**Study protocol**

1. Title : Effect of opioid sparing protocol on the oxygen desaturation index among undiagnosed high risk OSA patients undergoing surgery.
2. Background and literature review :

Obstructive sleep apnea (OSA) is characterized by the intermittent disruption of air flow during sleep as a result of pharyngeal muscles relaxation and collapse of airway. Clinically, OSA is diagnosed by polysomnography (PSG), with an apnea-hypopneic index (AHI) of 5 or greater.

This is of particular concern as the population of obese Malaysian is increasing. 19.5% of Malaysian are obese in a health survey by Wan Nazaimoon (2011), and frequently obesity is associated with OSA. Another cross sectional survey by Kamil et al to determine the prevalence of snoring and breathing pauses during sleep in adult Malaysian population found that 7% (8.8% male, 5.1% female) are clinically suspected to have OSA. In German, Kulhmey et al reported a lower prevalence (4.4%) of patient who probably has OSA from their pre-admission clinic for surgery.

Commonly used anesthetic drugs such as sedatives and opioids are well known for their respiratory depression effect, and OSA patients are more sensitive to these medications compared to their control group. Gislason et al showed that there were increase of endogenous opiods in the cerebrospinal fluids of patients with OSA, thus contribute to the increased sensitivity to opioids among this group. Brown et al demonstrated that reduce morphine requirement in children who had pre op noctural oxygen saturation of <85% compare to > 85%, suggesting that the intermittent noctural hypoxia which is a characteristic of OSA is associated with increase sensitivity to opioids. Anaesthetic agents decrease muscle and neural activity that is important to maintain upper airway, increase propensity of upper airway collapsed, suggested that OSA patient who already has pre operative upper aiway instability are at a heightened risk(Shin et al) . Therefore, patients with OSA are at risk of desaturation and hypoxia postoperatively which can be life threatening.

Study by Chung et al in 2014 showed that there was disturbance of the REM and non-REM sleep pattern, and a significant change of cumulative time below 90% among OSA patients pre and post operatively; ODI of these patients was also increased on post op D3, D5 and D7 as compared to pre op baseline ODI, although it was not statistically significant. In an observational study by Hwang et al, pre operative 5 episode of more when desaturation more than 4% of the baseline (defined as ODI 4%≥ 5), along with clinical features of OSA,is independently associated with increased rate of post operative complications, specifically respiratory and cardiovascular adverse events. It is commonly believed that post operative opioid increased episode of respiratory depression among OSA patients by its effect on opioids receptor in the respiratory centre and also reduce airway diameters through its effect on upper airway dilator muscles. The apnea effect is shown by Water et al, where small doses of fentanyl can induce apnea in spontaneous breathing children under inhalational anaesthesia. Several studies had shown that reduced morphine dosage by adding ketamine will reduce desaturation episodes and respiratory parameter in thoracic surgery/thoracotomy (Nesher, Mitchelet et al).

In view of these, it is reasonable to reduce opioid usage as analgesia especially in OSA patients. Peripheral Nerve block has been shown to reduce post operative cumulative opioids usage (Chiono, Schusz) and less episode of desaturation (Catley, Schusz), but the population was not targeted towards OSA patients. Frances et al found an association between post operative opioids with central apnea but not obstructive apnea in non-OSA group, but that was not shown in OSA group. Blake et al study also showed the association with central apnea but not obstructive apnea.

The present literatures with regards to the usage of peripheral nerve blocks as supplementary analgesia in OSA patients is scarce. We postulate that using peripheral nerve block in high-risk OSA patients undergoing general anaesthesia, will reduce post-operative oxygen desaturation.

It is unrealistic to have every patient who has suspicious features of OSA to undergo PSG before operation, as the waiting list for PSG can be weeks to months. A lot of validated questionnaire are available in order to detect or triage the patient with risk of OSA, such as SACS, Berlin questionnaire and STOPBANG. STOPBANG questionnaire include 8 yes or no questions on Loud Snoring, Tiredness, observed apnea, high blood pressure, BMI, age, neck circumferences and male gender. Despite its simplicity, it is validated among obese and morbidly obese surgical patient, to identify moderate to severe OSA (Chung et al). It is also useful to triage patients for diagnostic evaluation or to exclude from harm (Farney et al). A Cut off point of ≥3 has high sensitivity of 90% and high positive predictive value of 85% to identify OSA in the obese surgical patients. (Chung 2013). In this study, we are interest in the high risk group of OSA patients, hence a cutoff point of ≥5 was chosen. STOPBANG score of ≥5 is classified as high risk of having moderate to severe OSA. (Chung 2016).

Oxygen Desaturation index, as defined as average numbers per hour of desaturation of ≥4% below the baseline lasting 10s or longer (*American Academy of Sleep Medicine)* . ODI per se does not lead to a conclusion of diagnosis, however study has shown good correlation of ODI to Apnea-hypopnea index (r> 0.98, William Tsai), where AHI currently is used to classify severity of OSA. A study by Chung et al also reported a good correlation of ODI with AHI if compare with cumulative time below 90%, and served as a better predictor. According to that study, ODI > 10% (from high resolution nocturnal oximetry) gives a sensitivity of 93% and specificity of 73% to detect undiagnosed sleep-disordered breathing in surgical patients.

1. Hypothesis: An opioid-sparing protocol, using regional nerve block as post-op analgesia, can reduce oxygen desaturation among patients at high risk of OSA undergoing general anaesthesia.

Objectives: To compare an opioid-sparing protocol using regional nerve block to the conventional opioid-based analgesia, with regard to their effects on post-operative desaturation, sedation and analgesic efficacy among patients at high risk of OSA undergoing general anaesthesia.

Primary outcome: post-operative ODI Day 1 - Day 3

Secondary outcome: cumulative post-operative morphine usage, pain score, sedation score, length of hospital stay.

1. Methodology:

Study Design : Randomized Controlled Trial

Study Population: all patients at high risk of moderate-severe OSA (STOPBANG ≥5) who are undergoing general anaesthesia for upper or lower limb surgery, in which complete analgesia can be achieved using regional nerve block.

Inclusion criteria

* Aged 18 years old and above
* STOPBANG score of 5 or more.
* ASA 1 or 2
* Patient is scheduled for a surgical procedure that is expected to:
  + Undergo general anesthesia
  + post-operative analgesia can be achieved completely by regional nerve blocks.
  + Remain hospitalized for at least 48 hours postoperatively
* Orthopaedic surgery involving the upper limb (below shoulder) or lower limb (knee and below)

Exclusion criteria

* Pregnant
* ASA 3 and above
* Patients who require post-operative ventilation
* Diagnosed to have OSA and on night CPAP therapy
* Contraindicated for peripheral nerve block (such as coagulopathy, allergic to local anaesthetics, and patient refusal)
* Underlying irreversible respiratory disease
* Postoperative analgesia of the procedure that cannot be achieved with up to two peripheral nerve blocks.
* Require surgery in other part of the body

Sample Size**:** the mean and standard deviation from the first 20 recruited patients as samples for pilot study will be use to derive the sample size for this project. This is done by power study, which is performed by using web based sample size calculator <http://www.stat.ubc.ca/~rollin/stats/ssize/n2.html> .

During pre-anaesthetic assessment in ward and clinic, all patients will be screened by the medical officers using STOP BANG questionnaire. Patients who score ≥5 will be recruited. Randomization is done using a pre-randomised system, in which a sealed envelope containing information on group allocation and intra-operative instruction will be attached to each numbered-CRF folder. Once a patient agrees to participate, the investigator will take a CRF folder following sequence and open the attached envelope. All recruited patient will have the baseline ODI measured the night before surgery. All opioids given within the past 24 hours (dose and time) will be recorded.

In the conventional arm, induction is carried out using the technique chosen by the attending anaesthetist. Boluses of short acting opioids (alfentanil or fentanyl) may be given during induction or intraoperatively. IV morphine 0.1mg per kg of lean body weight (ideal body weight + 40%) will be given. Additional doses of morphine maybe given intraoperatively if deems indicated by the attending anaesthetist.

While in the interventional arm, the peripheral nerve block will be given before the induction of general anaesthesia. The local anaesthetic for peripheral nerve block can either be ropivacaine or levo-bupivacaine, with the total dose not exceeding the recommended maximum dose (Ropivacaine 3mg/kg, levo-bupivacaine 2mg/kg). The induction technique will be chosen by the attending anaesthetist. Long-acting opioids should be avoided, if possible.

* Both arms will have a balanced anaesthesia with or without muscle relaxant. Anaesthesia is maintained between minimum alveolar concentration of1.0-1.2 if using inhalational agent, or BIS of 40-60 if using total intravenous anaesthesia. Multimodal analgesia (intravenous paracetamol and cyclooxygenase II inhibitor) will also be given, if not contraindicated. Intraoperative opioids maybe given according to the clinical judgment of the attending anaesthetist. Patient who developed adverse event intraoperatively that require post operative ventilation will be excluded from the analysis. At the end of surgery, the usual extubation criteria applies. All patients will receive a patient-controlled analgesia morphine after the surgery.

Post-extubation, 5L/min oxygen via face mask will be given for half an hour. In the recovery area, patient will be monitored for significant respiratory events: apnea, increased FiO2 requirement, pain-sedation mismatch (sedation score of ≥2, or episodes of desaturation of ≤ 90%). Patient who has recurrent respiratory event will be admitted to a monitored bed (acute bed/HDU/ICU) as per institutional protocol. In the ward, nasal prong oxygen 3L/min will be given overnight on post-op D1, then off on D2 morning. Post op D1 is counted immediately after end of operation.

The ODI will be measured consecutively for 3 nights post-operatively. The APS medical officer will review patients in ward, assessing the pain score, total morphine usage, sedation score and oxygen saturations.

1. Ethical clearance: This study protocol has been reviewed and approved by the board of University Malaya ethical committee.
2. Statistical Analysis

P value of <0.05 was chosen as the level of significance. Type II error of 10%.Report as using power (90%).

Statistical analysis will be analysis with software SPSS IBM version 23.

Descriptive statistics will performed to find the prevalence of ODI for the different group, it will also use to present all of the scenario of our study variables.

Post op morphine usage and ODI will be analyzed using unpaired student t-test/Mann Whitney-U test.

1. Limitation of study

This study was intented to target the undiagnosed group of severe OSA patients, however the patients selection was based on STOPBANG score rather than the diagnostic tool PSG. This is because the waiting period for the PSG test may be up to 1 year and most patients require the surgery as soon as possible. Therefore there is still a chance that these patients are not fully representative of the real high risk OSA patients.