remifentanil & TCI propofol without NMBA.

CHAPTER 2: STUDY PROTOCOL

2.1 RESEARCH METHODS AND METHODOLOGY

2.1.1 Research Design

Double-blind, superiority, placebo controlled, parallel-group (computerized random numbers) randomized controlled trial.

2.1.2 Study Period

Jun 2020 – Aug 2021

2.1.3 Study Population

Malaysian adults (male and female): 18 years - 65 years of age.

2.1.4 Study Area

Hospital Universiti Sains Malaya, Kota Bharu, Malaysia.

2.1.5 Sampling Method

Convenience sampling

2.2 PATIENT SELECTION AND RECRUITMENT

Patients scheduled for elective surgery were approached 1 or 2 days prior to the operation, using convenience sampling. The elective lists were available at the General Operation Theatre Reception with the assigned anaesthetist medical officer.

Potential subjects were screened using the inclusion and exclusion criteria by the medical officer (MO) incharge (anaesthetist medical officer – having minimum of 2 years clinical experience in anaesthesia) for their operation theatre (OT). If appropriate for the study, the subjects were reassessed (history, appropriate examination, and investigations) by the principal investigator prior to the operation.

To address the issue of vulnerability, written and verbal details of the study were provided, and queries addressed. Subjects chose to participate in the study entirely voluntarily, they were aware that they may refuse to take part or may stop their participation in the study at any time without any penalty or loss of benefits to which they were otherwise entitled to.

If they agreed, written informed consent from participants was taken by the principal investigator.

Using a computer-generated randomization table, (equal randomization, 1:1) 60 patients will be assigned to

Group TL: 10% Topical Lignocaine spray, TCI propofol and TCI remifentanil (n = 30),

and Group NS: Control/Placebo group: NS spray, TCI propofol and TCI remifentanil (n = 30).

Study conducted after getting institutional ethical committee approval and written informed consent from all the patients involved.

2.3 SUBJECT SELECTION CRITERIA

2.3.1 Inclusion Criteria

- Adult males and females, from ages 18 years to 65 years
- Fully capable to understand verbal and/ or written information and make informed decisions for themselves
- ASA (American Society of Anesthesiologists) Physical Status Classification System I (normal healthy patient) and II (patient with mild systemic disease) physical status.
- Non-pregnant
- Patients with anticipated easy to normal level of difficulty in intubation: as described in earlier anaesthesia records, and/or clinical evidence: combination of
- normal gross facial/head and neck features
- modified Mallampati[44] score 1 or 2
- thyromental distance of more than 6 cm
- mouth opening of more than 3 cm (interincisor gap – IIG)
- sternomental distance more than 12.5 cm
- upper lip bite test grade A or B
- cervical spine range of movement of more than 90^{o} (anterior plus posterior flexion)
- Undergoing routine elective surgery (general surgery, gynecological, neurosurgical, orthopaedics, ear surgeries) requiring general anaesthesia and endotracheal

intubation.

- BMI less than 30 kg/m^2

2.3.2 Exclusion Criteria

- ASA III or higher
- Patients with anticipated difficulty in intubation as described in previous anaesthesia records, and/or evidence of difficult airway: combination of
    - Mallampati [44] score 3 or 4
    - thyromental distance (TMD) of less than 6 cm
    - mouth opening of less than 3 cm (interincisor gap – IIG)
    - sternomental distance (SMD) less than 12.5 cm
    - upper lip bite test (ULBT) grade C
    - receding mandible
    - cervical spine range of movement of less than 90^o (anterior plus posterior flexion)
- Body mass index from greater than or equal to 30 kg/m^2
- Respiratory tract illnesses (list is not limited to):
    - Clinical evidence (by history, examination and/or investigations) of current upper respiratory infection (URI)
    - History, clinical evidence (by examination and/or investigations) of recent URI (2 to 4 weeks since resolution of symptoms – depending on severity of symptoms)

- Current or recent (by history, examination and/or investigations) - lower respiratory tract infection (such as community acquired pneumonia). Minimum of 1 month since resolution of symptoms.
- Recent and recurrent hospital admissions due to respiratory tract infections (equal or more than 3 hospitalizations)
- Bronchial asthma
- Chronic Obstructive Airway Disease (COPD)
- Bronchiectasis
- Airway or Lung carcinoma
- Lung parenchymal diseases e.g., sarcoidosis, fibrosis

- Known pulmonary embolism, pneumothorax, atelectasis
- Smoking – history of smoking within 6 weeks
- Gastroesophageal reflux on medication
- Pregnancy or post-partum
- Airway/throat surgeries
- Allergies to any of the study drugs or material
- Neurological/psychiatric disorders: seizure disorder, history of stroke with residual neurological signs and symptoms
- Inability to understand verbal and/ or written information
- Undergoing regular treatment with psycho-pharmaceutical agents and/or opioids.

2.4 SAMPLE SIZE ESTIMATION

Objective #1: To compare the intubating conditions (acceptable – excellent & good or unacceptable – poor) provided by topical lignocaine with TCI remifentanil and propofol versus Control (TCI remifentanil and propofol).

Two independent proportion formula:

For specific objective 1, sample size was calculated using by PS software (Dupont & Plummer, 1990)[45].

The formula was: $\mathbf{n = (Z_{\alpha/2}+Z_{\beta})^2 * (p_1(1-p_1)+p_2(1-p_2)) / (p_1-p_2)^2}$, where:

$Z_{\alpha/2}$ = value of the standard normal distribution cutting off probability $\alpha = 1.96$ for $\alpha = 0.05$ (two tailed)

Z_{β} = Value of the standard normal distribution cutting off probability $\beta = 0.8$ for 80% power

m = ratio of patient (number of patient not exposed to factor over number of patient exposed to the factor. Suppose patients were randomized into both groups with 1:1 ratio, we use 1.

P_0 = proportion of satisfactory intubation among patient in controlled group (group 2)

P_1 = proportion of satisfactory intubation among patient in lignocaine group (group 1)

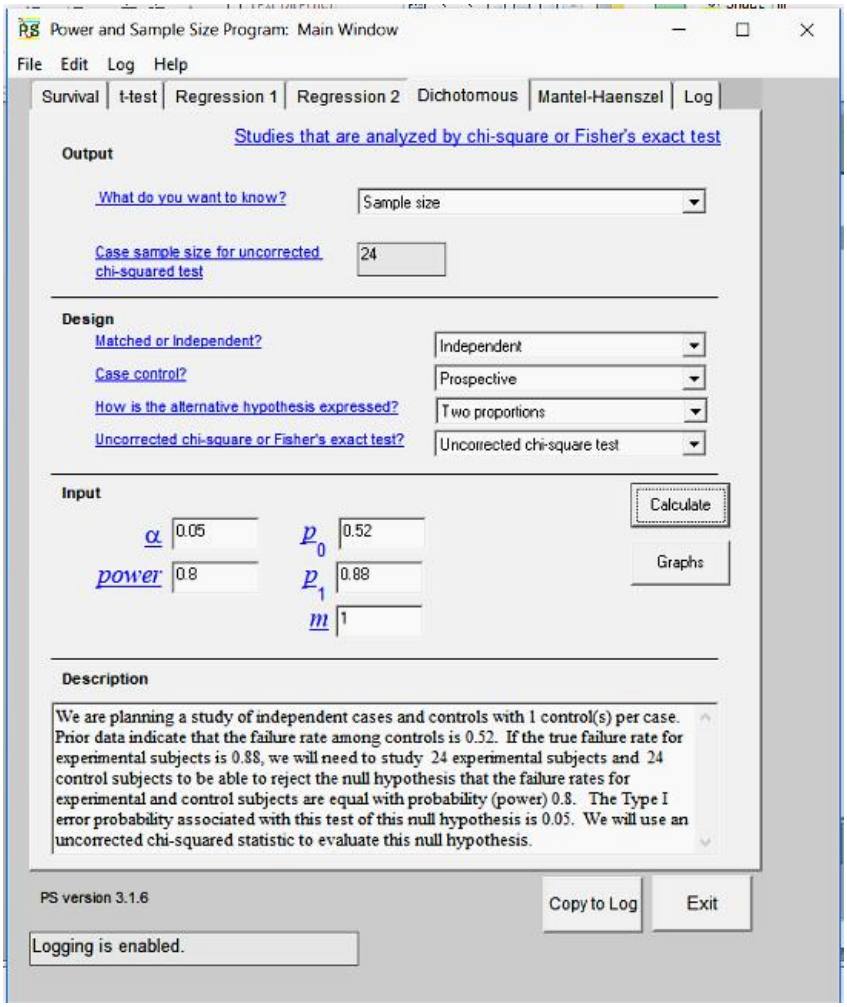
2013: Jin-Soo Kim et al. The overall intubating condition was regarded as clinically acceptable (excellent or good) in 13 out of 25 (52%) patients in the control group and in 22

out of 25 (88%) in lidocaine group, and there was a significant difference between two groups for acceptable intubating condition (P = 0.005) [29]

Level of significance is set at $p < 0.05$ and Z value is 1.96. Calculated sample size is inflated by 20% to take subject drop-out and missing data into account.

Final sample size: 24 + 20% = (28.8) 29

Variable	P_0	P_1	m	Reference	Sample size per group
Acceptable intubation conditions	0.52	0.88	1	Table, Kim et al, 2013 [29]	25/25



Objective #2: To compare the proportion of patients requiring rescue muscle relaxant for intubation.

Two independent proportion formula:

For specific objective 2, sample size was calculated using by PS software (Dupont & Plummer, 1990) [45]. The formula was:

$\mathbf{n = (Z_{\alpha/2}+Z_{\beta})^2 * (p_1(1-p_1)+p_2(1-p_2)) / (p_1-p_2)^2}$, where:

$Z_{\alpha/2}$ = value of the standard normal distribution cutting off probability $\alpha = 1.96$ for $\alpha = 0.05$ (two tailed)

Z_{β} = Value of the standard normal distribution cutting off probability $\beta = 0.8$ for 80% power

m = ratio of patient (number of patients not exposed to factor over number of patients exposed to the factor. Suppose patients were randomized into both groups with 1:1 ratio, we use 1.

P_0 = proportion of patients requiring rescue neuromuscular blocking agent in control group (group 2)

P_1 = proportion of patients requiring rescue neuromuscular blocking agent in lignocaine group (group 1)

2013: Jin-Soo Kim et al. [29] Intubating conditions were poor in 12/25 and 3/25 patients in the control and lidocaine groups, respectively (P = 0.005).

In the above study, cases that were found to have poor conditions were dealt with by increasing the target concentrations of remifentanil and propofol. Therefore, no neuromuscular relaxant was given.

For our study, our methodology dictated that any case deemed as 'poor intubating conditions' shall be given rescue NMBA. Hence, we can estimate the expected requirement by using the above data.

Level of significance is set at $p < 0.05$ and Z value is 1.96

Calculated sample size is inflated by 20% to consider of possible subject drop-out and missing data. In addition, subjects falling under acceptable condition, yet requiring muscle relaxant rescue for other reasons are also taken into account.

Final sample size: 24 + 20% = (28.8) 29

Variable	P0	P1	m	Reference	Sample size per group
Poor intubation conditions	0.48	0.12	1	Table3, Kim et al, 2013 [29]	25/25

Table 3. Intubation Conditions and Causes of Unacceptable Intubating Condition

	Control (n = 25)	Lidocaine (n = 25)
Acceptable		
Overall	13	22*
Excellent	6	14*
Good	7	8
Unacceptable		
Poor	12	3
Cause of unacceptable intubating condition		
Difficult laryngoscopy	4	1
Closed vocal cord	6	2
Vigorous coughing	12	3*

Values are number of patients. *P < 0.05, vs. control group.