Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: single-blinded randomised placebo-controlled trial.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology. Johannesburg, 2023

Declaration

I, Koji Wakabayashi, declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

20 April 2023

Abstract

Background

Extubation at the end of general anaesthesia should be performed in a way that ensures patient comfort and minimizes cardiorespiratory changes to prevent harm. Several drugs have been shown to attenuate these changes during emergence. The aim of our study was to investigate if a sub-hypnotic dose of propofol is able to produce such favourable peri-extubation conditions.

Methods

Fifty ASA grade I-II patients (aged 18-70) undergoing elective abdominal or pelvic surgery under general anaesthesia with a volatile agent were randomly assigned to a propofol group (P=28) or a control group (C=22). At the end of surgery, once the minimal alveolar concentration reached 0.6, patients received either propofol 0.5 mg kg^{-1} or an equivalent volume of isotonic saline intravenously. The primary outcome was the incidence and severity of bucking and coughing observed during emergence, with the assessment performed by a blinded anaesthetist. Haemodynamic parameters, airway responses, extubation complications and time to extubation were evaluated during the emergence period at predetermined intervals.

Results

The demographic and clinical characteristics of the two groups were comparable prior to surgery. Results indicated the incidence and severity of bucking at extubation was significantly lower (21.4%) in the propofol group compared to the control group (68.2%) ($p<0.001$). Similarly, patients in the propofol group had significantly fewer heart rate ($p=0.031$) and systolic blood pressure changes at extubation ($p=0.031$).

Conclusion

The addition of propofol 0.5 mg kg^{-1} prior to extubation successfully attenuated cardiorespiratory responses following general anaesthesia in ASA I-II adult patients undergoing elective abdominal or pelvic surgery, but did not reduce the overall incidence of cough at extubation.

Acknowledgements

The author would like to thank the following people:

Dr Tristan Leonard, for his willingness to embark on this journey without hesitation, for his guidance, motivation and dedication throughout this process.

Dr Alexis Oosthuizen, for her commitment, motivation, dedication, attention to every detail and faith in this project from the start.

The participants, for being willing to enrol in our trial.

Prof Palesa Chakane and Dr Jacob Moutlana for believing in this project from the outset.

The Department of Anaesthesiology at Chris Hani Baragwanath Hospital, for being willing to participate in theatre to assess extubation while being blinded to the study.

To my wife Rebecca van Dorsten, for her unending support and input throughout this project, no matter the time of day. Without you I wouldn't have made it through this.

To Kobus le Roux, for his guidance, and persistence in completing this research project, while helping other candidates without wanting anything in return.

To my daughter Eleanore, who made it all worthwhile.

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Abbreviations

MMed	Master of Medicine degree
CHBAH	Chris Hani Baragwanath Academic Hospital
Wits	The University of the Witwatersrand
KW	Researcher Koji Wakabayashi
TL	Researcher Tristan Leonard
AO	Researcher Alexis Oosthuizen
TT	Tracheal tube
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
Sats	Pulse oximetric saturation value
HR	Heart rate
IV	Intravenous
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

Statement

The Research Report consists of a literature review, author's guidelines, draft article, study proposal, and annexures. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article complies with the author's guidelines of the British Journal of Anaesthesia, the journal to which it is intended to be submitted, and may therefore differ from the rest of the Research Report. These differences include the referencing style, margins, and numbering of figures and tables.

Position statement

I am a registrar in the Department of Anaesthesiology at the University of the Witwatersrand (Wits). I started my anaesthetic training as a medical officer at Thelle Mogoerane Regional Hospital, before deciding to pursue this specialty in an academic institution. I chose the Wits Anaesthesiology Academic training program for its academic record of brilliance and world class teaching in the field of anaesthesia. The exposure to generalised and specialised fields of anaesthesia during the training circuit, with a wide variety of patients, pathology and presentations is what sets it apart from other universities.

Airway management is one of the core skills in anaesthesia, with initial teaching focused on becoming comfortable with this aspect of patient management. At the start of my career, I remember receiving abundant advice on how to conduct a smooth anaesthetic induction and intubation, with several strategies laid out for different scenarios. However, I remember always feeling unsure of how to conduct a smooth emergence and extubation, with a passive approach being employed at this stage of the anaesthetic – suction the airway, stimulate the patient, and remove the endotracheal tube once the patient feels enough discomfort to want to remove it himself. Despite requesting advice on this subject, not much was forthcoming. I kept having patients strain and cough against the tracheal tubes (TT), breath holding and prolonging their awakening due to their intolerance of the TT. I remember my first experience of emergence laryngospasm in a child one month into my training, and felt helpless in not being able to have been better at waking the child. The patient spent one night intubated in ICU, and despite being completely fine at discharge, I still felt guilty.

Once I joined the academic training circuit, I took it upon myself to find out how the experts/consultants and senior trainees handled emergence and extubation. Since the theatre complex of a tertiary institute such as Chris Hani Baragwanath Academic Hospital would be caring for sick patients where perioperative cardiorespiratory changes could be detrimental, I was keen to learn and apply practical approaches to prevent these changes. I enjoyed the academic discussions that spawned from this interest, and I become even more interested to develop my own approach in order to achieve a satisfying extubation experience for the patient and myself: one where the patient gently opens their eyes, and allows me to remove the TT without any straining or coughing. From time to time, I was graced with exactly such

an extubation, but could not pin down what went right and what had led to such a beautiful emergence.

Soon afterwards, the Sars-CoV-2 pandemic hit South Africa, and our department drew up guidelines for inducing COVID-19 positive patients and a controlled, coughless intubation strategy was implemented. When it came to extubation, however, no clear protocol or approach to prevent coughing at emergence was forthcoming. I decided to delve into the literature to find different pharmacological approaches, and found that several expensive and often unavailable drugs in our setting were proven to work. I needed to find something cost effective and in easy reach that might help, and was fortunate enough to stumble upon research that studied the use of propofol to wake up patients.

Extubation at the end of general anaesthesia should be performed in a way to ensure patient comfort with minimal cardiorespiratory changes in order to prevent harm, as well as practitioner safety. The pursuit of this ideal is what drove me to complete this small drug trial.

Section 1: Review of the literature

In this section, literature regarding extubation and its physiological consequences, as well as approaches to its treatment will be presented.

1.1 Introduction

Tracheal extubation represents a critical point at the end of a general anaesthetic. Cardiovascular, respiratory and endocrine responses are common and predictable throughout this time. This cascade of events is known as the extubation response .[1–4]

As the plane of anaesthesia lightens at the end of surgery, proprioceptors in the tracheal and pharyngeal region are stimulated by the endotracheal tube. These afferent fibres of the glossopharyngeal and vagus nerves send impulses to the brainstem, initiating a somatovisceral reflex that leads to a rise in plasma catecholamine levels.[2,4,5]

Cardiovascular manifestations of this response commonly include cardiac arrhythmias, tachycardia, hypertensive as well as hypotensive periods and myocardial ischemia.[3,6] Sympathetic activation can also lead to a prolonged increase in myocardial oxygen consumption, as well as activation of the renin-angiotensin-aldosterone system.[2,3,5] Bradycardia may occur in infants as the autonomic equivalent to this response due to an increased vagal tone.[7]

Respiratory phenomena at extubation include coughing, bucking, laryngospasm, bronchospasm, apnoea and desaturation. The resultant uncoupling of pulmonary blood flow and ventilated lung units can lead to a persistent reduction in arterial oxygen, thereby increasing the risk of postoperative hypoxia.[8] Furthermore, the risk of aspiration, airway obstruction, pulmonary oedema and airway trauma are potential complications that more commonly occur at extubation than at any other time during anaesthesia.[9]

Stimulation of the central nervous system at emergence and extubation results in a measurable increase in electroencephalographic activity, indicating an increased cerebral metabolic rate and cerebral blood flow. The incidence of agitation and delirium are also increased at this time. Intracranial, intraocular and intraabdominal pressures rise, leading to a transient rise in bleeding risk.[10–12]

1.2 Complications and adverse events during extubation

In most patients the physiological changes that occur at the time of extubation are transient and do not result in significant long-term morbidity. However, it can have deleterious effects in certain situations.

Coughing and bucking at emergence can lead to wound dehiscence, intracerebral bleeding after neurosurgical procedures, haematoma formation after thyroid or neck surgery, and visual compromise after ophthalmic procedures. Therefore, a smooth emergence from anaesthesia is preferable for many surgical procedures, such as in otorhinolaryngology and neurosurgery.[13–15]

The cardiovascular instability in response to extubation may be poorly tolerated in patients with preexisting hypertension, coronary artery disease and peripheral vascular compromise. The associated increase in myocardial oxygen consumption can lead to an increased risk of myocardial ischaemia and infarction that persist into the postoperative period.[16–18]

Agitation, sedation and nausea and vomiting can lead to respiratory depression, aspiration and a prolonged stay in the post anaesthesia care unit. Laryngospasm and bronchospasm at emergence can result in desaturation, haemodynamic instability and hypoxaemia that is poorly tolerated in patients with limited respiratory reserve, obstructive lung pathology, and pulmonary vascular disease.[19,20]

Extubation is classified as an aerosol generating procedure and in light of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has garnered more attention.[21,22] Compared with intubation, extubation produced a 15-fold higher aerosol yield,[23] indicating it is a higher risk procedure. Despite this, many more efforts and guidelines are being focused on intubation. Due to the proximity of the anaesthetist and other health care workers to the patient at the time of extubation, as well as the high risk of coughing during extubation, antitussive efforts have recently been recommended in handling SARS-CoV-2 positive patients presenting for anaesthesia.[21,24]

It is generally recognized as good anaesthetic practice to blunt the cardiorespiratory response to intubation. Its mechanism is well understood, and targeted attenuation of this response is performed regularly at induction.[7,25–27] However, there is a higher rate of complications associated with extubation than intubation[12] and extubation has been found to have a three times higher incidence of adverse events.[28]

Cardiorespiratory complications associated with extubation, however, are not usually reported if they occur and are often viewed as acceptable physiological consequences. Hence, the complications associated with extubation are underreported and difficult to track in literature, despite being common, predictable and potentially severe.[1,4,28,29] Recently, reviews on the active management of this phase of anaesthesia have been done.[22,30,31]

1.3 Approaches to a smooth extubation

Achieving a smooth extubation, during which the cardiorespiratory response is attenuated, should result in a comfortable patient with intact haemodynamic parameters and stable ventilation.[22] Strategies to attenuate the physiological changes during extubation include pharmacological and technical methods.

1.3.1 Non-pharmacological approaches

Removing the endotracheal tube while the patient is still in a deep plane of anaesthesia has been shown to reduce the risk of peri-extubation cough and other associated complications.[32,33] Performing deep extubation however results in a loss of airway control with an increased risk of aspiration and pharyngeal obstruction. Hence, no overall reduction in adverse events between deep and awake extubation was noted in several studies, with no difference in airway complications despite a reduction in cough incidence.[32–34]

Exchanging the endotracheal tube with a laryngeal mask airway at the end of surgery is commonly known as the Bailey's manoeuvre, and has been shown to achieve a smooth emergence from anaesthesia.[35,36] Several studies noted a reduced incidence of cardiovascular and respiratory complications at emergence,[37,38] while maintaining airway patency that would be lost with deep extubation alone.[39] The downside to this technique is the increased cost of exchanging equipment.

Preventing stimulation during emergence prior to awake extubation is another technique which has been shown to reduce the incidence of cardiorespiratory responses at extubation.[40] A significant reduction in severe cough, laryngospasm and haemodynamic alterations is accompanied by potentially longer awakening times with no change in peri-extubation sore throat incidence.[41] This approach is often called the "no-touch" technique.

1.3.2 Pharmacological approaches

Pharmacological approaches include the use of beta-blockers,[10,42,43] calcium channel blockers,[44,45] opioids,[46,47] α-2 agonists[48,49] and local anaesthetics.[11,15] Their varying mechanisms of action have led to different effectiveness in blunting the extubation response, with few studies directly comparing one to another.[22,30]

1.3.2.1 Lignocaine

The use of lignocaine is well established in anaesthesia and has been shown to effectively obtund the extubation response.[30,31] Its mechanism of action includes peripheral and central activity. It has local anaesthetic effects on airway mucosal receptors when applied either topically or intravenously,[50–53] and acts centrally by modulating excitatory neural signal transduction and suppressing catecholamine release.[54,55]

Administering lignocaine intravenously prior to extubation has been shown to attenuate the haemodynamic changes associated with extubation in several studies.[11,14,56] It was discovered that a plasma concentration of 3 mcg/ml was required to suppress respiratory reflexes, and that the intravenous lignocaine effects were short-lived. The depressant effect was noted to be highest immediately after administration, and ended up only being 53% as effective after 15 minutes.[56] Furthermore, intravenous lignocaine was also found to increase the time taken to awaken from anesthesia.[14] Hence, the timing of lignocaine administration, as well as the correct dose are important in preventing the cardiorespiratory response during extubation.[50]

Lignocaine has also been administered into the endotracheal cuff to prevent coughing and bucking at extubation.[57,58] Studies found that this intervention improved the physiological response to extubation, with alkalinized lignocaine proving most effective.[57] The main risk of this method was cuff rupture and pressure necrosis of the cuff on airway mucosa. A more concentrated dose of 4% lignocaine was used to achieve good outcomes.

The use of modified endotracheal tubes that allow lignocaine to be administered topically prior to extubation has also shown good results.[50,59] Perforations built into the design at the distal end of the endotracheal tube served as ports to administer lignocaine topically around the cuff. However, frequent occlusion of the perforations by mucosal secretions were noted to have hindered the expected efficacy. It was also postulated that the act of spraying through the ports might have stimulated coughing at the time of lignocaine administration.[50]

Furthermore, the cost of producing and procuring the modified tubes was 1.5 times higher than the endotracheal tubes in general use.

Intratracheal lignocaine instillation via the tube has also been studied with mixed results. Endotracheal administration of lignocaine before intubation has been shown to decrease coughing at extubation[60] and this effect lasted up to two hours after lignocaine was sprayed.[52] Although systemic absorption of drug resulted in an average serum level of 0.47 mcg/ml after two hours,[53] which is far below the effective level required to have a central effect,[56] endotracheal lignocaine was noted to be effective for a prolonged time due to its avid binding with the airway mucosa. When comparing its efficacy in craniotomy patients, there was no difference in endotracheal and intravenous lignocaine administration[15] when given 20 minutes before emergence from anaesthesia. Some evidence exists that endotracheal lignocaine is as effective as intravenous lignocaine.[61] However, endotracheal lignocaine has also been shown to attenuate the cardiorespiratory responses to extubation more effectively than other forms of administration.[51]

1.3.2.2 Propofol

Propofol is a commonly available and widely used drug in anaesthesia. Its pharmacokinetic profile provides a rapid onset and predictable offset of drug effect, which allows for either bolus administration or maintenance of anaesthesia with continuous infusion. Its mechanism of action includes peripheral and central activity, with potentiation of γ-aminobutyric acid type A receptor activation and inhibition of further synaptic transmission, as well as inhibition of release of the excitatory neurotransmitter glutamate.[62]

Sub-anaesthetic doses of propofol are known to induce sedative, anti-nausea and anxiolytic effects in a dose-dependent manner.[63] Its administration is associated with blunting of airway reflexes[63–66] and this property allows for its use in the effective treatment of laryngospasm at extubation.[67–69] The cardiovascular effects of propofol include a reduction in the mean arterial pressure and blunting of the baroreceptor reflex, thereby preventing an increase in heart rate in response to a drop in blood pressure.[62,63] Its central effects include an overall inhibition of excitatory signal transduction, which leads to a smooth, rapid emergence after propofol administration.[64] Based on this effect, sub-hypnotic doses of propofol have been shown to reduce the incidence and severity of emergence agitation after surgery in children.[70]

The respiratory, cardiovascular and central effects of propofol described above make it an effective drug to use for attenuation of the extubation response.

These features have led research into its efficacy in producing favourable extubating conditions.

Fentanyl-induced cough is a phenomenon commonly noted during induction of a general anaesthetic after intravenous administration of fentanyl, and occurs due to an increased vagal tone and histamine release, resulting in bronchoconstriction and cough.[71] Several studies have shown that a sub-hypnotic dose of propofol prior to giving fentanyl is able to effectively reduce this cough response.[72,73]

Total intravenous anaesthesia (TIVA) with a propofol infusion is a general anaesthetic technique used for many surgical procedures where microvascular structures are involved, including otorhinolaryngology and neurosurgery. Smooth emergence is a benefit noted after propofol TIVA, with its airway reflex suppression resulting in significantly less coughing and haemodynamic changes at extubation when compared to a balanced anaesthetic technique.[74] However, further research also showed that the airway protection afforded by the cough reflex was not adversely affected by residual sedation after propofol administration.[75] Hence patients would not be at an increased risk of uncleared secretions or aspiration after extubation.

The efficacy of a sub-hypnotic dose of propofol to reduce the risk of laryngospasm after extubation was compared in a group of patients with using either a benzodiazepine or a placebo.[67] Results showed a significant reduction in laryngospasm risk with propofol administration prior to extubation after oropharyngeal surgery. Furthermore, it was also shown that the incidence and severity of post-operative cough was reduced in the patient group that received propofol.

Several studies have compared the efficacy of propofol attenuating the extubation response with the efficacy of ketamine, as a combination with ketamine and with a placebo.[69,76–78] Although the combination of sub-hypnotic doses of propofol and ketamine was shown by Safavi et al[69] to be most effective in suppressing cough at extubation, the use of propofol alone also showed a significant reduction of incidence and severity of cough. Another study by Pak et al[76] showed that the incidence of coughless emergence was highest with propofol use, and that the severity of cough was significantly less when using either propofol or ketamine.

The efficacy of low dose propofol administration at extubation was also compared directly with the administration of a placebo. Studies by Ozturk et al[78] and Jung et al[79] researching sub-hypnotic propofol doses after elective surgery showed that the cardiorespiratory response to extubation was significantly attenuated. The time to awareness, extubation and residual sedation was not prolonged after the propofol dose, while the haemodynamic parameters were similar to the placebo group. Another study by Vaziri et al[80] showed that propofol administration two minutes before removal of the endotracheal tube was able to prevent the expected increase in the haemodynamic parameters at the time of extubation.

1.3.2.3 Dexmedetomidine

Dexmedetomidine is an α-2 agonist that reduces autonomic activity by inhibiting central noradrenergic release in the locus coeruleus, thereby producing analgesic and sedative effects without respiratory depression.[81] These properties have led to research in its wide range of uses in anaesthesia as a versatile drug, with great potential in many clinical situations. Multiple studies have noted its usefulness at both intubation and extubation, by producing good endotracheal tube tolerance and haemodynamic stability.[21,82,83] However, due to its sedative effects, dose and timing of administration has been the focus in research for its use during emergence.[30]

Administering a single dose of dexmedetomidine at 0.5 mcg/kg intravenously at the end of surgery was shown to alleviate the extubation response, with a reduction in other postoperative complications including nausea, vomiting and agitation.[84,85] Similarly, when compared with placebo, dexmedetomidine at a dose of 0.75 mcg/kg fifteen minutes prior to extubation was able to produce a smooth emergence.[49] Bradycardia and hypotension were side effects of its use, but did not require active intervention in the study group and produced no postoperative morbidity. Doses of 0.5 mcg/kg, 0.7 mcg/kg and 1.0 mcg/kg have been compared for use in attenuating the extubation response,[85,86] with all doses able to achieve the desired effect. The higher dose resulted in a coughless emergence with more significant haemodynamic instability, while the lower doses were still able to alleviate respiratory agitation. Infusions of dexmedetomidine at 0.2 mcg/kg per hour and 0.4 mcg/kg per hour that continued until awake extubation were also shown to attenuate the stress response without increasing emergence time.[31,48]

The benefits of dexmedetomidine are well established in intensive care by decreasing agitation and delirium in mechanically ventilated patients.[87] A recent review demonstrated its reliability in reducing the time to extubation in patients that were difficult to wean from assisted ventilation, while reducing agitator responses to extubation with no alterations in clinical outcomes.[88]

1.3.2.4 Opioids

Opioids act on receptors distributed throughout the central nervous system and have a blunting effect on the sympathetic, vagal, adrenal, respiratory and cardiovascular systems.[89] Although their main anaesthetic use focuses on the provision of analgesia, other uses include their ability to attenuate the haemodynamic responses to intubation and extubation.[30,31,90] Tramadol at 1 mg/kg was shown to reduce peri-extubation coughing, as well as decreasing the risk for laryngospasm, postoperative shivering and agitation.[46] Similarly, oxycodone at 0.08 mg/kg and fentanyl 1 mcg/kg administration prior to end of surgery were equally effective in producing a smooth emergence compared with placebo.[91] Moreover, fentanyl at 1 mcg/kg was also shown to be superior to lignocaine in alleviating the extubation response.[92]

However, remifentanil has been noted to produce the most favourable extubation quality of all opioids, due to its ultrashort duration of action and intense autonomic attenuation.[30,90,93] This pharmacokinetic profile usually requires it be given as an infusion, with broad ranges at peri-extubation able to produce varying cardiorespiratory attenuation. A target effect site concentration of 2.14 ng/ml was shown to reliably abolish coughing at emergence without causing hypoventilation and haemodynamic disturbances in thyroid surgery.[94] A higher effect site concentration of 2.92 n/ml prevented emergence coughing in laryngomicroscopic surgery, although time to extubation and hypoventilation were increased.[95] At a concentration of 2.6ng/ml, remifentanil produced coughless extubation conditions with haemodynamic stability and mild respiratory depression, which resolved acutely without intervention.[96] A continuous remifentanil infusion of 0.2 mcg/kg per minute was also shown to produce a smooth extubation with no adverse effects.[47]

1.3.2.5 Calcium channel blockers and beta blockers

Since the cardiovascular response at emergence is driven by the autonomic nervous system, studies into the use of vasoactive drugs to dampen this response have been conducted. Calcium channel blockers act by inhibiting calcium ion influx through various types of calcium channels into contractile myocardial and vascular smooth muscle cells.[97] Beta blockers prevent sympathetic activation of inotropic and chronotropic effects on the myocardium.[98] This results in their widespread use for a variety of cardiovascular indications, including their ability to produce favourable haemodynamic conditions for extubation.

Diltiazem given at 0.1 mg/kg prior to extubation was shown to be as effective as lignocaine 1 mg/kg in attenuating cardiovascular changes at emergence, whereas a dose of diltiazem at 0.2 mg/kg showed an even greater ability to attenuate this response.[99] No haemodynamic side-effects at these doses required intervention. When comparing calcium channel blockers, however, it was shown that verapamil at a dose of 0.1 mg/kg was more effective than diltiazem at preventing the cardiovascular response to extubation.[45] The use of verapamil at this dose was confirmed,[44] although another study revealed that dexmedetomidine was able to attenuate the extubation response more effectively when compared with verapamil.[100]

Labetalol at a dose of 0.25 mg/kg was shown to be more effective than either fentanyl or lignocaine in alleviating the autonomic response to extubation.[101] Esmolol and labetalol were both effective in producing favourable extubation conditions, but esmolol at 1.5 mg/kg blunted the haemodynamic response better.[10] When compared with propofol and lignocaine, esmolol was noted to elicit its attenuating effects more rapidly, with less sedation and similar reductions in coughing and bucking as the other two drugs.[102,103] It was also able to prevent the haemodynamic changes at extubation in neurosurgery, where smooth emergence was critical.[43] Doses up to 2 mg/kg were tolerated well, with larger doses causing significant decreases in systolic blood pressures during emergence.[42]

1.4 Summary

Extubation should be performed in a way to ensure patient comfort with minimal cardiorespiratory changes in order to prevent harm. Furthermore, in view of its aerosol generating risk in the era of SARS-CoV-2, an active approach should be adopted to protect those in close proximity at the time of endotracheal tube removal. Hence, the advantages of smooth emergence exceed simply maintaining oxygenation and ventilation until the patient is ready to be extubated at the end of a general anaesthetic.[8,28,29,93] Reviews and analyses of studies that aim to produce a smooth emergence have consistently demonstrated that all approaches have improved odds of reducing cough at extubation in comparison with placebo or no action.[22,30,31] Hence it follows that actively managing emergence and extubation is more beneficial for patient and practitioner than doing nothing at all.

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Section 2: Author's guidelines

British Journal of Anaesthesia Guide for Authors

Aims and Scope

The British Journal of Anaesthesia (BJA) publishes high-impact original work in all branches of anaesthesia, critical care medicine, pain medicine and perioperative medicine including fundamental, translational and clinical sciences, clinical practice, technology, education and training. In addition, the *Journal* publishes review articles, important case reports, correspondence and special articles of general interest.

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The standard layout of a manuscript is:

Title page

Abstract including Keywords (see further guidance on when to use a Structured Abstract)

Introduction

Methods

Results

Discussion

Details of authors' contributions

Acknowledgements

Declaration of interests

Funding

Appendices (if applicable)

References

Tables (including a title and legend, with any essential abbreviations defined)

Legends to figures

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What is known / unknown about it

Hypothesis

Aim of your study

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Ethics approval / licence (including date and administering institution)

Registration (including date) (if applicable)

Patient population

Inclusion / exclusion criteria

Conduct of the study

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The study was approved by the appropriate Ethics authority.

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[Note: abbreviations for odds ratio (OR) and 95% confidence interval (95% CI) are acceptable provided they are defined in text/abstract].

"…lidocaine-group: 48 (23) mg (mean (SD)) vs placebo-group: 51(19) mg, *P*=0.22."

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Acknowledgements

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Section 3: Draft Article

Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: single-blinded randomised placebo-controlled trial.

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Running title: Low dose propofol blunts the extubation response
Keywords: low dose propofol, blunt extubation, extubation cough, extubation response
Trial Registration: The National Health Research Database, GP_202101_034

Abstract

Background

Extubation at the end of general anaesthesia should be performed in a way that ensures patient comfort and minimises cardiorespiratory changes to prevent harm. Several drugs have been shown to attenuate these changes during emergence. The aim of our study was to investigate if a sub-hypnotic dose of propofol is able to produce such favourable peri-extubation conditions.

Methods

Fifty ASA grade I-II patients (aged 18-70) undergoing elective abdominal or pelvic surgery under general anaesthesia with a volatile agent were randomly assigned to a propofol group (n=28) or a control group (n=22). At the end of surgery, once the minimal alveolar concentration reached 0.6, patients received either propofol 0.5 mg kg^{-1} or an equivalent volume of 0.9% normal saline intravenously. The primary outcome was the incidence and severity of bucking and coughing observed during emergence, with the assessment performed by a blinded anaesthetist. Haemodynamic parameters, airway responses, extubation complications and time to extubation were evaluated during the emergence period at predetermined intervals.

Results

The demographic and clinical characteristics of the two groups were comparable prior to surgery. Results indicated the incidence and severity of bucking at extubation was significantly lower in the propofol group (21.4%) compared to the control group (68.2%; p<0.001). Similarly, patients in the propofol group had significantly fewer heart rate (p=0.031) and systolic blood pressure (p=0.031) changes at extubation. No differences between the two groups in incidence of severe coughing was found (83.3% vs 72.7%; p=0.18).

Conclusion

The addition of propofol 0.5 mg kg^{-1} prior to extubation successfully attenuated cardiorespiratory responses following general anaesthesia in ASA I-II adult patients undergoing elective abdominal or pelvic surgery, but did not reduce the overall incidence of cough at extubation.

Introduction

Tracheal extubation represents a critical point at the end of general anaesthesia (GA). The process is associated with transient physiological changes that trigger a range of cardiovascular and respiratory responses.[1–3] While the physiological changes are well tolerated by most patients, they can be harmful. Adverse cardiovascular outcomes include cardiac arrhythmias, tachycardia, hypertensive as well as hypotensive periods, myocardial ischaemia and a prolonged increase in myocardial oxygen consumption.[1,3,4] Adverse respiratory sequelae include coughing, bucking, laryngospasm, bronchospasm, apnoea and desaturation.[3,5,6] Avoiding adverse cardiorespiratory responses at extubation is a key concern for anaesthetists.[7] Furthermore, procedures involving microsurgery require a smooth, coughless emergence to preserve delicate repairs.[5,8] Antitussive strategies at extubation have become particularly relevant in the era of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) due to its aerosol generating risk for healthcare professionals.[9,10]

A variety of technical methods and pharmacological agents have been shown to facilitate a smooth extubation with minimal cardiovascular and respiratory responses.[11] Some of the more frequently studied intravenous (IV) agents that have demonstrated effectiveness in attenuating cardiorespiratory responses at extubation include lignocaine, alpha 2 adrenergic agonists, calcium channel blockers, beta-blockers, and opioids.[11,12] Non-pharmacological strategies include removing the tracheal tube (TT) while the patient is in a deep plane of anaesthesia, performing the Bailey's manoeuvre, and performing a "no-touch" technique.[13,14]

More recently, the use of propofol (2,6-diisopropylphenol) to minimise cardiorespiratory responses and facilitate a smooth emergence following extubation has been studied.[15-26] Propofol is listed on the World Health Organization (WHO) essential drugs list and is readily available in operating theatres in many countries,[27] relatively inexpensive compared to newer anaesthetic drugs,[28,29] and there are relatively few contraindications to its use.[30] Sub-anaesthetic doses of propofol are known to induce sedative and anxiolytic effects in a dose-dependent manner, while its anti-emetic properties reduce the incidence of nausea and vomiting after GA.[30] Its administration is associated with blunting of airway reflexes, allowing for its use as an effective treatment for laryngospasm at extubation.[18–20,24] Results from several studies have shown that sub-hypnotic doses of propofol in the range of 0.25 - 0.5 mg kg^{-1} significantly reduced cardiorespiratory changes in patients following extubation compared to control groups.[17,18,20,21,26]

These findings have not been universal however, with other studies using similar protocols finding either no significant effect,[16] or showing non-superior effects when compared with other interventions.[23,25]

Considering the high incidence of coughing at extubation[21] with potentially serious consequences at the time of TT manipulation,[1,3] the aim of this study was to investigate the efficacy of a sub-hypnotic dose of propofol in attenuating the cardiorespiratory response to extubation. We hypothesised that the incidence and severity of bucking and coughing would be significantly lower in adult patients who received a low dose of propofol IV (0.5 mg kg^{-1}) compared to those who received placebo during emergence from TT extubation following GA. Based on other studies using the same propofol dose, we assumed the incidence of coughing at extubation to be 33%. Haemodynamic parameters, airway complications and time to extubation were also evaluated during emergence.

Methods

Ethical Approval

Ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand prior to commencement (Ethics number: M210232 obtained on 22 April 2021; National Health Research Database study number: GP_202101_034). Informed written consent was obtained from each participant prior to participating in the study. Patient confidentiality was maintained throughout the study.

Study Design and Participants

A prospective, randomised, placebo-controlled, parallel-group trial with single blinding was conducted. Adult patients (aged 18 to 70 years) who presented for elective abdominal or pelvic surgery under GA at Chris Hani Baragwanath Academic Hospital in South Africa from April to October 2021 were invited to participate in the study. Patients were required to have an American Society of Anesthesia (ASA) physical status I-II. Patients with contraindications to receiving propofol, hypotension at the end of surgery, or for whom different extubation plans (e.g.: deep extubation, extubation in ICU) were excluded from the study. Patients were randomly allocated to either the intervention group (propofol) or the control group (placebo) with 1:1 allocation ratio. Simple randomisation was performed once the patient was in theatre by the study's Principal Investigator (KW) using the "RandomIZE" application program. KW generated all allocation sequences, enrolled patients and assigned them to either group. Concealment of group allocation was achieved by restricting access to the enrolment results of the application program to all other assessors. Patients and outcome assessors were kept blinded to their group allocation.

Sample size calculations, based on the incidence of post-extubation cough from previous studies[21,31], indicated a sample of 22 patients per group would sufficiently power the study to detect a 33% difference in cough between the two groups, assuming an α-level of 0.05 and power (1-β) of 80%. Once both groups achieved their enrolment targets of a minimum of 22 patients using simple randomisation, the study was stopped.

All patients were nil per os for eight hours preoperatively, and no anxiolytic premedication was administered. Once in the operating room, non-invasive blood pressure, pulse oximetry, temperature, end tidal carbon dioxide (EtCO2) and electrocardiogram (ECG) were monitored at 1–3-minute intervals. Anaesthesia was induced with 1–2 mcg kg^{-1} fentanyl and 2.5 mg kg^{-1} propofol IV. Once the patient became unconscious, 0.6 mg kg^{-1} rocuronium was administered IV and tracheal intubation performed. Anaesthesia was maintained with a low flow mixture of oxygen, medical air and sevoflurane to maintain a minimum alveolar concentration (MAC) of 1.0, with controlled ventilation to achieve an $EtCO_2$ of 35-45 mmHg. Vital signs were maintained within 20% of their baseline values intraoperatively until emergence, and analgesia was provided with 0.1 mg kg^{-1} morphine IV and 1g paracetamol IV. Supplemental analgesia with 1 mcg kg^{-1} fentanyl boluses IV was provided as necessary. At the end of surgery, sevoflurane was discontinued, gentle oropharyngeal suction was performed and manual ventilation with 95% oxygen was achieved. The level of neuromuscular paralysis was assessed using train-of-four (TOF) stimulation monitoring. Once a TOF count of 3 or 4 was measured, neostigmine 2.5 mg and glycopyrrolate 0.4 mg IV were administered. Two anaesthetists were involved in the extubation process. At a MAC value of 0.6, the second anaesthetist was asked to leave the operating theatre momentarily, while the first anaesthetist (KW) administered either propofol (0.5 mg kg^{-1}) or placebo (equivalent volume of 0.9% saline) to the patient. Once the intervention was completed, the second anaesthetist returned and KW performed a standardised extubation.

The second anaesthetist, who was blinded to the intervention, recorded a set of data during the emergence and extubation process.

The primary endpoint was measured by separately recording the amount and severity of bucking and coughing against the TT using a modified Minogue scale:[32]

(i) Grade 1 indicated no coughing or bucking;
(ii) Grade 2 indicated one to two coughs or bucking;
(iii) Grade 3 indicated sustained coughs or bucking less than 5 seconds;
(iv) Grade 4 indicated severe or repetitive coughing or bucking lasting longer than 5 seconds.

Cardiorespiratory parameters, including systolic, diastolic and mean arterial blood pressures (BP), heart rate (HR) and pulse oximetry, as well as the time to emergence were recorded throughout the extubation process. Once the patient opened their eyes with purposeful movement, with a TOF ratio > 0.9 and adequate spontaneous ventilation, the TT was removed. Oxygen supplementation was continued for 1-5 minutes. Cardiorespiratory complications including laryngospasm, bronchospasm, tachycardia and hypertension were recorded during extubation and treated if necessary. The patient was then transferred to the post anaesthesia care unit (PACU). During PACU stay, a final set of vitals was recorded.

Data Analysis

Completed assessment forms were entered into a Microsoft Excel database once data collection was complete, and exported into Stata 14.2 (StataCorp. 2015. College Station, TX, USA) for analysis. The demographic and clinical profiles of enrolled patients included in the analysis were described using descriptive statistics (frequencies and percentages for categorical data) as well as means and standard deviations for continuous variables. These descriptive analyses compared those in the intervention and control groups and assessed adequacy of randomisation.

The effect of low dose propofol was determined using a generalised linear model appropriate for the frequency of cough, and poor (> 20% change from baseline) haemodynamic response. Univariate and multivariate correlation analyses were used to identify factors (independently and in combination) associated with cough, bucking and poor haemodynamic responses as a composite outcome, adjusting for the intervention arm and other covariates.

Differences between the two groups were assessed using the Student's unpaired t-test for continuous data and the Mann-Whitney U test for non-normally distributed continuous data and the Chi-squared test for categorical data. A value of $p<0.05$ was considered statistically significant.

The report was prepared in line with the CONSORT guidelines for reporting randomised control trials, as stipulated in the EQUATOR Network.

Results

Sixty-two patients aged 18 years and older were screened and fifty patients enrolled during the study period. Twenty-eight (56%) were randomised into the Propofol group and 22 (44%) into the Control group (Figure 1). All patients completed the study, and assessor blinding was maintained throughout. Key demographic and clinical characteristics of participants are summarised in Table 1, and the two groups were comparable, with no significant differences in age, sex, ASA physical status or time from intervention to extubation.

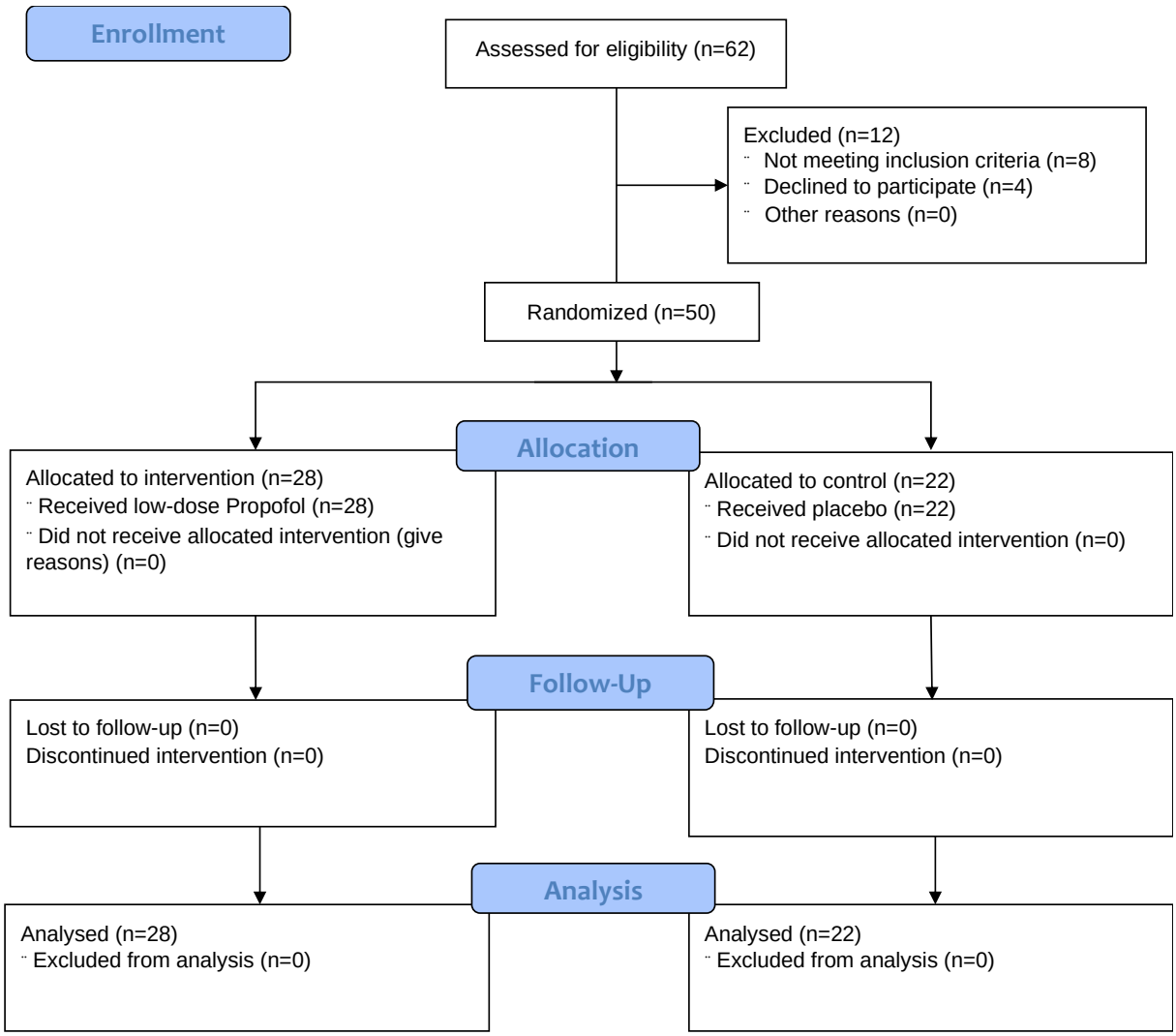


Figure 1: Consolidated Standards of Reporting Trials flow diagram of patient selection.

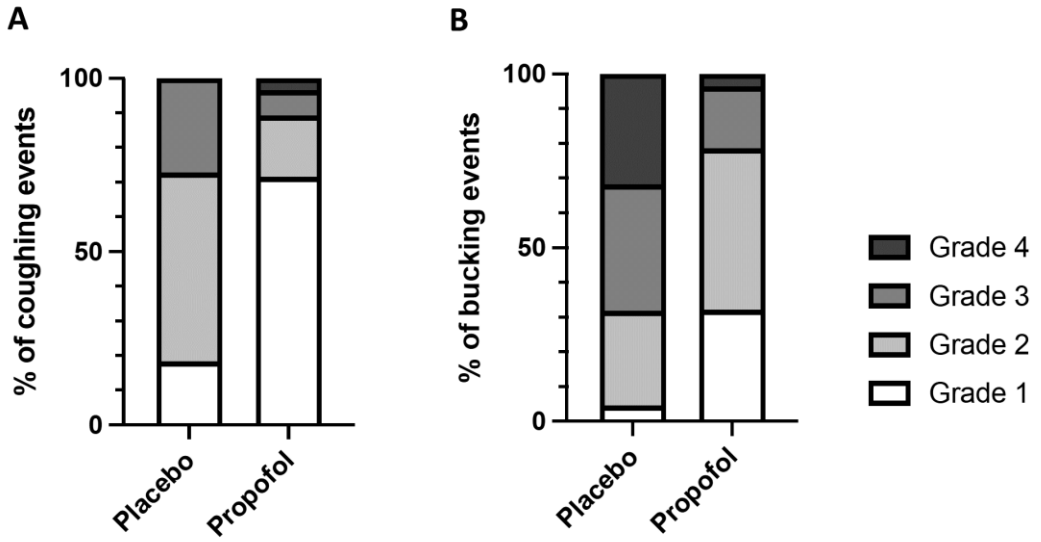
	Propofol (n=28)	Placebo (n=22)	p-value
Age (years) (mean ± SD)	49.0 ± 16.9	48.5 ± 12.7	0.917
Sex, male (n, %)	14 (50.0)	11 (50.0)	1.000
ASA Status			
ASA 1 (n, %)	7 (25.0)	7 (31.8)	0.594
ASA 2 (n, %)	21 (75.0)	15 (68.2)	
One or more comorbidities (n, %)			
No	9 (32.1)	11 (50.0)	0.201
Yes*	19 (67.9)	11 (50.0)	
One or more risk factors at extubation (n, %)			
No	17 (60.7)	15 (68.2)	0.585
Yes**	11 (39.3)	7 (31.8)	
Time from intervention to extubation in minutes (minutes) (mean ± SD)	11 ± 3.5	13 ± 5.2	0.175

Table 1: Patient demographics and clinical characteristics of primary analysis. Presented as either frequency (number and percentage of total) or mean (standard deviation). SD, standard deviation. *HIV, hypertension, diabetes, obesity, anaemia. **Includes morbid obesity, recent URTI, smoking.

Frequency and severity of bucking and coughing at extubation

Overall, 21 participants experienced severe bucking, representing an incidence of 42.0% (95% confidence interval [CI]: 28.8 - 56.4%), while nine participants had severe cough at extubation equating to an incidence of 18% (95% CI: 9.4 - 31.7%). Participants in the propofol group experienced significantly less bucking and had significantly lower bucking severity scores compared to the control group (21.4% versus 68.2%; $p = 0.001$; and 1.93 versus 2.95; $p<0.001$) (Figure 2A). The coughing severity scores were also significantly lower in the propofol versus the control group (1.43 versus 2.09; $p = 0.003$) (Figure 2B) and there were fewer complications at extubation (21.4% versus 50.0%; $p = 0.034$).

There were, however, no differences between the two groups in incidence of severe coughing. The incidence and severity scores of coughing and bucking, and complication rates for both groups at extubation are summarised in Figure 2C.



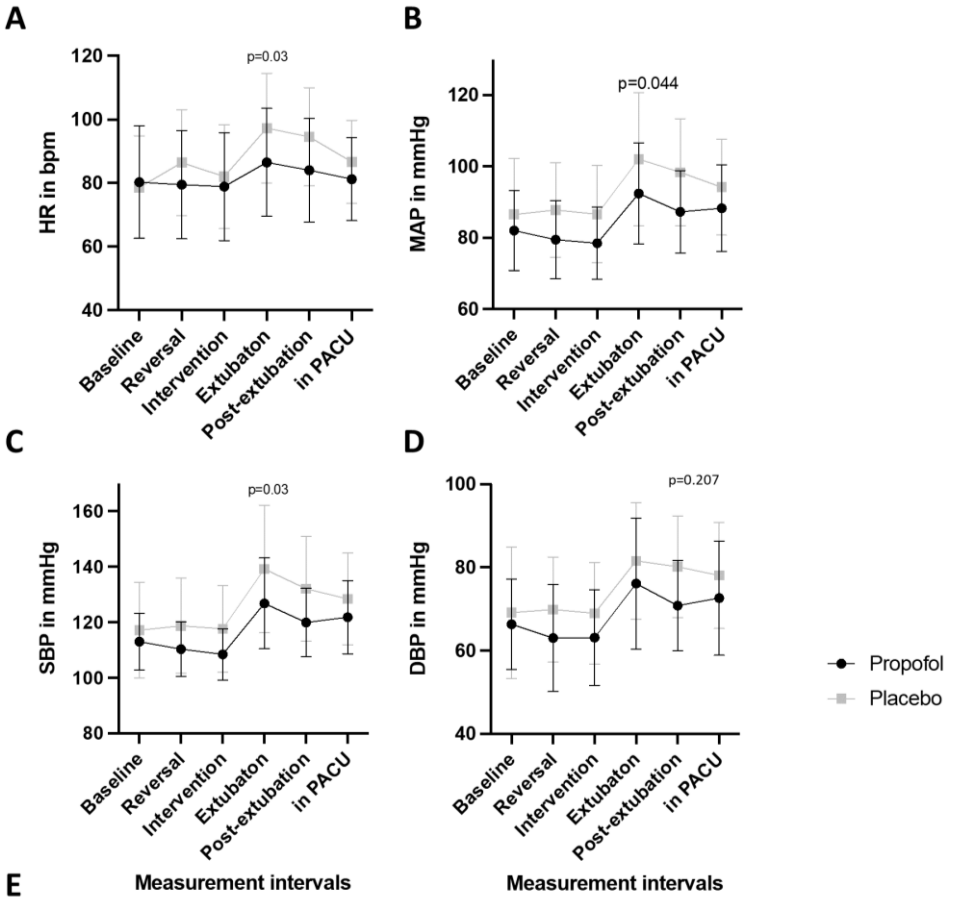
C

	Propofol (n=28)	Placebo (n=22)	p-value
Bucking severity score (mean ± SD)	1.93 ± 0.81	2.95 ± 0.90	<0.001 ***
Severe bucking (n, %)			0.001 **
No	22 (78.6)	7 (31.8)	
Yes	6 (21.4)	15 (68.2)	
Coughing severity score (mean ± SD)	1.43 ± 0.79	2.09 ± 0.68	0.003 **
Severe coughing (n, %)			0.180
No	25 (82.3)	16 (72.7)	
Yes	3 (10.7)	6 (27.3)	
Extubation complications (n,%)			0.034*
No	22 (78.6)	11 (50.0)	
Yes	6 (21.4)	11 (50.0)	

Figure 2: Incidence and severity scores of coughing and bucking at extubation. (A) Comparison of frequency and severity grade of coughing between the placebo and propofol groups at extubation. (B) Comparison of frequency and severity grade of bucking between the placebo and propofol groups during emergence. (C) Representation of composite outcomes of bucking and coughing severity scores (grade 3-4), incidence of severe bucking and coughing, and incidence of extubation complications (tachycardia, hypertension, laryngospasm, bronchospasm, desaturation, apnoea). Grade 1, no coughing or bucking; Grade 2, one to two coughs or bucking; Grade 3, sustained coughs or bucking less than 5 seconds; Grade 4, severe or repetitive coughing or bucking lasting longer than 5 seconds. * $p<0.05$; ** $p<0.01$; ***$p<0.005$. SD, standard deviation.

Haemodynamic changes at extubation

Compared to the control group, patients in the propofol group had significantly lower heart rates at extubation (86.5 bpm versus 97.3 bpm; $p = 0.031$) (Figure 3A). They also exhibited significantly less rise in systolic blood pressure compared to the control group (126.8 mmHg versus 139.2 mmHg; $p = 0.031$) (Figure 3C) and had lower mean arterial pressure readings (92.4 mmHg versus 102.0 mmHg; $p = 0.044$) at extubation (Figure 3B).



E

	Propofol (n=28)	Placebo (n=22)	p-value
Heart rate bpm, (mean ± SD)	86.5 ± 17.0	97.3 ± 17.3	0.031 *
Systolic blood pressure in mmHg (mean ± SD)	126.8 ± 16.4	139.2 ± 23.0	0.031 *
Diastolic blood pressure in mmHg (mean ± SD)	76.1 ± 15.8	81.6 ± 14.1	0.207
Mean arterial pressure in mmHg (mean ± SD)	92.4 ± 14.2	102.0 ± 18.7	0.044 *
Oxygen saturation in % (mean ± SD)	97.4 ± 2.2	97.8 ± 2.6	0.570

F

	Propofol (n=28)	Placebo (n=22)	X^2 test p-value
Poor HR response to extubation (n,%)			
No	21 (75.0)	9 (40.9)	0.015 *
Yes	7 (25.0)	13 (59.1)	
Poor SBP response to extubation (n,%)			
No	20 (71.4)	14 (63.6)	0.058
Yes	8 (28.6)	8 (36.4)	
Poor DBP response to extubation (n,%)			
No	15 (53.6)	12 (54.6)	0.945
Yes	13 (46.4)	10 (45.4)	
Poor MAP response to extubation (n,%)			
No	16 (57.1)	15 (68.2)	0.425
Yes	12 (42.9)	7 (31.8)	

Figure 3: Haemodynamic changes from baseline measurement through emergence, extubation and PACU stay. (A) Comparison of heart rate changes between the placebo and propofol groups (p=0.03 at extubation). (B) Comparison of mean arterial pressure changes between the placebo and propofol (p=0.044 at extubation). (C) Comparison of systolic pressure changes between the placebo and propofol groups (p=0.03). (D) Comparison of diastolic pressure changes between the placebo and propofol groups. (E) Representation of mean differences of haemodynamic measures between the placebo and propofol groups at extubation. (Continued on next page)

(F) Representation of composite haemodynamic changes from baseline to extubation between the placebo and propofol groups. A poor response was defined as a change of > 20% from baseline. * p<0.05. HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PACU, post anaesthesia care unit; SD, standard deviation.

Diastolic blood pressure changes did not significantly differ between the two groups (Figure 3D). More patients in the control group exhibited an increase in HR at extubation compared to the propofol group (59.1% versus 25.0%; p = 0.015) (Figure 3F), although no other significant differences between the two groups were observed. The haemodynamic measures at extubation are summarised in Figure 3E.

Correlation between cardiac and respiratory changes at extubation

Analysis within both groups of bucking and cough severity scores and haemodynamic changes around extubation showed a positive correlation relationship. There was a moderate correlation between higher bucking severity scores and HR increases at emergence (Pearson's r = 0.478; 95% CI: 0.2232, 0.6728; p = 0.004). We also observed a significant increase in heart rates at extubation in groups with higher bucking severity scores, specifically when comparing bucking severity grades of 1 to 3 (p = 0.0326), and 1 to 4 (p = 0.0056) (Figure 4B). There was a weak positive correlation trend between higher cough severity scores and HR increases at emergence (r = 0.2559, 95% CI: -0.03259, 0.5051; p = 0.07) (Figure 4C). However, there was no significant increase in HR at extubation in groups with higher cough severity grades (p= ns) (Figure 4D)

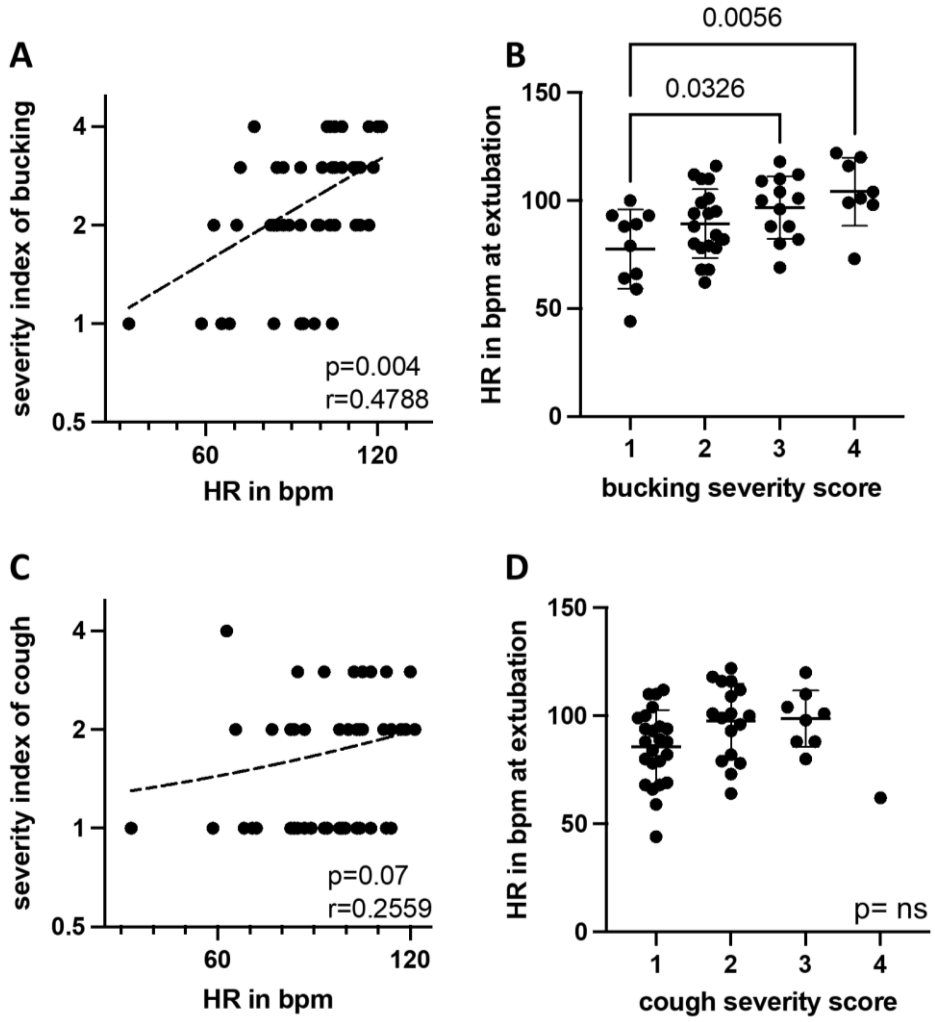


Figure 4: Subgroup analysis of bucking and coughing severity scores with heart rate changes at emergence and extubation using linear regression models. (A) Positive correlation relationship between higher bucking severity scores and heart rate increases at emergence (Pearsons r =0.4788, p=0.004). (B) Heart rate changes at extubation based on bucking severity scores with mean and standard deviations (1 vs 3, p=0.0326; 1 vs 4, p=0.0056). (C) Positive correlation relationship between higher coughing severity scores and heart rate increases at extubation (Pearsons r =0.2559, p=0.07). (D) Heart rate changes at extubation based on cough severity scores with mean and standard deviations. HR, heart rate. Grade 1, no coughing or bucking; Grade 2, one to two coughs or bucking; Grade 3, sustained coughs or bucking less than 5 seconds; Grade 4, severe or repetitive coughing or bucking lasting longer than 5 seconds.

Discussion

The results of this study show that a sub-hypnotic dose of propofol at 0.5 mg kg^{-1} significantly reduced the incidence and severity of bucking, as well as the severity of coughing at extubation when compared to a placebo. Furthermore, administering low dose propofol during emergence from GA significantly attenuated heart rate, systolic and mean blood pressure changes. Fewer complications were encountered at extubation in the propofol group. However, the incidence of coughing at extubation was not attenuated by low dose propofol. There were no significant differences in extubation time between the two groups. Higher bucking severity scores correlated with higher heart rates at extubation in both groups.

Previous studies have reported mixed results with low dose propofol administration at emergence from anaesthesia. Jung and colleagues[21] found that a 0.3 mg kg^{-1} dose of propofol reduced the incidence and severity of coughing in adults undergoing nasal surgery. Similar studies in paediatric populations found that propofol at 0.25 - 0.5 mg kg^{-1} was able to reduce coughing in children at emergence from general anaesthesia.[20,22] At a dose of 0.8 mg kg^{-1}, propofol reduced the incidence and severity of cough and laryngospasm in adults undergoing oropharyngeal procedures.[18] Savafi and colleagues[25] used 0.25 mg kg^{-1} propofol and also found a reduced incidence of cough at emergence. However, Moein Vaziri and colleagues[16] found that propofol at 0.5 mg kg^{-1} did not result in significant haemodynamic and respiratory outcomes at extubation. Similarly, a study by Ozturk and colleagues[17] showed that propofol at 0.5 mg kg^{-1} was not able to reduce coughing in children at extubation. When comparing low dose propofol with other interventions, Nagrale and colleagues[23] found that although propofol 0.5 mg kg^{-1} blunted the coughing and bucking response to extubation, esmolol was superior in effect.[23] Overall, the time to extubation was not prolonged with propofol administration in any of the above studies.

Tracheal intubation remains the focus of research and guidelines when it comes to airway management. However, the Royal College of Anaesthetists' 4th National Audit Project (NAP4) found that more cardiorespiratory complications occurred during emergence and extubation than at any other time during GA.[33] Many complications at emergence may appear transitory and minor, but the NAP4 results noted that all complications were both preventable, and had the potential to result in long-term morbidity and mortality. Hence, it is important to recognise that airway management actually extends into the postoperative period. In our study, propofol was shown to reduce the incidence of complications at this critical point.

Following the findings of NAP4, the Difficult Airway Society published general guidelines on the management of tracheal extubation, and included recommendations for improving physiological conditions at emergence.[34] However, there is still a lack of large scale trials on optimal attenuation strategies peri-extubation, but it is clear from reviews on the topic that any intervention is better than placebo or no intervention.[11] The rapid onset of action and the short duration of propofol makes it an ideal drug for attenuating the cardiovascular responses to tracheal extubation, as shown in several studies.[18,20-22,25]

Blunting the extubation response has been shown to reduce sympathetic nervous system activation during emergence and improve patient recovery.[1] However, although extubation is often associated with bucking, previous studies investigating propofol and other agents did not assess their effects on bucking. Our study found a positive correlation between higher bucking severity scores and increased heart rates at extubation, indicating that the presence of one of these findings would likely predict the presence of the other.

Bucking against the TT was shown to pre-empt bronchospasm, and prevention of bucking was described as a successful method in preventing bronchospasm.[35] Furthermore, perioperative cardiorespiratory aberrations apart from coughing have been found to affect patient outcomes in terms of myocardial injury, morbidity and postoperative mortality.[36–38]

Intraoperative tachycardia and hypertension were independently found to predict morbidity in the postoperative period.[37] Tachycardia was also associated with worse outcomes, leading to increased morbidity, mortality, as well as prolonged hospital length of stay.[36] Hence, blunting these cardiorespiratory changes at emergence may improve patient recovery and postoperative outcomes. In our study, low dose propofol was shown to significantly blunt these responses at extubation.

The mechanism of action of propofol includes peripheral and central activity, with potentiation of γ-aminobutyric acid type A receptor activation and inhibition of further synaptic transmission, as well as inhibition of release of the excitatory neurotransmitters.[39] The cardiovascular effects of propofol include a reduction in the mean arterial pressure and blunting of the baroreceptor reflex, thereby preventing an increase in heart rate in response to a drop in blood pressure.[39,40] Its central effects include an overall inhibition of excitatory signal transduction, which leads to a smooth, rapid emergence after propofol administration.[40] This may explain our findings of low dose propofol attenuates the cardiorespiratory changes at extubation.

The primary limitation of this study was our patient sample size that failed to provide sufficient power to detect a difference in our primary outcome - the incidence of cough - and confirm our hypothesis that propofol would reduce the incidence of cough at extubation compared to placebo. We had estimated that a sample size of 22 patients per group would provide sufficient power (1-β =80%) to detect a 33% difference in the incidence of cough between the two groups, based on previous studies.[21,31] However, the observed difference in cough between the two groups was considerably less (16.6%), meaning the sample size provided only 32% power to detect a difference. This result means that the sample size should have been approximately double (47 patients per group = a total of 94), to sufficiently power the study. Other limitations include the fact that the optimal subhypnotic dose of propofol has not been determined, meaning that the results we collected by administering 0.5 mg kg^{-1} propofol are not reflective of its ideal potential to blunt the extubation response. The optimal timing of when to administer propofol is also not known. The lack of double-blinding and assessor inter-rater variability may have contributed to cognitive and measurement biases.

In line with previous studies, our small randomised control trial has shown that the administration of a low dose of propofol significantly reduced cardiorespiratory responses at extubation. However, replication with larger sample sizes is required to confirm its efficacy in reducing bucking, coughing and haemodynamic aberrations. Due to the distinct differences in our patient population, the applicability of our study's findings to the general population cannot be guaranteed.

Additional larger studies with patient populations undergoing different types of surgery, including those with ASA status III and above are required before any recommendation regarding the use of low dose propofol to promote smooth emergence in these populations can be made. In addition to establishing efficacy, studies to determine the optimal dose of the drug are also required, particularly as previous studies used different doses, resulting in the safest, most effective dose not being known. Another important area for research is to determine the relative efficacy of propofol in comparison to other drugs that have also been shown to effectively facilitate a smooth extubation and minimise cardiovascular and respiratory responses to extubation, including lignocaine, dexmedetomidine, calcium channel blockers and beta blockers.[11]

Conclusion

Administering propofol 0.5mg kg^{-1} attenuates respiratory responses, particularly bucking, at extubation after general anaesthesia in healthy adults undergoing elective abdominal or pelvic surgery, without increasing the time to extubation. Low dose propofol blunts aberrations in heart rate, as well as systolic and mean blood pressures at extubation, with fewer complications at extubation.

Authors' contributions

KW: conceptualised the study design, wrote the study protocol, collected data, analysed the data, and wrote the first draft of the article.

TL: provided research support and assisted with study design, data analysis, data presentation and article drafting.

AO: provided research support and assisted with study design, data analysis, data presentation and article drafting.

Funding

The authors declare that no funding was received for this research project.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This research was done in partial fulfilment of a Master of Medicine degree.

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Section 4: Proposal

Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: Single-blinded randomized placebo-controlled trial

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4.1 Introduction

Endotracheal extubation is a commonly performed procedure and represents a critical point at the end of a general anaesthetic. Cardiovascular, respiratory and endocrine responses are common and predictable throughout this time. This cascade of events is known as the extubation response.[1–4]

At emergence, the plane of anaesthesia lightens and activation of the sympathetic nervous system occurs. This response is mediated by afferent stimulation of the glossopharyngeal and vagus nerves by the endotracheal tube,[28] and leads to catecholamine release which manifests mainly as cardiorespiratory changes.[4,5]

Respiratory phenomena at extubation include coughing, bucking on the tube, laryngospasm, bronchospasm, apnoea and desaturation. Cardiovascular manifestations include tachycardia and other cardiac arrhythmias, hypertensive as well as hypotensive periods and myocardial ischaemia. Intracranial, intraocular and intraabdominal pressures also increase during this time.[10–12]

In most patients the physiological changes that occur at the time of extubation are transient and do not result in significant long-term morbidity. However, it can have deleterious effects in certain situations. Patients with limited respiratory reserve, obstructive lung pathology, ischaemic heart disease and cerebral pathology can suffer serious sequelae.[19,20] Furthermore, smooth emergence from anaesthesia is preferable for many surgical procedures, such as in otorhinolaryngology and neurosurgery.[13–15]

It is generally recognized as good anaesthetic practice to blunt the cardiorespiratory response to intubation. Its mechanism is well understood, and targeted attenuation of this response is performed regularly at induction.[7,25–27] However, there is a higher rate of complications associated with extubation than intubation[12] and extubation has been found to have a three times higher incidence of adverse events.[28] As a result, reviews on the active management of this phase of anaesthesia have recently been done.[31,104]

Strategies to attenuate the physiological changes during extubation include pharmacological and technical methods. Pharmacological approaches include the use of beta-blockers, calcium channel blockers, opioids, α-2 agonists and local anaesthetics.[10,11,47–49] Technical approaches include deep extubation and substitution to a supraglottic airway device prior to emergence.[33,105] Recent research shows that remifentanil and dexmedetomidine infusions throughout the extubation process have the best outcomes, as these drugs provide good endotracheal tube tolerance and lead to a smooth emergence from anaesthesia.[31]

In our resource poor setting, however, regular use of these expensive drugs is not feasible. Therefore, is it prudent to investigate the use of a more cost-effective strategy.

Propofol is a commonly available and widely used drug in anaesthesia. Its pharmacokinetic profile provides a rapid onset and predictable offset of drug effect, which allows for either bolus administration or maintenance of anaesthesia with continuous infusion. Its mechanism of action includes peripheral and central activity, with potentiation of γ-aminobutyric acid type A receptor activation and inhibition of further synaptic transmission, as well as inhibition of release of the excitatory neurotransmitter glutamate.[62]

Sub-anaesthetic doses of propofol are known to induce sedative, anti-nausea and anxiolytic effects in a dose-dependent manner.[63] Its administration is associated with blunting of airway reflexes[63–66] and this property allows for its use in the effective treatment of laryngospasm at extubation.[67–69]. The cardiovascular effects of propofol include a reduction in the mean arterial pressure and blunting of the baroreceptor reflex, thereby preventing an increase in heart rate in response to a drop in blood pressure.[62,63] Its central effects include an overall inhibition of excitatory signal transduction, which leads to a smooth, rapid emergence after propofol administration.[64] Based on this effect, sub-hypnotic doses of propofol have been shown to reduce the incidence and severity of emergence agitation after surgery in children.[70]

The respiratory, cardiovascular and central effects of propofol described above make it an effective drug to use for attenuation of the extubation response.

It is these features that has led to research to study its efficacy in producing favourable extubating conditions.

Fentanyl-induced cough (FIC) is a phenomenon commonly noted during induction of a general anaesthetic after intravenous administration of fentanyl, and occurs due to an increased vagal tone and histamine release, resulting in bronchoconstriction and cough.[71] Several studies have shown that a sub-hypnotic dose of propofol prior to giving fentanyl is able to effectively reduce this cough response.[72,73]

Total intravenous anaesthesia (TIVA) with a propofol infusion is a general anaesthetic technique used for many surgical procedures where microvascular structures are involved, including otorhinolaryngology and neurosurgery. Smooth emergence is a benefit noted after propofol TIVA, with its airway reflex suppression resulting in significantly less coughing and haemodynamic changes at extubation when compared to a balanced anaesthetic technique.[74]

However, further research also showed that the airway protection afforded by the cough reflex was not adversely affected by residual sedation after propofol administration.[75] Hence patients would not be at an increased risk of uncleared secretions or aspiration after extubation.

The efficacy of a sub-hypnotic dose of propofol to reduce the risk of laryngospasm after extubation was compared to using either a benzodiazepine or a placebo.[67] Results showed a significant reduction in laryngospasm risk with propofol administration prior to extubation after oropharyngeal surgery. Furthermore, it was also shown that the incidence and severity of post-operative cough was reduced in the propofol group.

Several studies have compared the efficacy of propofol attenuating the extubation response against ketamine, as a combination with ketamine and against a placebo.[69,76–78] Although the combination of sub-hypnotic doses of propofol and ketamine was shown by Safavi et al[69] to be most effective in suppressing cough at extubation, the use of propofol alone also showed a significant reduction in incidence and severity of cough. Another study by Pak et al[76] showed that the incidence of coughless emergence was highest with propofol use, and that the severity of cough was significantly less when using either propofol or ketamine.

The efficacy of low dose propofol administration at extubation was also compared directly to a placebo. Studies by Ozturk et al[78] and Jung et al[79] researching sub-hypnotic propofol doses after elective surgery showed that the cardiorespiratory response to extubation was significantly attenuated. The time to awareness, extubation and residual sedation was not prolonged after the propofol dose, while the haemodynamic parameters were similar to the placebo group. Another study by Vaziri et al[80] showed that propofol administration two minutes before removal of the endotracheal tube was able to prevent the expected increase in the haemodynamic parameters at the time of extubation.

4.2 Problem Statement

The physiological response to extubation can have deleterious effects at the end of a general anaesthetic. Patients with respiratory compromise, reactive airway disease, cardiac disease or cerebral pathology require attenuation of this cardiorespiratory response. Furthermore, a smooth, coughless emergence is beneficial for many surgical procedures.

Propofol is known to blunt airway reflexes. Thus, administration of low dose propofol prior to extubation may attenuate the cardiorespiratory response and reduce the incidence and severity of coughing at the time of extubation.

Since propofol is readily available in theatre, this intervention could prove to be a cost-effective and easily implemented strategy to provide a smooth emergence from general anaesthesia, and could benefit both patient and practitioner, especially in the era of SARS-CoV-2.

4.3 Aims

The aim of this study is to assess the efficacy of low dose propofol in attenuating the cardiorespiratory response to extubation in a surgical population group at Chris Hani Baragwanath Academic Hospital (CHBAH).

4.4 Objectives

The objectives of this are to:

- Describe the incidence and severity of cough at extubation after general anaesthesia with and without intervention.
- Describe the haemodynamic outcomes at extubation with and without intervention.
- Describe the prevalence of sore throat in the immediate post-operative period after extubation with and without intervention.
- Compare the efficacy of low dose propofol with a placebo in attenuating the cardiorespiratory response to extubation when administered intravenously at the end of surgery.

4.5 Research Assumptions

The following definitions will be used in this study:

Intern: a qualified medical doctor having obtained their Bachelor of Medicine and Surgery in their undergraduate studies.

Medical officer: a qualified medical doctor working under supervision in the anaesthetic department who is not enrolled in a post graduate training program.

Registrar: a qualified medical doctor who is enrolled in a training post to become a specialist anaesthetist.

Consultant: a qualified medical doctor who has completed their training to become a specialist in the field of anaesthesiology. A career medical officer with more than ten years working experience in anaesthesia is considered as a consultant.

Adult: a person who is 18 years or older.

Extubation: the removal of an endotracheal tube from the trachea.

Cardiorespiratory response to extubation: the common and predictable cardiovascular, respiratory and endocrine responses that occur at the time of extubation. These include an increased heart rate, increased blood pressure, bucking and straining, coughing, laryngospasm, bronchospasm and apnoea.

Placebo: an intervention that does not exibit a therapeutic effect, used as a control in research.

4.6 Demarcation of the Study Field

The study will be undertaken in the theatre complex of CHBAH, which is a tertiary institute affiliated to the Department of Anaesthesiology at the University of the Witwatersrand. CHBAH is the third largest hospital in the world, with approximately 3200 beds, where over 65000 surgeries are performed in 25 theatres annually.

4.7 Ethical Considerations

Approval to conduct this study will be obtained from the Human Research Ethics Committee (Medical) and the Postgraduate Committee of the University of the Witwatersrand. Further approval from the Medical Advisory Committee at Chris Hani Baragwanath Hospital will be sought (Appendix 1). Approval from the Head of the Department of Anaesthesia will also be obtained (Appendix 2).

Patient consent will be sought at the time of the preoperative assessment. The details of the study will be explained to them and an information letter written in English will be provided (Appendix 3). Furthermore, written consent by the patient to participate in the study will be sought at that time (Appendix 4).

Confidentiality and anonymity of the patient will be ensured by assigning a study number to each set of data collected. A separate list of the patient's name and other identifying information that correlates to the study number will be generated and kept separately. The raw data will only be accessible to the researcher and their supervisors.

The collected data will be stored for six years digitally on a secure hard disk. The consent forms and data collection sheets will be kept in a locked cupboard for the same duration of time.

The study will be performed according to the principles of the Declaration of Helsinki[106] and the South African Guidelines for Good Clinical Practice.[107]

4.8 Data Collection

4.8.1 Research Design

The design of a study is the framework whereby the study aims to obtain answers and determines how data is collected, analysed and interpreted.[108,109]

This study design is that of a prospective, randomised, placebo-contolled trial with single blinding.

A prospective study follows a group of individuals with similar traits as they undergo different interventions to determine the rates of specific outcomes.[109] This study will collect data from two groups of patients receiving different interventions and determine the significance of the outcome differences.

Randomisation refers to the process whereby patients are allocated to groups by a system of chance.[109] Randomisation in this study will be done by a simple computer generated list, whereby the patients are randomly assigned to one of two groups. The assignment of patients to either group will be randomised prior to the intervention, and balanced according to their demographics.

A placebo is an intervention with no therapeutic effect.[109] The study will be placebo controlled, as the intervention of low dose propofol will be compared to the administration of a substance with no pharmacological effect, normal saline. One group of patients will receive low dose propofol at the end of surgery, while the other group will receive normal saline. The difference in the measured extubation responses in the two groups will then be compared to each other.

Blinding of a study is the process of preventing study participants from knowing information that may prejudice them to bias.[109] The study will be single blinded, as the patient will not know which group they will be assigned to and the anaesthetist assessing the extubation will also not be aware of what intervention was given prior to extubation. However, the primary investigator will administer the intervention, perform a standardized extubation and will be aware of which group the patient has been assigned.

4.8.2 Study Population

The study population will comprise all adult patients presenting for elective abdominal, gynaecological and urological surgery in the CHBAH theatre complex, that have undergone a general anaesthetic with endotracheal intubation.

4.8.3 Study Sample

4.8.3.1 Sample method

The sample population will consist of patients presenting to the CHBAH theatre complex for elective surgery. Consecutive, convenience sampling will be used for this study.

Consecutive sampling is the attempt by the researcher to include all available subjects in the study sample with convenience sampling referring to the use of the of the most readily available subjects [109]. In this study all patients booked on the relevant elective surgical lists will be approached to participate.

4.8.3.2 Sample size

The sample size of the study was determined in consultation with a biostatistician. Based on multiple previous studies where the incidence of cough was the primary endpoint, a 20% difference in the incidence of cough at emergence between the two study groups was deemed significant. Referring to previous studies, the incidence of cough was reported to be between 76 - 96%.[110]

The sample size for our study was calculated assuming an alpha=0.05, power of 90%, p1=82.5%, p2=27.5% and a ratio of 1 to give a minimum sample size of twenty-two per group and a total of forty-four patients for the study.

4.8.3.3 Inclusion and exclusion criteria

Inclusion criteria include:

a) ASA I and II
b) Elective surgery requiring tracheal intubation
c) Patients planned for awake extubation at the end of surgery
d) Age > 18 years

Exclusion criteria include

a) Patients unwilling to take part in the study
b) Contraindication to propofol administration
c) Patients or surgeries where a specific extubation plan is made (e.g. deep extubation)
d) Hypotension at the end of the procedure prior to intervention

4.8.4 Collection of Data

Patients will be randomized into two groups as follows:

Group A: Intravenous low dose propofol prior to extubation

Group B: Intravenous saline prior to extubation

Randomisation will be achieved using a computer-generated assignment of patients prior to extubation. Consent to participate in the study will be obtained at the preoperative assessment. The patient will be blinded to their assigned group.

Two anaesthetists will be present at the end of surgery to perform the extubation.

Anaesthetist 1, the primary investigator, will administer the intervention and perform the extubation procedure, while the assessment will be done by anaesthetist 2, who will be blinded to the intervention given. The extubation will be assessed using a prepared assessment sheet (see Appendix 5).

Once surgery has ended, agents for reversal of muscle relaxation will be administered, the patient's airway will be suctioned and maintenance of volatile anaesthetic agent will be stopped. Thereafter, baseline heart rate (HR), systolic and diastolic blood pressure (SBP and DBP) and mean arterial pressure (MAP) will be recorded. Once a minimum alveolar concentration (MAC) of 0.6 has been achieved, the intervention will be administered intravenously by the first anaesthetist. The intervention will be propofol at a dose of 0.5 mg kg^{-1} or an equivalent volume of 0.9% normal saline. The syringe will be covered so as to hide the contents from anaesthetist 2. The intravenous line will be covered to hide the potential residual white discoloration of propofol.

Anaesthetist 1 will extubate the patient once muscle relaxation is fully reversed, train-of-four (TOF) monitor ratio is >0.9 and the patient is responsive and able to maintain their own airway. The presence and severity of cough will be noted throughout the extubation process using the modified Minogue scale.[52,104] This scale has been used in several similar studies and provides a severity score of cough at extubation. HR, SBP, DBP and MAP will also be recorded before, at, and immediately after extubation. Overall satisfaction of the extubation experience and any complications will also be noted. Presence or absence of a sore throat, nausea and vomiting will be recorded in the recovery area.

The assessment sheet used to assess the extubation response will be used to collect the aforementioned objective and subjective data on one A4 paper.

The patient's study number will be used to assign the collected data to that specific patient, and no other personal identifying information will be recorded on the sheet. Timing of the intervention, as well as HR, SBP, DBP and MAP corresponding to significant times of the extubation process will be recorded on the sheet, as well as the presence and severity of cough at extubation. A subjective assessment of the smoothness of emergence will also be recorded at the end.

4.9 Data Analysis

Data will be recorded in theatre using a prepared extubation assessment form to ensure capturing of relevant parameters during the procedure. The data will subsequently be transferred onto a Microsoft Excel® spreadsheet. Data will be analysed in consultation with a biostatistician. Descriptive statistics will be used. Categorical data will be summarized using frequencies and percentages. Continuous variables that are normally distributed will be described using means and standard deviations and those that are not normally distributed will use medians and interquartile ranges. Comparison of categorical variables between the treatment and placebo groups will be done with the Fisher's exact or Chi-square test. Comparison of continuous variables between groups will be done using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. A p-value of less than 0.05 will be deemed statistically significant.

4.10 Significance of the Study

The insertion of an endotracheal tube at the induction of anaesthesia produces an intubation response, which is treated actively by anaesthetists in the majority of cases. Although this response has no long-term sequelae for most patients, it is common practice to blunt this response pharmacologically.

A similar physiological response occurs when the endotracheal tube is removed. This physiological response, however, is almost always treated passively by anaesthetists, even though a smooth, coughless emergence is more pleasant for both patient and practitioner.

Patients with limited cerebral, cardiovascular, or respiratory reserve can suffer serious sequelae during extubation and would benefit from attenuation of the extubation response.[19,20] Furthermore, smooth emergence from anaesthesia is preferable for many surgical procedures, such as in otorhinolaryngology, ophthalmology, and neurosurgery.[13–15]

Administering a low dose of propofol prior to extubation may attenuate the cardiorespiratory response and reduce the incidence and severity of coughing at the time of extubation.

This intervention could prove to be a cost-effective and easily implemented strategy to provide a smooth emergence from general anaesthesia, and could benefit both patient and practitioner, especially in the era of SARS-Cov-2.

4.11 Validity and Reliability of the Study

Validity and reliability in research are used to assess the quality of a study.

Validity is concerned with the accuracy and truthfulness of scientific findings.[108]

Reliability is concerned with consistency, stability and repeatability of the researcher's accounts, as well as the accurate collection and recording of information.[108]

The validity and reliability of the study will be ensured by:

a) Appropriate study design
b) Appropriate sample size
c) Using a consistent measure to assess the intervention, e.g. the extubation assessment form
d) Statistical analysis done in conjunction with a biostatistician

4.12 Potential limitations

a) Randomisation of patients might lead to uneven demographic profiles
b) Due to theatre staff allocation, double-blinding of study is impractical
c) Limited exposure to relevant theatre lists might prolong data collection
d) Inter-rater variability when assessing extubation response, as anaesthetist 2 will not be the same person for every assessment
e) Confounding factors might be difficult to assess

f)

4.13 Project outline

Activity	Sep 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021	Mar 2021	Apr 2021	May 2021	Jun 2021	Jul 2021	Aug 2021
Proposal preparation	■											
Literature review	■											
Proposal submission		■										
Ethics approval			■	■								
Postgraduate approval					■	■	■					
Data collection								■	■	■		
Data analysis											■	
Draft article											■	
Submission												■

4.14 Financial plan

The Department of Anaesthesia will bear the cost of printing and paper for the postgraduate approval.

Item	Price per page	Number of pages	Copies	Total
Proposal	1	20	10	R200
Ethics	1	10	25	R250
Post graduate form	1	2	6	R12
Complete report	1	100	4	R400
Grand total				R 862

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4.17 Appendices

4.17.1 Appendix 1

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 23 February 2021

TITLE OF PROJECT:

Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: Single-blinded randomised placebo controlled trial.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr Koji Wakabayashi

Department: Anaesthesia

Supervisor/s : Dr T Leonard

Permission Head Department (where research conducted): Yes

NHRD No. 202101 -034

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

.....
Recommended
(On behalf of the MAC)
2021/02/23

.....
Approved/Not Approved
Hospital ManagementDate:
Date: 24/02/2021

4.17.2 Appendix 2

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

UNIVERSITY OF THE WITWATERSRAND
JOHANNESBURG

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
DIRECTORATE - ANAESTHESIA
Enquiries: Dr P Mogane
Tel. number: (011) 933-9334
Email: Palesa.Mogane@wits.ac.za

29 January 2021

To whom it may concern

RE: PERMISSION TO CONDUCT RESEARCH

This serves to confirm that I grant permission to Dr Koji Wakabayashi to conduct research involving the Department of Anaesthesia at the Chris Hani Baragwanath Academic Hospital. The research topic is titled: **Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: Single-blinded randomized placebo controlled trial.**

I'd like to wish him luck in this endeavor and I am happy to support him wherever possible.

Kind regards.

Dr Palesa Mogane
Chief Specialist and Head of Department
Department of Anaesthesiology
Chris Hani Baragwanath Academic Hospital
University of Witwatersrand
Email: Palesa.Mogane@wits.ac.za

4.17.3 Appendix 3

Study Information Sheet

for Patients Participating in Study

Title of Research:	Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: Single-blinded placebo controlled trial
Principal Researcher:	Dr Koji Wakabayashi
Department:	Anaesthesia
Affiliation:	University of the Witwatersrand
Supervisors:	Dr Tristan Leonard
	Dr Alexis Oosthuizen

Introduction

You are kindly invited to take part in a clinical study at Chris Hani Baragwanath Hospital. Before signing the consent form and agreeing to participate in this study, it is important that you read and understand what will happen during the study and why it is being conducted. This sheet will provide you with information about the research we are conducting in our operating theatres. Please read through this information sheet carefully and ask as many questions as you like. The principal researcher will explain any information you do not understand. Whether you choose to take part in this study or not, your decision will not influence the level of care that you will receive in any way. Thank you for taking your time to read through this document.

Purpose of the research

When you come to theatre for your operation, we will make you sleep for the duration of the surgery. In order to do this safely, we will have to place a special tube into your mouth, to help you to breathe while you sleep.

We are researching how to improve the safety and comfort of patients at the end of the surgery, when it is time to wake up from anaesthesia and remove this tube. When patients wake up from the anaesthetic at the end of the operation, the feeling of the tube in the throat can make people cough and increase their blood pressure and heart rate. There is a drug that we can give that may make patients more comfortable as they wake up while we remove the tube from your throat. We are doing this research to find out if this drug called Propofol helps patients wake up more smoothly from a general anaesthetic. This technique is not routine care, and so we are inviting you to take part in this research study to investigate if this new technique can improve patient care.

Type of Research Intervention

This research will involve a single injection in your drip at the end of your operation. The drug we will inject into your drip will either be water or the drug called Propofol. This drug is used every day in theatre and is safe to use for most anaesthesia.

Participant selection

We are inviting all adult patients who are coming to Chris Hani Baragwanath Academic Hospital theatres for a general anaesthetic during their planned operation.

Voluntary Participation

It is your decision entirely whether you want to be part of this research or not. Your participation is voluntary, and your decision will not affect the services you receive in theatre for your operation. If you choose not to take part in this research, you will be offered the routine treatment at the end of your operation. You can change your mind at any time, even if you agree to participate at this time.

Procedures and Protocol

We want to see if giving propofol when waking patients up at the end of an operation is more comfortable and safer than the usual way patients wake up. To do this, we will place patients into two groups. Your group is selected by chance, and you will not know which group you will be placed into.

Patients in one group will be given a placebo medicine. This is a pretend medicine that has no effect on a patient since it is only water. It does not harm any patients.

Patients in the other group will be given a small dose of Propofol. This drug is used every day in theatres to make patients sleep, but has also shown in many research studies to help patients wake up more smoothly when the operation is finished.

At the time when you are waking up, we will give you either the Placebo medicine or Propofol, and then watch you carefully as you wake up. We will measure your blood pressure, your heart rate, and your breathing every minute. When you are more awake, we will also check with you how you feel and if you feel you woke up nicely from your operation.

Risks

If we give you the Placebo medicine (water) into your drip, there is no risk at all to you. If we give you Propofol into your drip, it might take you longer to wake up from your operation, and might make you feel tired once you have woken up. Your blood pressure may be a bit low for a few minutes after giving you Propofol. Giving you Propofol at the end of your surgery might cause adverse events that are currently unforeseeable.

Benefits

If we give you the Placebo medicine (water) into your drip, there is no risk or benefit to you. If we give you Propofol into your drip, it may help you wake up more smoothly from your operation. It can help you not to cough and raise your blood pressure or heart rate when we take out the breathing tube as you wake up. It may also help to prevent you from having a sore throat at the end of the operation. It may also prevent you from feeling nauseous and vomiting when you wake up.

Confidentiality

The personal information that we collect from this study will not be shared and will be kept safe. Only the researchers will have access to it.

Your data will be given a number instead of using your name. Your information will not be shared or given to anyone that is not involved in this research.

Right to Refuse or Withdraw

You do not have to participate in this research if you do not want to. You may also change your mind in taking part in this research at any point. This is entirely your decision and your rights will be respected. There will be no penalty nor change in your level of care if you refuse to participate in the study and you do not have to give any reason for decision. Any data collected from you will be destroyed if you change your mind at any time and wish not to participate.

Contact Details

If you would like further information about this study at any time, or to report any adverse events or concerns while participating in this study, please contact the principal researcher Dr Koji Wakabayashi on the telephone number 011 888 2570, or by email on 303319@students.wits.ac.za. The contact number for the supervisors of this study is 011 933 9564 and their email addresses are tristan.leonard@wits.ac.za and alexis.oosthuizen@gmail.com.

Human Research Ethics Committee

This research has been approved by the Human Research Ethics Committee (medical) of the University of the Witwatersrand in Johannesburg. A principal function of this committee is to protect the rights and dignity of all human subjects who volunteer to participate in any research project, as well as to ensure the integrity of the research.

If you have any concern over the way this study is being conducted, please contact the Chairperson of this Committee, Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on clement.penny@wits.ac.za.

The telephone numbers for the Committee secretariat are 011 717 2700/1234/2656 and their e-mail addresses are mapula.ramail@wits.ac.za, rhulani.mkansi@wits.ac.za and zanele.ndlovu@wits.ac.za.

Thank you once again for reading this study information document.

4.17.4 Appendix 4

PART II: Certificate of Consent

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I voluntarily agree to participate in this research study.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

(If illiterate)

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ **AND** **Thumb print of participant**

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands the research being done.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this consent has been provided to the participant.

Print Name of Researcher/person taking the consent _____

Signature of Researcher /person taking the consent _____

Date _____

Day/month/year

4.17.5 Appendix 5

Assessment of Extubation

Study Number: **Gender:** **Age:**

Group Allocation:

Date:

Procedure:

Co-morbidities:

ASA status:

Assessor rank: Consultant/Registrar/Medical Officer/Intern

Time of intervention:

Time of extubation:

Bucking Severity at extubation

Grade 1: None; no bucking against tube

Grade 2: Mild; bucking once or twice

Grade 3: Moderate; bucking up to 3 times against tube, or sustained straining up to 5 seconds

Grade 4: Severe; bucking more than 3 times against tube, or sustained straining more than 5 seconds

Cough Severity at extubation

Grade 1: No coughing or muscular stiffness

Grade 2: Coughing once or twice, or transient cough response to removal of endotracheal tube that resolved with extubation

Grade 3: less than or equal to 3 coughs lasting 1-2 seconds, or total duration of coughing lasting less than 5 seconds

Grade 4: more than 3 coughs with each lasting more than 2 seconds, total duration of coughing lasting more than 5 seconds

	Baseline	After suction/ Reversal	1min after intervention	At extubation	1min post extubation	PACU
HR						
SBP						
DBP						
MAP						

Complications:

None

Laryngospasm / Bronchospasm / Aspiration / Vomiting / Desaturation

Hypotension / Hypertension

Arrhythmia / Bradycardia / Tachycardia (20% increase from baseline)

Sore Throat in PACU: Yes / No

Risk factors:

Recent upper respiratory illness

Asthma, Chronic Obstructive Pulmonary Disease or other Reactive Airway Disease

Smoking or only recent smoking cessation (less than 6 weeks)

Morbid obesity (BMI >40, or BMI >35 with obesity-related health conditions)

Other:

Assessor experience: Improved/Normal/Worse than usual

Investigator experience: Improved/Normal/Worse than usual

Assessor name: _____

Assessor sign.: _____

Section 5 Annexures

5.1 Ethical Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Postgraduate Affairs)

TO: Dr K Wakabayashi
School of Clinical Medicine
Department of Anaesthesia
Medical School
University

E-mail: drkojiwaka@gmail.com

CC: Supervisor: Drs T Leonard and A Oosthuizen
<Tristan.Leonard@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2021/04/22

REF: R14/49

PROTOCOL NO: **M210232** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: single-blinded randomized placebo-controlled trial*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr K Wakabayashi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210232

NAME: (Principal Investigator) Dr K Wakabayashi

DEPARTMENT: School of Clinical Medicine
Department of Anaesthesia
Medical School
University

PROJECT TITLE: *Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: single-blinded randomized placebo-controlled trial*

DATE CONSIDERED: 2021/02/26

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Drs T Leonard and A Oosthuizen

APPROVED BY: Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2021/04/22

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **February** and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date

5.2 Graduate studies approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

15 February 2021
Person No: 303319
PAG

Dr K Wakabayashi
P O Box 2566
Cresta
2194
South Africa

Dear Dr Koji Wakabayashi

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Low dose propofol as an effective method in attenuating the cardiorespiratory response to extubation: Single-blinded randomized placebo controlled trial.* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.3 Turnitin Report

turnitin report.docx

ORIGINALITY REPORT

18%	14%	15%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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