

**PROPOFOL SEDATION IN ORTHOPAEDIC  
SURGERY UNDER CENTRAL NEURAXIAL  
BLOCK: PATIENT-CONTROLLED SEDATION  
VERSUS TARGET-CONTROLLED INFUSION**

**DR. LIM SHIN HOEI**  
**BM (University of Southampton, UK)**

**UNIVERSITI KEBANGSAAN MALAYSIA**

## **INTRODUCTION**

Regional anaesthesia is one of the mainstays of anaesthesia methods in various disciplines particularly orthopaedic surgeries. Patient communication intra-operatively is one of its main forte, not to mention reduced cost with less complications and faster patient recovery.<sup>1,2</sup> However, the state of consciousness can potentially cause patient anxiety and non-cooperation which may interfere with surgery, therefore reduce surgeon and patient satisfaction. Sedation has an essential role in balancing the pros and cons of regional anaesthesia.

Sedation has its spectrum ranging from anxiolysis to deep sedation.<sup>3</sup> Within this range, conscious sedation or monitored anaesthesia care sedation is usually provided by the anaesthetist to supplement regional anaesthesia. It aims for a comfortable and pain-free patient who is sedated but remains arousable, able to obey commands and maintain their airway independently.<sup>4</sup> However, it is difficult to judge precisely the amount of sedative required for adequate patient sedation, comfort and analgesia as patients' needs differ.<sup>5,6</sup>

Propofol remains the most attractive choice of drug for sedation due to its favourable pharmacokinetic profile, which results in fast induction, easy control of depth of sedation and rapid recovery.<sup>7</sup> Apart from its rapid onset and offset, propofol has anxiolytic, amnesic and anti-emetic effects, making it the nearest to ideal agent for sedation during surgery under regional anaesthesia.<sup>7</sup> Propofol can be infused by a manually controlled volumetric infusion pump, or targeted to a specific plasma or effect site concentration using target-controlled infusion (TCI) devices.<sup>8</sup> Target-controlled infusion allows the anaesthetist to set the desired target plasma or effect site concentration and the TCI pump adjusts infusion rate according to the pharmacokinetic model of the drug.<sup>9</sup> Target-controlled infusion improve drug titration as it better matches the drug concentration profile to the rapidly changing intra-operative drug requirement compared to manually controlled infusion.<sup>10</sup>

Patient-controlled sedation (PCS) is a valid option for surgeries or procedures under regional anaesthesia. It is a well-established technique, initially adapted from post-surgery patient controlled analgesia.<sup>11,12</sup> First reported in 1991, Rudkin et al studied PCS with propofol in patients undergoing dental extractions under local anaesthesia.<sup>13</sup> Park and Watkins studied the efficacy of anaesthetist-controlled sedation (ACS) versus PCS, both using bolus delivered

midazolam and fentanyl, in patients undergoing lower extremity and lower abdominal procedures under epidural anaesthesia.<sup>14</sup> In both studies, PCS resulted in significant satisfactory response from the patients. In 2000, Girdler et al reported that patients utilizing PCS with propofol reached target sedation faster, though not significant, than patients with ACS of continuous propofol infusion in surgeries under local anaesthesia.<sup>15</sup> In 2008, Wahlen et al reported significantly lower plasma and effect-site propofol concentration with high degree of patient satisfaction among patients on PCS compared to ACS of continuous propofol infusion in patients undergoing total knee and hip replacements under spinal anaesthesia.<sup>16</sup>

This study aims to compare the effectiveness of ACS using TCI sedation (TCIS), versus PCS in patients undergoing lower limb orthopaedic surgery under central neuraxial block (CNB). If PCS could be shown to be superior in terms of reduced propofol requirement, in addition to improved safety, sedation quality and patient satisfaction, it could be an alternative sedation option, or replace ACS as the current means of sedation in surgeries under CNB.

## **OBJECTIVES**

### **Primary objective**

To compare total propofol requirement between propofol sedation using patient-controlled sedation versus target-controlled infusion, in patients undergoing lower limb orthopaedic surgery under central neuraxial block.

### **Secondary objective**

To compare complications, sedation quality and patient satisfaction.

## **MATERIALS AND METHODS**

This prospective, randomised clinical trial will be submitted for approval from the Research Committee of the Department of Anaesthesiology & Intensive Care, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and the Medical Research & Ethics Committee, UKMMC. Once ethical approval has been obtained, the subjects will be screened by the principal investigator during the pre-operative visit. Patient inclusion and exclusion criteria include:

### **Inclusion Criteria:**

1. American Society of Anesthesiologists (ASA) I or II.
2. Aged 18-65 years.
3. Elective lower limb orthopaedic surgery under CNB anticipated to last for 1.5 to 2 hours

### **Exclusion Criteria:**

1. Body Mass Index (BMI)  $> 30\text{kg/m}^2$
2. Unable to cooperate (eg. mental disorders, language barrier)
3. Drug abuse
4. Alcoholism (chronic daily alcohol intake greater than 75 g of pure alcohol for  $\geq 2$  years<sup>17</sup>, where 75g of alcohol = 5 cans of beer, 1 bottle of wine or half a pint of distilled spirit)
5. Contraindications to the study drugs
6. Pregnancy
7. Significant pulmonary or cardiovascular diseases, including Obstructive Sleep Apnoea (OSA) and Obesity Hypoventilation Syndrome (OHS)
8. Features of difficult airway

During the pre-operative visit, the patient will be briefed on the study and informed consent obtained. They will also be assessed for pre-operative anxiety by using the Amsterdam Pre-operative Anxiety and Information Scale (APAIS; Appendix 1)<sup>18</sup>, where only the anxiety components of the original questionnaire will be assessed. Patients will be graded on a five-point Likert scale from 1 = not at all, to 5 = extremely anxious. A patient with score  $\geq 11$  is considered anxious.<sup>18</sup>

All patients will be given pre-medication of oral midazolam 3.75 or 7.5 mg accordingly. Subjects will be randomised via computer generated block randomisation into Group PCS and Group TCIS. The study will be conducted by multiple anaesthesia medical officers. In the operating theatre, standard monitoring will include electrocardiogram (ECG), non-invasive blood pressure, pulse oximetry and transthoracic impedance pneumography. Baseline readings will be recorded. Intravenous access will be established with an 18G cannula and normal saline 0.9% infused.

Central neuraxial block will be performed under aseptic technique by the anaesthesia medical officer in-charge and the L2-3 or L3-L4 intervertebral space sought with the patient sitting. The subarachnoid space will be located using a pencil 27G (B Braun, Germany) spinal needle and hyperbaric bupivacaine 0.5% plus fentanyl 15-25 µg will be administered. In the case of combined spinal-epidural anaesthesia (CSE), the epidural space will be located with a Tuohy 18G epidural needle, and the epidural catheter secured in place (Espocan®, B Braun, Germany). After establishing an adequate sensory level, surgery will be allowed to proceed, and PCS or TCIS commenced. Patients with failed subarachnoid block or sensory block inadequate for surgery will be dropped out from the study. All patients will receive oxygen supplement of 5L/min via a face mask. Heart rate (HR), blood pressure (BP), oxygen saturation (SpO<sub>2</sub>) and respiratory rate (RR) will be monitored and documented every 5 minutes. Patients will be kept warm with standard intra-operative warming devices during the surgery.

Propofol will be premixed with lignocaine where 10 mg of lignocaine will be added to every 100 mg propofol 1% to reduce the intensity of pain on injection with propofol.<sup>19,20</sup> Patients in Group PCS will receive intravenous (IV) propofol (Lipuro® 1%, B.Braun, Germany) via a Graseby® Omnifuse patient controlled analgesia (PCA) (Smith's Medical, UK) infusion pump. The machine will be set to deliver a demand bolus dose of 0.25 mg/kg with no lockout interval or basal infusion.<sup>12</sup> The patient will be instructed to press on a hand-held device as often as required to achieve their desired level of comfort or sedation. The sedation level will be assessed using the Observer's Assessment of Alertness/Sedation Scale (OAA/S; Appendix 2) every 5 minutes in the first 30 minutes, followed by every 20 minutes thereafter.

Patients in Group TCIS will receive IV propofol (Lipuro® 1%, B.Braun, Germany) via a Graseby® Omnifusion target-controlled infusion (TCI) pump (Graseby Medical, Watford,

U.K) targeting an initial effect site concentration (Cet) of 0.6 µg /ml, using the Schnider pharmacokinetic model.<sup>12</sup> Upon attainment of 0.6 µg /ml Cet, the patient's sedation level will be assessed. The Cet will be increased or reduced accordingly by 0.2 µg/ml to attain an OAA/S score of 3. After equilibrium between predicted and set concentration is achieved, OAA/S score is re-assessed and adjustment of Cet is made until OAA/S score of 3 achieved. The induction time, which is the time taken to reach OAA/S of 3, will be documented in both groups. Thereafter the OAS/S will be assessed every 20 minutes.

Complications from sedation will be managed as follows:

1. Hypotension (systolic BP 20% below baseline) will be treated with administration of IV fluid and titrated bolus doses of IV ephedrine 6 mg or IV phenylephrine 100 µg as required.
2. Bradycardia (HR < 40bpm) will be treated with IV atropine 0.6mg.
3. Respiratory depression (RR < 8 breaths/min) and oxygen desaturation (SpO<sub>2</sub> < 95%) will be managed by verbal or tactile stimuli, and titrating down Cet by 0.2 µg/ml in the TCI group, delivering 100% oxygen by applying airway maintenance manoeuvres and assisted ventilation as necessary.
4. Over-sedation (OAS/S score ≤ 2) will be managed by verbal or tactile stimuli, and titrating down Cet by 0.2 µg/ml.

The use of airway adjuncts or intubation will be considered depending on the severity of respiratory compromise. These patients will be excluded from analysis of recovery characteristics.

Sedative administration will be terminated (T<sub>0</sub>) at the completion of surgery. At the recovery area, standard monitoring will be employed. The medical officer in the recovery room will assess the OAS/S score every 5 minutes. The recovery time, which is the time taken to reach OAS/S 5 from T<sub>0</sub> will be documented. Total propofol requirement in both groups will be calculated in mg/kg/hour.

Before discharge from the recovery room, patient satisfaction with sedation was measured using a 10-point verbal rating scale, 1 being extremely dissatisfied and 10 being extremely satisfied.

## **STATISTICAL ANALYSIS**

### **Sample size calculation**

The  $\alpha$  value is set at 0.05 and power of study at 80%. Sample size calculation was based on mean propofol requirement for sedation in a study by Singh T *et al.*<sup>21</sup> We expect a difference of 0.5 mg/kg/hour of propofol between Groups PCS and TCIS.

The sample size was calculated using the 'Power and Sample Size Calculations' program.

Sample size calculated using t- test.

Requested output: Sample size

Independent

Alpha = 0.05; power = 0.8;  $\delta = 0.5$ ;  $\sigma = 0.74$ ; M = 1

Case sample size for t-test = 35

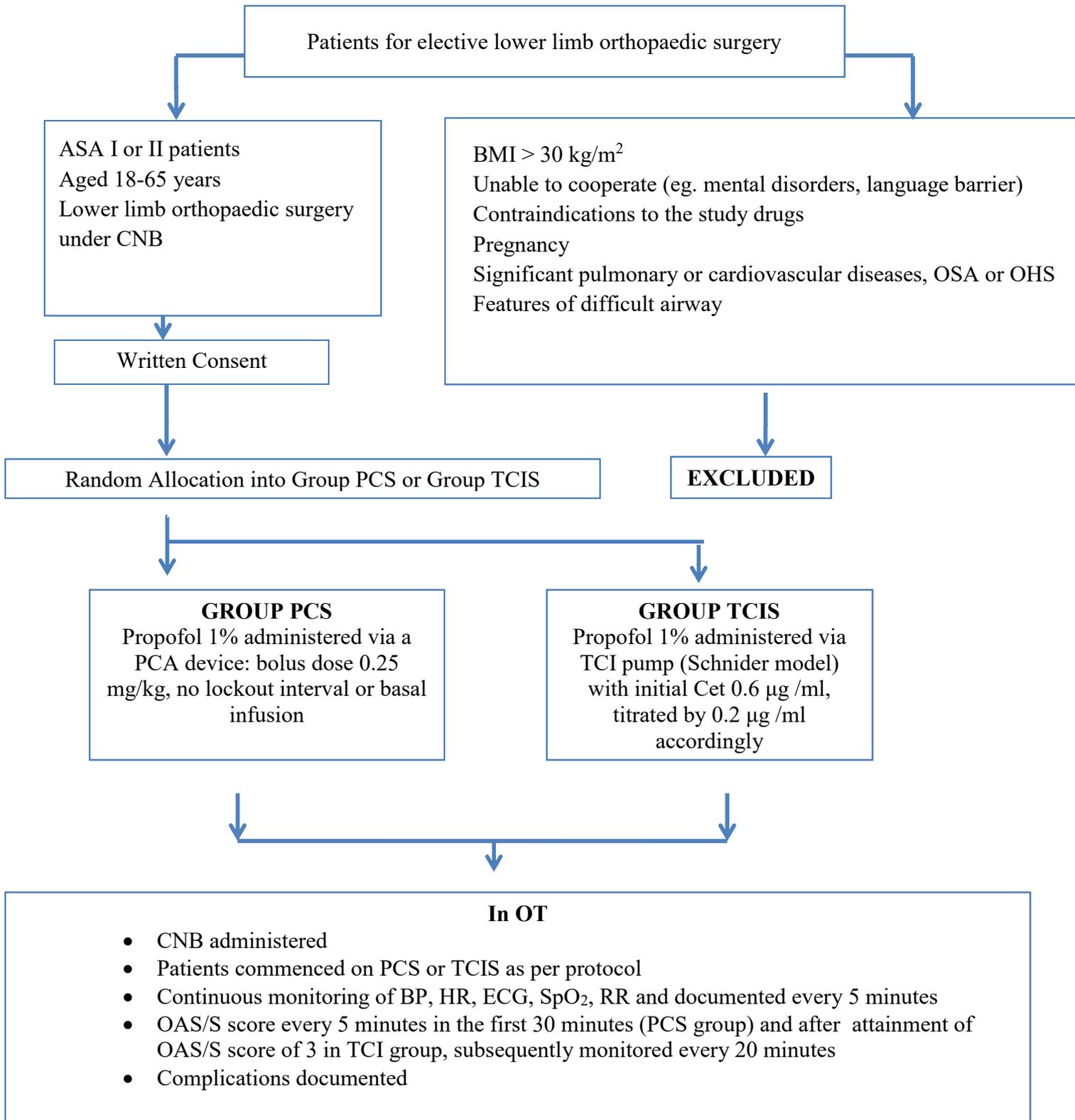
Total sample size: 35 x 2 plus 10% drop-out rate = 78

Sample size = 39 per study group.

### **Statistical tests**

Demographic data and total propofol requirement will be analysed using the student's t-test (or Mann Whitney-U test for non-parametric data). Patients' satisfaction score will be compared using the student's t-test. The satisfaction level of anxious patients in PCS group and TCIS group is compared by using the t-test. A p-value  $< 0.05$  will be considered statistically significant.

### FLOW CHART



**DATA COLLECTION FORM**

Study ID:					Study group	<input type="checkbox"/> PCS <input type="checkbox"/> TCIS
Age:		Gender:		Race:		
Height (m):		Weight (kg):		BMI:		ASA:
Diagnosis:				Surgical procedure:		

Time surgery commenced:

Time sedation commenced:

Time to reach OASS score 3: \_\_\_\_\_ min

Time surgery ended:

Time sedation terminated (To):

Total propofol requirement: \_\_\_\_\_ mg

Time of arrival at the recovery room:

Time to reach OASS score 5: \_\_\_\_\_ min

Time discharged from recovery room:

COMPLICATIONS	YES	NO	RESCUE/REMARKS
Systolic BP < 20% baseline			
HR < 40 bpm			
RR < 8/min			
SpO <sub>2</sub> < 95%			
OAS/S ≤ 2			

**Monitoring chart**

<b>Time (min)</b>	<b>Baseline</b>	<b>5</b>	<b>10</b>	<b>15</b>	<b>20</b>	<b>25</b>	<b>30</b>	<b>35</b>	<b>40</b>	<b>45</b>	<b>50</b>	<b>55</b>	<b>60</b>	<b>65</b>	<b>70</b>	<b>75</b>	<b>80</b>	<b>85</b>	<b>90</b>	<b>95</b>	<b>100</b>	
<b>BP (mmHg)</b>																						
<b>HR (bpm)</b>																						
<b>SpO<sub>2</sub> (%)</b>																						
<b>RR(per min)</b>																						
<b>OAS/S score</b>																						
<b>Cet (ng/ml)</b> <b>*TCIS only</b>																						

<b>Time (min)</b>		<b>105</b>	<b>110</b>	<b>115</b>	<b>120</b>	<b>125</b>	<b>130</b>	<b>135</b>	<b>140</b>	<b>145</b>	<b>150</b>	<b>155</b>	<b>160</b>	<b>165</b>	<b>170</b>	<b>175</b>	<b>180</b>	<b>185</b>	<b>190</b>	<b>195</b>	<b>200</b>	
<b>BP (mmHg)</b>																						
<b>HR(bpm)</b>																						
<b>SpO<sub>2</sub> (%)</b>																						
<b>RR(per min)</b>																						
<b>OAS/S score</b>																						
<b>Cet (ng/ml)</b> <b>*TCIS only</b>																						

(OAS/S charting for PCS: Every 5 mins for 30 mins, thereafter every 20 mins. TCIS: Adjustent of targeted effect site concentration until OASS score 3, thereafter every 20 mins)

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### **Appendix 1: The Amsterdam Preoperative Anxiety and Information Scale (APAIS)**

(The measure of agreement with these statements is graded on a five-point Likert scale from 1 = not at all, to 5 = extremely)

#### English version<sup>18</sup>

1. I am worried about the anesthetic.
2. The anesthetic is on my mind continually.
3. I am worried about the procedure.
4. The procedure is on my mind continually.

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#### Malay version<sup>22</sup>

1. Saya bimbang tentang pembiusan saya.
2. pembiusan sentiasa berada di fikiran saya.
3. Saya bimbang tentang prosedur pembedahan saya.
4. Prosedur pembedahan sentiasa berada di fikiran saya.

**Appendix 2: Observer's Assessment of Alertness/Sedation (OAA/S) Scale**

Score	Observation
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking