EFFICACY AND SAFETY OF NON-OPIOID BASED VERSUS OPIOID-BASED MULTIMODAL ANALGESIA IN PATIENTS UNDERGOING ELECTIVE LAPAROSCOPIC CHOLECYSTECTOMY: A RANDOMIZED CONTROLLED TRIAL

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LIST OF ABBREVIATIONS AND SYMBOLS

ABW	Actual body weight
AE	Adverse event
ASA	American Society Of Anaesthesiology
AUC	Area Under the Curve
BMI	Body mass index
BP	Blood pressure
CRC	Clinical Research Centre
CRF	Case report Form
CV	Curriculum vitae
Fio2	Fraction of oxygen
GA	General anaesthesia
GCP	Good Clinical Practice
H	Hour
HQE	Hospital Queen Elizabeth
HUSM	Hospital University Sains Malaysia
IBW	Ideal body weight
IC	Identification Card
ID	Identification
IEC	Independent Ethics Committee
IRB	Independent Review Board
LA	Local anaesthesia
LBW	Lean body weight
MAC	Minimum Alveolar Concentration
Mcg	Microgram
Mg	Milligram
Ml	Millilitre
mmHg	Millimetre mercury
MOH	Ministry Of Health
NMRR	National Medical Research Register
NOBMA	Non-Opioid Based Multimodal Analgesia
OBMA	Opioid Based Multimodal Analgesia
PCA	Patient control analgesia
PONV	Postoperative nausea & vomiting
Post-op	Post-operative
PR	Pulse Rate
SAE	Serious adverse effect
Spo2	Blood oxygen saturation
TV	Tidal volume
VAS	Visual analogue score

GLOSSARY OF TERMS

(Comprehensive list of commonly used terms is found in Malaysian Guidelines for GCP)

Eligible	Qualified for enrolment into the study based on strict adherence to inclusion and exclusion criteria.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and therefore included in analysis.
Investigator	Treating physician
Monitor	An individual assigned by CRC who is responsible for assuring proper conduct of a clinical study.
Protocol amendment	Any change in a study protocol that affects the safety of subjects, the scope, design, assessments, or scientific validity of the clinical investigation.
Subject(s)	Individuals enrolled in the clinical study.
Case report form (CRF)	A printed, optical, or electronic document used to record protocol required information for each subject in the study
Confidentiality	Prevention of unauthorized disclosure of a sponsor's proprietary information or of a subject's identity and personal medication information
Control Group	The group of patients who receive the standard treatment (no treatment or placebo) and who is compared to the group of patients receiving the investigational treatment
Exclusion criteria	Rules of eligibility that exclude an individual from participation in a study
Inclusion Criteria	Rules of eligibility that an individual must meet in order to participate in a clinical study. See eligibility criteria.
Informed Consent	A process by which a subject voluntarily confirms his or her willingness to participate in a clinical trial after being informed of all aspects relevant to the subject's decision to participate. The Declaration of Helsinki states that in any human research, each potential subject must be adequately informed of the aims, methods, anticipated benefits, potential hazards, and discomforts that study participation might entail. Informed consent is typically documented via a written, signed, and dated consent form.
Prospective Studies	Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data.
Voluntary	Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate
Experimental Study	True experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing causal inference about the effects of the interventions under investigation

ABSTRAK

Latar Belakang:

Pembedahan laparoskopi pembuangan pundi hempedu mengakibatkan kesakitan dan pengurangan keperluan ubat penahan sakit lepas pembedahan postoperatif dalam keperluan pembedahan terbuka pembuangan pundi hempedu. Walau bagaimanapun, sesetengah pesakit masih mengalami kesakitan yang sederhana dan parah selama 24 jam selepas pembedahan. Ubat penahan sakit tanpa opioid terbukti berkesan dalam mengurangkan kesakitan selepas pembedahan berbanding dengan analgesia berasaskan opioid, kerana opioid menghasilkan lebih banyak kesan sampingan.

Tujuan

Kajian ini dijalankan untuk menentukan keberkesanan dan keselamatan ubat penahan sakit tanpa opioid berbanding dengan ubat penahan sakit berasaskan opioid untuk kawalan tahap kesakitan selepas pembedahan elektif laparoskopi pembuangan pundi hempedu.

Kaedah

Peserta dibahagikan kepada dua kumpulan dengan menggunakan rawak komputer. Kedua-dua kumpulan diinduksi dengan menggunakan ubat bius penuh yang sama menggunakan intravena fentanyl 2mcg / kg ABW, propofol

intravena 2mg / kg LBW diikuti oleh sevoflurane pada 1MAC dalam oksigen / udara dan Rocuronium intravena 0.6mg / kg ABW untuk memudahkan intubasi. Kumpulan A menerima infusi dexmedetomidine intravena 0.5mcg/kg/jam dan infusi ketamine intravena 0.25 mg/kg/min manakala kumpulan B menerima 0.1mg/kg morfin. Sebarang perubahan hemodinamik direkodkan ketika penyisipan trocar, kemasukan gas dan akhir pembedahan. Kesakitan analog visual (VAS) ditentukan setelah tamat pembedahan pada jam 1 jam, 4 jam, 8 jam dan 12 jam. Jumlah ubat tambahan penahan kesakitan (fentanyl intravena) yang diperlukan berbanding kedua-dua kumpulan ini dan kejadian muntah-muntah selepas pembedahan telah didokumenkan.

Keputusan:

Secara keseluruhan, kami menganalisis 30 pesakit di setiap kumpulan yang menerima NOBMA dan OBMA. Berbanding dengan margin *noninferiority* yang telah ditetapkan, perbezaan min Skor kesakitan AUC antara pesakit yang menerima ubat tahan sakit tanpa opioid dan ubat tahan sakit opioid dalam masa 12 jam adalah -2.15 (1 sisi 97.5% CI: ∞, 1.09). CI atas jauh lebih rendah daripada margin *non inferiority* yang telah ditentukan sebanyak 4 (nilai p untuk noninferiority = 0.0002), menunjukkan rawatan non-opioid didapati non-inferior (tidak-rendah) daripada rawatan opioid dalam mengurangkan kesakitan dalam masa 12 jam pada pembedahan laparoskopi pembuangan pundi hempedu. Tahap kegagalan ubat tahan sakit yang lebih tinggi (n = 5,16.7%) dicatat pada pesakit opioid, namun, terdapat lebih banyak pesakit yang mengalami tahap kesakitan <4 (n = 28, 93.3%) di kalangan pesakit yang menerima ubat tahan

sakit tanpa opioid. Secara rawak kepada pesakit menerima ubat tahan sakit tanpa opioid mengalami peratusan kejadian loya / muntah yang rendah berbanding peaskit menerima ubat tahan sakit opioid dalam masa 12 jam (NOBMA = 6.7% vs OBMA = 36.7%, χ = 31.8, p <0.001), menunjukkan kelebihan NOBMA untuk kedua-dua hasil. Parameter hemodinamik adalah sama dalam kedua-dua kumpulan semasa penyisihan trocar, *insufflation* gas dan akhir pembedahan.

Kesimpulannya

Berbanding dengan OBMA, kajian menunjukkan bahawa NOBMA non -inferior (tidak rendah) dalam memberikan tahap yang rendah dan muntah mual selepas pembedahan laparoskopi pembuangan pundi hempedu.

ABSTRACT

Background

Laparoscopic cholecystectomy resulted in less postoperative pain and reduction in the need for analgesia compared to open cholecystectomy. However, some patients still experience moderate to severe pain for 24 hours postoperative. Non-opioid based multimodal analgesia is proven to be comparatively effective than opioid-based analgesia in reducing postoperative pain while reducing the side effects from opioid usage.

Objective

To determine the efficacy and safety of non-opioid based multimodal analgesia compared to standard opioid-based multimodal analgesia for postoperative pain control in elective laparoscopic cholecystectomy.

Method

Participants were divided equally into two groups by using computer-generated randomization. Both groups were induced with the same anaesthetic agent for induction of anaesthesia by using intravenous fentanyl 2mcg/kg ABW, intravenous propofol 2mg/kg LBW followed by sevoflurane at 1MAC in oxygen/air and intravenous Rocuronium 0.6mg/kg ABW to facilitate intubation. For intraoperative analgesic, Group A received intravenous

dexmedetomidine infusion 0.5-1 mcg/kg/hour and intravenous ketamine infusion 0.125-0.25 mg/kg/min whereas group B received 0.05-0.1mg/kg morphine. Intraoperative hemodynamic fluctuation was recorded during trocar insertion, gas insufflation, and end of surgery. The visual analogue pain (VAS) were determined at 1 hour, 4 hours, 8 hours, and 12 hours post-operation. Total rescue analgesia (intravenous fentanyl) needed were compared between these two groups, and the incidence of postoperative nausea vomiting were documented.

Result

Overall, we analysed 30 patients in each arm receiving NOBMA and OBMA. Compared with preset noninferiority margins, the mean differences in AUC pain Score between the non-opioid analgesic group and opioid analgesic group within 12 hours was -2.15 (1-sided 97.5% CI: ∞, 1.09). The upper CI was significantly lower than the predetermined non-inferiority margin of 4 (p-value for noninferiority=0.0002), indicating non-opioid treatment was found to be non-inferior to opioid treatment in pain relief within 12 hours in post laparoscopic Cholecystectomy.

There was higher prevalence of analgesic failure (n=5,16.7%) was recorded in opioid groups patients. Nevertheless, more patients experienced pain score <4 (n=28, 93.3%) in those who received non-opioid treatment. Patients randomised to non-opioid group experienced significantly low percentage of nausea/vomiting incidence compare to opioid group within 12 hours (non-

opioid group=6.7% vs. opioid group=36.7%, χ= 31.8, $p<0.001$), indicating superiority of NOBMA for both outcomes.

Hemodynamic parameter shows non-inferiority in both groups during trocar insertion, gas insufflation, and end of surgery.

Conclusion

Compared with OBMA, the study suggests that NOBMA provides non-inferior postoperative analgesia and less for postoperative nausea vomiting in patient undergoing laparoscopic cholecystectomy.

CHAPTER 1: INTRODUCTION

1.1 Literature Review

Laparoscopic cholecystectomy resulted in less post-operative pain and reduction in the need for analgesic, as compared to open cholecystectomy (1). Although pain after laparoscopic cholecystectomy is less intense than that after open cholecystectomy, some patients still experience considerable discomfort during the first 24 hours postoperative (1).

Thus, laparoscopic cholecystectomy belongs to those surgical procedures with the highest incidence of moderate to severe pain for 24 hours postoperatively. This acute perioperative pain can produce structural and functional changes in the pain pathway, resulting in hyperalgesia and central sensitization (2). Increasing the problem of acute perioperative neuropathic pain is being recognized (2).

Intraoperative use of opioids has become a standard practice in most hospital settings. It is also the mainstay of perioperative analgesia but can have several well-known dose-related side-effects (2). Recently, there has been concern that large doses of opioids may cause acute tolerance and hyperalgesia, resulting in worsening pain control (2). This has been labeled as an opioid paradox: the more opioids that is given intra-operatively, the more is needed postoperatively, and the pain score will be high (3). Some authors suggest that if no opioids were given intra-operatively, less opioids would be needed postoperatively as tolerance has not destroyed the mu-receptor system yet (4).

Hence, various drugs and techniques have been used as part of multimodal analgesia with the aim of improving pain management and decreasing opioid consumption and opioid-related side-effects (3). Non-opioid based multimodal analgesia is an alternative option. Multimodal analgesia includes local anaesthesia and systemic drugs, which aim to reduce the dose of any single agent, thereby reducing potential dose adverse effects. Thus, opioids sparing usage during anaesthesia is possible without hemodynamic instability. This may provide benefits to the patients undergoing laparoscopic cholecystectomy and facilitate post-operative analgesia. Non-opioid based multimodal analgesia aim to enhance these goal of reducing opioid related adverse effects.

1.2 Non-Opioid Based Multimodal Analgesia

Evidence-based multimodal opioid-sparing analgesia has become an alternative in managing post-surgical pain in the last two decades (5). Evidence indicates that multimodal pain management is the best way to reduce opioid consumption. The perioperative use of non-opioid based multimodal analgesia allows preemptive blocking of receptors in the complex pain pathway both centrally and peripherally (6). Preoperative use of acetaminophen, COX inhibitor, and GABA analogue has been associated with decreased postoperative usage of opioids. Intraoperative use of agent that lead to opioid-sparing effects via sodium channel blocker, G-protein couple receptor blocker, NMDA receptor blocker, central alpha-2 agonist, and anti-inflammatory effects can make opioid-free anaesthesia possible (7, 8).

1.2.1 Dexmedetomidine

A recent study reported that an agonist with higher alpha-2 adrenoreceptor selectivity would show a more potent analgesic effect and be more suitable for pain treatment (9). Dexmedetomidine is a highly selective alpha-2 adrenoreceptor agonist developed in the 1990s, and it was first used as a short-term sedative in intensive care units (10). It provides sedation, analgesia, and sympatholysis. (11)

Clinical studies have confirmed its potential as an adjuvant for pain treatment, mostly in acute perioperative settings. Perioperative use of intravenous Dexmedetomidine administration is associated with reduction in post-operative pain intensity, analgesic consumption, and postoperative nausea vomiting without increasing the risk of opioid-related side effects such as respiratory depression (12). These characteristics make dexmedetomidine a useful anaesthetic adjunct during operation. A study done by dong-jian Ge et al found that the intraoperative dexmedetomidine helped relieve both resting and moving postoperative acute pain. Moreover, patient who receives intraoperative Dexmedetomidine group consumed less morphine postoperatively (13). The analgesic and opioid-sparing effects of dexmedetomidine have been well described in previous studies concerning both adults and children (13).

The administration of Dexmedetomidine bolus initially results in activation of alpha-2 adrenoreceptor on vascular smooth muscle. This leads to initial vasoconstriction and transient increase in blood pressure, followed by reflex bradycardia. It also increases the risk of arterial hypotension without causing respiratory depression. For clinical decision-making, the beneficial effect should outweigh the risk. Various doses and regimes are described in the literature. One of the regimes recommends that infusion can be started at 0.4mcg/kg/hr followed by 0.2mcg/kg/hr by end of operation (14). A study was done by Park et al., dexmedetomidine significantly reduces pain score after laparoscopic cholecystectomy with multimodal analgesia for 1 hour postoperative but does not from 1 hour to 24 hours after the operation. Although there is no significant difference in both dexmedetomidine group and placebo group in VAS from 1 hour after the operation, the amount of the analgesic requirements shows significant difference (15). Dexmedetomidine might be helpful for the postoperative pain after laparoscopic cholecystectomy with multimodal analgesia (15). This result is consistent with other studies (16).

1.2.2 Ketamine

Ketamine has been widely used as an adjuvant analgesic in a variety of perioperative pain settings (17, 18). Ketamine is an N-methyl-D-aspartate receptor antagonist that provides sedation and analgesia but in different receptor binding. It also acts on other nociceptive

related sites including the muscarinic, monoaminergic, and opioid receptor as well as voltage-gated sodium and L-type calcium channels. It prevents central sensitisation and assists in neural modulation by blocking the spinal cord neurons from hyper-excitable peripheral nociceptive stimulation (19-21). Multiple studies have described the use of small-dose ketamine no more than 1.2mg/kg/hr when used as continuous infusion and no more than 1mg/kg when given as a bolus appear to have an opioid-sparing effect with greater patient and physician acceptance (22). It leads to a reduction of up to 20-25% in pain intensity and 30-50% in analgesic consumption within 48 hours after surgery (Level 1) (17, 18). Parikh et al. administered a bolus dose of 0.15mg/kg, followed by an infusion of 0.12mg/kg/hr and reported a 68% reduction of morphine consumption 24 hours postoperative (23). Pain scores significantly reduced for 12 hours postoperative with ketamine (VAS pain scores for ketamine=20 vs placebo=74 on a 100-mm VAS) (23). The lower but effective ketamine dose serves as an opioid-sparing drug that plays an important role in the treatment of acute postoperative pain (18). Ketamine also has indirect sympathomimetic effect, which may be beneficial intra-operatively. Therefore, combination of both drugs will be able to reduce pain scores through synergistic mechanism with better hemodynamic control intra-operatively. The major side effects are uncommon, psychomimetic effects such as hallucination, nightmares, sedation, nausea, vomiting, tachycardia and hypertension. The psychomimetic effect were more common in patients undergoing

awake procedures than after procedures under general anaesthesia (Level 1) (17). Twenty-six clinical trials assess the safety of continuous infusion of low dose ketamine (IV infusion rate less than 1.2mg/kg/hr) ranged from only intraoperative to 48 hours postoperative, revealed that continuous ketamine infusion is not associated with serious side effect. This conclusion is based on a total of 1,689 patients, 940 of whom who received ketamine (23). Review of the literatures has reported ketamine's role as an adjuvant therapy to be able to provide better anti-nociception by decreasing opioid consumption, prolonging the duration of analgesia while having fewer side-effects (24) (25) (26) (27).

1.3 Opioid-Based Multimodal Analgesia

Opioids are the mainstay of perioperative pain management which has been used as current standard practice in most hospital in Malaysia but the use of opioids, even though effective, can result in a myriad of post-operative side effects such as delayed emergence, somnolence, dizziness, pruritus, nausea, vomiting, ileus, constipation, urinary retention, respiratory depression, acute tolerance by desensitization and hyperalgesia (16). Additionally, evidence is now mounting that opioid-induced immunosuppression, which may affect the outcome of surgery, including the increased risk of infection and increase risk of metastasis in the cancer population (10), hence lead to prolong hospital stay and morbidities. Furthermore, short-acting opioids used during anesthesia may lead to acute opioid-induced tolerance and hyperalgesia (19), which can be difficult to treat postoperatively. These side effects are some of the

important reasons why opioid is not use in ERAS protocols. They prevent smooth postoperative recovery and can delay hospital discharge, which leads to prolonged hospital stay, unnecessary readmissions, increase morbidity, and increased healthcare costs (19). Uncontrolled severe acute pain can cause permanent conformation in spinal cord pathways and cause debilitating chronic pain syndrome (20). As a result, it may lead to debilitating psychological problems like anger, depression, and fear in the future.

1.3.1 Enhanced Recovery After Surgery (ERAS)

Enhances recovery after surgery is an evidence-based multimodal perioperative protocol that focused on stress reduction and promotion of a return to function (28). It has been proven to lower both recovery time and postoperative complication rates while being cost-effective at the same time (33). ERAS focuses on counseling preoperatively, optimizing nutrition, standardizing analgesia without opioid use, minimizing electrolyte and fluids imbalance, using the most minimally invasive approaches, and promoting early ambulation and feeding. In ERAS, non-opioid based multimodal analgesia is the cornerstone of modern pain control for the patient undergoing enhanced colorectal recovery programmed, which was pioneered by Professor Henrik Kehlet in Denmark since the early 1990s. They implement the use of simple analgesia such as paracetamol and non-steroidal anti-inflammatory drugs, regional analgesia while avoiding the use of long-lasting opiates where possible

CHAPTER 2: OBJECTIVES OF STUDY

2.1 General Objective

To evaluate the efficacy and side-effect of non-opioid based versus opioid-based multimodal analgesia in patient undergoing elective laparoscopic cholecystectomy

2.2 Specific Objectives

1. To compare the pain score in both groups by using a visual analogue score within 12 hours postoperative.
2. To compare the analgesic failure rate (define as a visual analogue score of more than 3) in both groups in 12 hours.
3. To compare the percentage of postoperative nausea vomiting in both groups within 12 hours.
4. To compare hemodynamic (heart rate and blood pressure) changes during trocar insertion, insufflation, and end of surgery in both groups.

2.3 Hypothesis

2.3.1 Null hypothesis:

1. Non-opioid based multimodal analgesia is less effective than opioid-based analgesia in reducing pain score (area under the curve for pain score) during the first 12 hours postoperatively by using visual analogue (VAS).