THE EFFICACY OF PARECOXIB 20MG AS AN ADJUNCT IN 0.75% ROPIVACAINE IN SUPRACLAVICULAR BRACHIAL PLEUXS BLOCK FOR UPPER LIMB SURGERY

Primary Investigator: 1) **DR VIVEKANANDA GUNASEKARAN**
(MBBS (Manipal), MMed Anaesthesiology (USM))

Co-investigators: 1) **DR MUHAMMAD IRFAN ABDUL JALAL**
(MBChB BAO (Queen's University of Belfast), PhD (Newcastle University))

2) **DR WAN MOHD NAZARUDDIN WAN HASSAN**
(MD (UKM), MMed Anaesthesiology (USM))

3) **DR RHENDRA HARDY MOHD ZAINI**
(MD (USM), MMed Anaesthesiology (USM))

4) **DR WAN NOR ARIFIN WAN MANSOR**
(MD (UIA), MSc Medical Statistics (USM))

UNIVERSITI SAINS MALAYSIA

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ABSTRACT

Introduction

Brachial plexus block (BPB) is a critical method in providing anaesthesia for upper limb surgery. Parecoxib, a specific COX-2 inhibitor, has the potential as an adjunct for 0.75% ropivacaine in supraclavicular BP block setting.

Objectives

To investigate whether the efficacy of supraclavicular brachical block is enhanced by the addition of 20 mg parecoxib to 0.75% ropivacaine in patients undergoing upper limb surgery.

Methods

This is a double-blind, active-controlled, parallel group, prospective randomized clinical trial conducted between 20th June and 28th August 2017 involving eighty six (n=86) adults whose age were between 18 and 65 years old, with ASA grade I or II and undergoing various upper limb surgeries whose durations were between 1 and 4 hours. The subjects were block-randomized in 1:1 ratio into two groups; group 1 received adjunct IV parecoxib and 0.75% ropivacaine whilst group 2 received 0.75% ropivacaine alone. The primary end-points are the duration and onset of sensory and motor block and the proportions of complete motor and sensory block at 30 minutes following supraclavicular BP block. The significance of the differences in trial endpoints were statistically tested using Mann-Whitney and Chi-square tests.

Results

Eighty six (n=86) subjects were randomised to either group and analysed. There were higher durations of sensory and motor blocks in the adjunct parecoxib + ropivacaine group compared to the ropivacaine-only groups (sensory block duration: 6.5 hours vs 5.0 hours, median difference = 1.5 hours, p value <0.001; motor block duration: 4.84 hours vs 3.86 hours, median difference = 0.97 hours, p value <0.001). No significant differences between the two intervention arms with respect to sensory (9 minutes vs 9 minutes, median difference = 0 minute, p value = 0.511) and motor blockades (17 minutes vs 18 minutes, median difference = 1 minute, p value = 0.832) onset. Besides, there no significant difference in terms of complete sensory and motor blockades at 30 minutes post supraclavicular block between parecoxib + ropivacaine and ropivacaine-only groups (sensory blockade at 30 minutes: 100% vs 97.7 %, p value = 1.000; motor blockade at 30 minute = 100% vs 97.7%, p value = 1.000). No adverse events were reported in both intervention arms and the trial was not ended prematurely.

Conclusion

Adjunct parecoxib significantly enhances the durations of sensory and motor blockades, but not their onset and complete sensory and motor block at 30 minutes following supraclavicular brachial plexus block.

(395 words)

SECTION ONE

INTRODUCTION

Brachial plexus block (BPB) has enjoyed ubiquitious popularity for upper limb surgeries (Raju and Coventry, 2013). It provides sufficient anaesthesia for surgical procedures involving upper limbs due to the propinquity of the brachial plexus' trunks and division when they pass the first rib (Gamo *et al.*, 2014).

There are a few common techniques for BPB and one of the most frequently-utilised one is supraclavicular BPB (Raju and Coventry, 2013). It is not only an efficient mode of anaesthesia intraoperatively, but it is can also provide a quick-onset and dense anaesthesia for surgical procedures that involve the proximal mid-humerus down to the distal hand with excellent safety profile (Raju and Coventry, 2013; Gamo *et al.*, 2014). The supraclavicular block (SCB) is performed above the clavicle and aims at the level of the nerve trunks or division of brachial plexus (BP). Other frequently-employed alternatives include infraclavicular block, interscalene block and axillary BPB (Raju and Coventry, 2013).

Nowadays, all techniques for BPB have been widely performed under ultrasound (US) guidance and this new modality has been proven to enhance the success rate of BPB and lessen the complications involved with BPB; for instance pneumothorax, intraneural local anesthetic (LA) injection, nerve injuries etc (Chan *et al.*, 2003; Peterson *et al.*, 2002). US-guided SCB is aimed to circumferentially disseminate local anaesthetic (LA) agent perineurally, a location that is close to the subclavian artery (Chan *et al.*, 2003).

There are few adjunct drugs that can be mixed with LA to speed up the onset as well as prolong the duration of the block. These drugs can also minimise the potential of overdose that may lead to severe and fatal LA toxicity. Parecoxib (Dynastat®) is one of

the relatively recently-developed therapeutic agents that are studied at present as an adjunct to LA (Liu *et al.* 2013). It acts by inhibiting the function of the constitutive COX-2, an isoform of cyclooxygenase (COX) (Liu *et al.* 2013).

The aims of the study are to investigate the effect of parecoxib as an adjunct in Ropivacaine 0.75% for ultrasound guided SCB. Possible side effects are due to the onset of block, duration of block and haemodynamic instability. Prolonged duration of anaesthesia was particularly singled out as one of the important end-points to be investigated and compared between the recipients of adjunct parecoxib + ropivacaine 0.75% and single-agent ropivacaine 0.75% (i.e ropivacaine 0.75% only without the adjunct parecoxib).

There are several studies that have demonstrated that the presence of COX-2 in the dorsal horn of spinal cord could regulate spinal nociceptive transmission (Resnick *et* al, 1998; Martin *et al.*, 2007; Li *et al*., 2009) Furthermore, there are findings from other studies that suggested adding a COX-2 antagonist directly on the central or peripheral nerve might have a better analgesic effect than intravenously (Yamamoto *et al.*, 1998, Kim *et al.*, 2011; Liu *et al.*, 2013). Principally, COX-2 inhibitors reduce inflammation and hyperalgesia by reducing prostaglandin production (Yaksh *et al.*, 2001). However, the role of COX-2 in the central nervous system is of more importance. Inflammation can induce COX-2 production and will lead to prostanoids release that will sensitize the peripheral nociceptor terminals and produce localized pain hypersensitivity (Vardeh *et al.*, 2009). It is hence thought that the administration of COX-2 antagonist on spinal or peripheral nerves may be a more effective mode of pain relief than the intravenous or intramuscular route.

Further details will be discussed in section 2.

SECTION TWO

LITERATURE REVIEW

2.1 SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

Brachial plexus block (BPB) is an indispensable method of providing anaesthesia for surgery of the upper limb. The most customarily-used technique is the axillary, perivascular approach because it is trivial to perform and the low risk of complications associated with this approach. Nevertheless, the brachial plexus blockade may stay incomplete because the musculocutaneous and axillary nerves diverge from the brachial plexus sheath proximal to the puncture site.

The subclavian perivascular technique which was originally pioneered by Winnie and Collins (1964) and the traditional supraclavicular method devised and introduced by Kulenkampff and Persky (1928) are the two most commonly utilised methods for BPB in the clinical setting. These techniques require needle insertion caudally and perpendicular to the brachial plexus. The supraclavicular technique directs the needle toward the first rib close to the pleura. This approach provides a greater extent of BP block than the axillary approach since it includes the musculocutaneous and the axillary nerve blockades, but it possesses a greater risk of serious and potentially fatal complications. For instance, the incidence of pneumothorax associated with the traditional Kulenkampff technique is between 0.6% and 6.0% (Neal, 2009). Other complications that should also be seriously taken into consideration are haematomas attributed to the puncture of a major blood vessel and unwanted dissemination of local anaesthetics leading to the paresis of stellate ganglion as well as the phrenic (hemidiaphragmatic paresis) and recurrent laryngeal nerves (voice hoarseness), hypotension and bradycardia associated with the interscalene approach (13 to 24%) (Neal, 2009).

To boost the success rate and to evade the aforesaid complications, Ting and Sivagnanaratnam (1989) developed the use of ultrasonography in the performance of an axillary BPB. This approach permits the verification of the cannula localization and enables the visualisation of the spread of the local aneaesthetics within the plexus sheath. Using this technique, Ting and Sivagnanaratnam reported a 100% success rate without any complications (Ting and Sivagnanaratnam, 1989).

In another study by Kapral and others (1994), the researchers adapted the method developed by Ting and Sivagnanratnam and used it for the supraclavicular paravascular approach of BPB. The authors investigated the utility and impact of ultrasonic cannula guidance for supraclavicular puncture of the brachial plexus sheath against the axillary approach in terms of success, rate, onset and the frequency of complications. They found that 95% of the subjects in both groups experienced satisfactory analgesia. Nevertheless, 25% of subjects in the axillary approach group experienced incomplete sensory block whilst none of the subjects in the supraclavicular paravascular approach had incomplete sensory block. The authors concluded that the ultrasonography-guided approach for the supraclavicular block is comparatively as safe as the axillary approach, with a larger extent of block than the axillary approach.

Besides, Chan and colleagues (2003) also researched the utility of ultrasound-guided supraclavicular approach for BPB. The rationale for further researching and developing this technique, according to the authors, is that it can be utilised to precisely and accurately locate the brachial plexus, hence reducing the procedure-related pain associated with imprecise anatomical landmark localisation based on the trial and error approach and potential pneumothorax. The authors observed that in 40 patients who received BPB for their elective upper-limb surgeries via this new approach, low pain score during their postoperative care at post-anaesthesia care unit (PACU) (mean score

of 0.3 out of 10) and high satisfaction in regard to pain control (median score of 9 out of 10) were reported. Two failures were recorded which were attributed to subcutaneous injection of bupivacaine and partial intravascular local anaesthetic injection which led to block failure at 30 minutes post injection. Two study participants experienced complications postoperatively which include Horner's syndrome and transient paraesthesia that lasted for less than 48 hours. No incidence of pneumothorax was reported. The findings of this study were further corroborated by a subsequent study by Chan *et al*. (2007) who demonstrated that the ultrasound guidance enhanced the success rate of axillary BPB (defined as the absence of sensation in upper limb areas supplied by the median, ulnar and radial nerves at 30 minutes following axillary BPB) in 188 patients who had elective hand surgeries. Apart from that, there were less number of patients in the US group who needed supplemental nerve blocks and general anaesthesia in comparison to the other group whose subjects underwent axillary BPB guided only by a nerve stimulator. The findings of this trial, hence, conclusively showed the superiority of this ultrasound-guidance technique over the other alternative methods for BPB.

There are also controversies on whether single injection (SI) ultrasound-guided eight-ball corner pocket technique or the triple injection (TI) is superior. Frederickson and colleagues (2010) established that the SI is superior to the TI method with respect to reducing the procedural time (SI vs TI: 117s vs 158s, p value = 0.002) whilst there were significant higher percentages of patients in the SI group experiencing complete motor and sensory blockades at 20 minutes post injection than the TI group (the percentages of patients experiencing full motor and sensory block at area supplied by radial nerve; SI vs TI: 88% vs 55%, p value = 0.02). Even though the SI approach has been established to have the best success rate, this method may fall short from adequately anaesthesizing the upper part of the brachial plexus, resulting in an incomplete block of the territories

innvervated by nerves originated from the upper brachial plexus, such as areas supplied by the ulnar nerve (Frederickson *et al.,* (2009)). This is further emphasized in a study by Thompson and Rorie (1983) who re-evaluated the anatomical aspect of brachial plexus sheath utilising dye injections were to assist with the visualisation of the anatomical compartments in cadavers. They then extended their study by confirming the multi-compartmental nature of the brachial plexus sheath anatomy in surgical patients using computed tomography (CT) dye studies (Thompson and Rorie, 1983). They also established that an injection into a solitary brachial plexus site did not lead to an ample dispersal of the injected dye into all brachial plexus sheath compartments which is formed by septae or a tight muscular membrane that restricted the dissemination of local anaesthetic agent circumferentially (Thompson and Rorie 1983).

There are also two other studies who also substantiated the findings of Thompson and Rorie (1983) which also proved the existence of septae segregating the brachial plexus into a multi-compartmental structure and the authors hypothesised that multiple injections is the most sensible approach for brachial plexus blockade (Vester-Andersen *et al.,* 1986, Partridge *et al.,* 1987). Nevertheless, those functional anatomical studies were only performed on cadaveric specimens and their results were not completely convincing to be accurately extrapolated to predict the onset of nerve blockades clinically.

Nevertheless, according to another study by Arab *et al.,* (2014), the TI technique had a more rapid onset and complete block in the first 20 minutes after injection than the SI technique. However, there was no difference in terms of the success rate for surgical anaesthesia at 30 minutes post injection. However, there were findings in other studies that are incongruent with the results obtained by Arab *et al.,* (2014). Tran *et al.,* (2010), Tran *et al.,* (2012) and Roy *et al.,* (2012) demonstrated that there are no significant advantages in employing the double injection technique for brachial plexus blockade via

all kind of approaches (supraclavicular, infraclavicular or axillary) over single injection technique. It is worth mentioning, however, that despite the many similarities of Arab et al. (2014) study with these three studies, there are differences in the Arab and colleagues (2014)'s study design that may make their findings more relevant and accurate. Firstly, the authors employed different sites when giving the injection. Secondly, they only focused on 1 type of surgical procedure and thus eliminating any confounders arising from the surgical stimulus or location of the surgery. Finally, the authors assessed the study outcomes in a different but more accurate fashion in which they chose sensory block of the 5 nerves as their primary end point. However, more studies are required to verify the findings of Arab *et al.,* (2014) and deliver the final verdict on this never-ending controversial issue.

2.2 ROPIVACAINE: PHARMACOLOGICAL PROPERTIES

Ropivacaine is chemically a long-acting regional anaesthetic of amide group that is structurally related to Bupivacaine. In contrast with Bupivacaine, Ropivacaine is a pure S(-) enantiomer, which is a racemate, developed for the purpose of lessening potential toxicity and enhancing relative sensory and motor blocking properties of other local anaesthetic agents.

Before we proceed further, the conceptual underpinning of enantiomers should be elucidated first. Enantiomers are chiral molecules that have two dissimilar spatial configurations, like the right and left-handed gloves (i.e. one is the mirror image of the other), which occur in equivalent quantities in a racemate. They are both pharmacologically active and can be optically distinguished by their effects on the rotation of the plane of a polarized light and hence they can be classified into either dextrorotatory (clockwise rotation, [R+]) or levorotatory (counterclockwise rotation [S-]) stereoisomers. The physicochemical properties of the enantiomeric molecules are

identical, but the two enantiomers can have substantially different behaviours in terms of their affinity for either the pharmacological site of action or the sites that account organotoxicity occurrence. The R[+] and S[-] enantiomers of local anaesthetics have been demonstrated to possess varied affinity for disparate sodium, potassium and calcium ion channels. This may explain the considerable diminution of neuro and cardiotoxicity of the S[-] enantiomer when comparison was made with the R[+] enantiomers of the same local anaesthetic compounds (Aberg 1972, Luduena *et al.,* 1972).

The progress in chemical technology has made the development of ropivacaine as an optically pure S[-] enantiomer from the chiral propivacaine a reality. It is a member of the pipecoloxylidides group which is a type of local anaesthetic. It has a propoyl group bonded to the nitrogen atom of piperidine, a slight difference to bupivacaine which has a butyl group linked to its piperidine group (McClure 1996).

2.2.1 Pharmacokinetics profiles of ropivacaine

2.2.1 (a) Absorption and distribution

The plasma concentration of ropivacaine, like any other local anaesthetic agent, is influenced by the vascularity of the injection sites, the total dose amount used and the route of administration, the rate of administration and the haemodynamic and circulatory condition of the patients (Simpson *et al.,* 2005). When ropivacaine was administered either intravenously or as continuous epidural infusion in normal healthy subjects, the pharmacokinetic of ropivacaine exhibited a first order linear property which means that an increase in the plasma concentration of ropivacaine is proportional to the dose given and this effect exists even when ropivacaine is increased up to 80 mg if given intravenously (Emanuelsson *et al.*, 1997; Simpson *et al.,* 2005) or up to 3 mg / mL if given via continuous epidural infusion (Emanuelsson *et al.*, 1995). If ropivacaine is epidurally given, it was observed that ropivacaine dosed at 150 mg is absorbed in entirety

from the epidural space in a biphasic fashion. The average half-life of ropivacaine during the introductory phase is about 14 minutes, followed by a more protracted phase that has a mean distribution $t_{1/2}$ of approximatelt 4.2 hours (Simpson *et al.,* 2005).

Ropivacaine is extensively bound (94%) to plasma protein, primarily to α1-acid glycoprotein (Burm *et al.,* 2000). The total plasma concentration ropivacaine increases during the steady epidural infusion of ropivacaine is attributed to a raise in the degree of protein binding and the subsequent diminishment in ropivacaine clearance (Burm *et al.,* 2000).

Ropivacaine quickly travels across the placenta when it is epidurally administered during Caesarean section, culminating in almost complete equilibrium of the unbounded fraction of ropivacaine in both maternal and foetal plasma (Ala-Kokko *et al.,* 1997). Nonetheless, when it comes to ropivacaine's total plasma concentration, the level of unbounded ropivacaine's total plasma concentration is higher in the maternal than in the foetal circulation due to the presence of a more elevated concentration of α1-acid glycoprotein-bound ropivacaine in the maternal than foetal plasma (Ala-Kokko *et al* 1997).

2.2.1 (b) Metabolism and excretion

Ropivacaine is largely metabolized in the liver, preferentially by aromatic hydroxylation, to 3`-hydroxy-ropivacaine by cytochrome P450 (CYP) 1A2 and N-dealkylation to 2`,6`-pipecoloxylidide by CYP3A4 (Ekstrom *et al.,* 1996). Ropivacaine is primarily excreted by the kidney which is responsible for 86% of the urinary excretion of ropivacaine following a solitary IV dose administration (Lee *et al.,* 1989). The mean±SD biological half-life ($t_{1/2}$) of ropivacaine post IV and epidural administration are 1.8±0.7 hours and 4.2±1.0 hours, respectively.

2.2.1 (c) Relative potency

A strict association is present between the extent of local anaesthetic's lipid solubility and its toxicological properties and potency. According to the studies which measured the minimum local anaesthetic concentration (MLAC), defined as the anaesthetic concentration that produces effective analgesia in 50% of patients (EC_{50}), ropivacaine exhibits comparable magnitude of potency to bupivacaine at greater doses, for instance the dose warranted for peripheral nerve blocks (McGrady and Litchfield 2004). However, at lower doses (e.g. the doses that are usually given for intrathecal or epidural analgesia), ropivacaine is surprisingly observed to be less potent than bupivacaine and levobupivacaine (McGrady and Litchfield 2004). Nevertheless, the provision of anaesthesia or analgesia to the patients is more clinically pertinent rather than worrying about the MLAC and this distinction in anaesthetic potency is commonly unnoticeable during the day-to-day clinical practice which involves administering ropivacaine at higher doses for routine surgical anaesthesia.

2.2.1 (d) Tolerability

Ropivacaine is generally well-tolerated in adults irrespective of the administration routes. The adverse events associated with reactions to ropivacaine are similar to those side effects produced by other amide-based local anaesthetics. In a meta-analysis based on the data from disparate but well-designed clinical trials, the adverse events experienced by ≥5% of patients who received ropivacaine 0.125-1% via myriad routes of administration for surgery, labour pain, Caesarean section, postoperative pain management, peripheral nerve block or local infiltration (n=1661) include hypotension (32%), nausea (17%), vomiting (7%), bradycardia (6%) and headache (5%) (Simpson *et al.,* 2005). These events are attributed to the nerve block received during such procedures and the adverse reactions also occurred in similar percentages among 0.25-0.75%

bupivacaine recipients (n=1433) (hypotension = 29%, nausea = 14%, vomiting = 6%, bradycardia = 5% and headeache = 5%,) given for the same indications. Apart from that, when the epidural route is employed for ropivacaine administration prior to surgery, the adverse events also occurred in a dose-dependent fashion, a characteristic that was similarly observed among patients who received similar doses of bupivacaine (Simpson *et al.,* 2005).

The incidence of ropivacaine-induced cardiovascular symptoms might be attributed to age factor. Patients whose age is more than 61 years and received epidural ropivacaine at 1% strength had significantly higher occurrences of bradycardia (58% vs 15% in patients aged 41-60 years; p value=0.005) and hypotension (74% vs 20%, in patients aged between 18 and 40 years; p value=0.002) (Simpson *et al.,* 2002). The cardiovascular events can also be linked to ropivacaine toxicity secondary to rapid IV injection or massive absorption from peripheral nerve blocks.

Apart from that, ropivacaine is also commonly well-tolerated in paediatric patients whose age ranged from 1 month to 15 years and irrespective of the route of administration (Bosenberg *et al.,* 2002). The overall incidence of ropivacaine-associated adverse events is low, with the most frequent reported adverse events are nausea and/or vomiting. Furthermore, foetus and neonates also tolerate ropivacaine well following its use for regional anaesthesia in women who underwent Caesarean section or during labour (Simpson *et al.,* 2005). The most commonly documented adverse events associated with ropivacaine in foetus and neonates are foetal bradycardia (12%), neonatal jaundice (8%) and unspecified neonatal complications (7%). These events occurred in similar percentages in both ropivacaine and bupivacaine recipients (12%, 8%, and 7%, respectively) (Simpson *et al.,* 2005). Moreover, according to a meta-analysis of six double-blind trials, ropivacaine did not affect the neonatal neurological and adaptive

capacity (NAC) score at 2 and 24 hours post labour. To corroborate this further, the total NAC scores were discovered to be significantly greater in neonates whose mothers had received ropivacaine rather than bupivacaine (Writer *et al.,* 1998). Accordingly, we can conclude that ropivacaine is relatively safer for use in paediatric population than other local anaesthetics.

2.2.2 Pharmacodynamic profiles of ropivacaine

2.2.2 (a) Mechanisms of action

Ropivacaine causes reversible inhibition of sodium ion influx and thereby blocks impulse conduction in nerve fibres (Hansen 2004). This action is potentiated by dose-dependent inhibition of potassium channels (Kindler *et al* 2003). Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres. As a result, it has selective action on the pain signal transmitted by the A, δ and C nerve fibres rather than Aβ nerve, which are more associated with motor function (Rosenberg and Heinonen 1983).

2.2.2 (b) Drug interactions

Care should be taken when Ropivacaine is used in patients who are also recipients of other local anaesthetics which are structurally related to amide-type local anaesthetics, since the effects of these drugs are additive. Ropivacaine is metabolised by Cytochrome P4501A2 (CYP1A2) into its major metabolite, 3-hydroxy ropivacaine (Arlander *et al.,* 1998). Thus, potent inhibitors of CYP1A2 such as fluvoxamine, if given concurrently with ropivacaine, may interfere with ropivacaine metabolism and this may lead to a raised level of plasma ropivacaine concentration (Arlander *et al.,* 1998). As a result, great caution is required when ropivacaine is concomitantly given with pharmacological agents which are CYP1A2 inhibitors as well. As further examples, possible interactions with pharmacological agents, for instance theophylline and imipramine which are also

metabolized by CYP1A2 may also occur through competitive inhibition (Jokinen *et al.,* 2001).

2.2.2 (c) Adverse effects on CNS and cardiovascular effects

Cardiotoxicity and neurotoxicity due to unintentional intravascular injection of ropivacaine appears to be low. According to a pooled analysis of data from approximately 3000 patients in 60 clinical studies, the incidence of probable accidental IV injection of ropivacaine was 0.2% (six patients) and only one patient experience convulsions (Selander *et al.,* 1997). No patient showed symptoms of cardiotoxicity.

It is well known fact that the CNS toxicity occurs before cardiotoxicity for local anaesthetic drugs. The signs and symptoms of CNS toxicity are usually excitatory in nature such as tremor, muscle twitching, shivering which are produced by the suppression of the central inhibitory pathway (Linsey *et al.,* 2014). However, when the plasma concentration of local anaesthetic agents further increases, it subsequently causes the excitatory pathway of CNS to be blocked and this results in myriads of clinical signs and symptoms of CNS suppression, for instance hypoventilation, respiratory depression and generalized convulsion (Linsey *et al.,* 2014).

Besides, when ropivacaine was administered intravenously, the CNS toxic effects also occurred earlier than the cardiotoxic symptoms and this happened when the IV ropivacaine was infused at a rate of 10mg/min or higher in healthy human subjects. It was also demonstrated by Groban 2003 that the dose required for inducing seizure in various animal models (rat, dog and sheep) was the highest for ropivacaine in comparison to levobupivacaine and bupivacaine. This means that ropivacaine has a lower potential for causing CNS toxicity than levobupivacaine and bupivacaine since it requires much higher doses than levobupivacaine and bupivacaine to induce convulsion in the animal models (Groban, 2003). Such findings were further endorsed by an old study by Knudsen *et al.*

(1997) who showed that 10 to 25% higher dose is required for ropivacaine than bupivacaine to cause neurotoxicity.

With regard to ropivacaine-associated cardiotoxicity, the clinical signs include significant changes in cardiac function involving the contractility, conduction time and QRS width occurred and the increase in a QRS width was found to be significantly smaller with ropivacaine than bupivacaine. Ropivacaine is known to be less lipophilic than bupivacaine and together with its stereoselective properties, this contributes to ropivacaine having a significantly higher threshold for cardiotoxicity than bupivacaine in animals and healthy volunteers (Hansen, 2004; Lefrant *et al.*, 2001). The lower lipophilicity of ropivacaine relative to bupivacaine is associated with lesser cardiodepressant effects of both ropivacaine isomers than bupivacaine isomers in animal studies. The mechanisms of ropivacaine cardiotoxicity are molecularly attributed to three main factors; the continuous blockade of the inactive and open sodium ion channels, resulting in the increased durations of PR interval and QRS complex which eventually causes a high susceptibility to re-entrant arrhythmias (Gristwood 2002). Besides, the inhibition of potassium ion channels which causes prolonged QT_c interval and the amplification of the degree of sodium channel block (Avery 1984) is another factor that may mechanistically explain the cardiotoxic effect of ropivacaine. Finally, the effects of ropivacaine on the metabolic efficiency of mitochondrial bioenergetics has also been proposed as one of the causes of ropivacaine cardiotoxicity (Sztark *et al.,* 1998, Sztark *et al*., 2000).

2.2.2 (d) Other clinical effects and adverse events

Besides the clinical effects and adverse events described above, it is also known that ropivacaine possesses biphasic effect on blood vessels. Ropivacaine induces vasoconstriction when it was intradermally injected at a low concentration (0.063 – 0.5%)

(Cederholm *et al.,* 1983). On the contrary, vasodilation was observed when higher concentration of ropivacaine (1%) was utilised (Cederholm *et al.,* 1983). Consequently, ropivacaine is a better alternative to bupivacaine due to its vasoconstrictive effect, when used in low dose, causes delays in systemic absorption and subsequent reduction system adverse effects. This desirable property can be further enhanced by the addition of epinephrine diluted to 1:200000 ratio into a 0.15 to 0.20% ropivacaine solution since this will further reduce the peak plasma concentration of ropivacaine (C_{max}) and prolong the time to peak plasma concentration (T_{max}) (Cuvillon *et al.,* 2009).

Ropivacaine has been demonstrated to cause the aggregation of plate in plasma at the following cocentrations; 3.75 and 1.88mg/ml (0.375% and 0.188%) which are equivalent to the ropivacaine concentrations that could be normally observed in the epidural space during the infusion of ropivacaine (Porter *et al.,* 2001). Besides, ropivacaine also possesses *in vitro* bacteriostatic activity against *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*, an effect that is similar to other anaesthetic agent (Kampe *et al.,* 2003).

2.2.3 The roles of ropivacaine in peripheral nerve blocks and upper limb surgery

Peripheral nerve block is utilised for anaesthesia for orthopaedic surgery, and the emergence and dissemination of local anaesthetic effect is regulated by the injection locality (Hofmann-Kiefer *et al.,* 2002). The authors also discovered that there were no significant differences between ropivacaine (dosed at 7.5 mg/ml) and bupivacaine (dosed at 5mg / ml) recipients in terms of the onset and quality of motor and sensory blockades when both drugs were administered for BPB via interscalene approach (Hoffman-Kiefer *et al.,* 2002).

Besides, other studies also demonstrated that the concentration of ropivacaine employed for long-acting sensory and motor blockades is either 0.5% or 0.75% for

axillary, interscalene and subclavian perivascular BPB (Casati *et al.*, 2003; Liisanantti *et al.*, 2004). The researchers found that 0.5 – 0.75% ropivacaine produced a similar quality of regional anaesthesia as either 0.5% bupivacaine or 0.5% levobupivacaine given as a bolus dose of 30 -45 ml (Casati *et al.*, 2003; Liisanantti *et al.*, 2004). Similar findings were also established in patients undergoing femoral and sciatic blockades for hallux valgus repair where the recipients of 25 ml of 0.75% ropivacaine had a significantly quicker onset of sensory block around the territories supplied by the femoral and sciatic nerve (ropivacaine vs bupivacaine: 14 minutes vs 37 minutes, p value = 0.002) and motor blockade (ropivacaine vs bupivacaine: 14 minutes vs 51 minutes, p value = 0.001) than those receiving 25 ml of 0.5% bupivacaine (Fanelli *et al.,* 1998). Besides, the durations of motor blockades at the knee and foot levels were longer in the recipients of ropivacaine and bupivacaine when comparison was made with mepivacaine recipients. Finally, Fanelli and colleagues (1998) also established that the total duration of analgesia was significantly longer in ropivacaine and bupivacaine than in the mepivacaine groups (ropivacaine vs bupivacaie vs mepivacaine: 670 minutes vs 880 minutes vs 251 minutes, p value = 0.001). Even though ropivacaine recipients had a relatively shorter mean duration of motor block at knee level and the total duration of analgesia than bupivacaine recipients, these differences were not statistically significant (Fanelli *et al,* 1998).

With respect to upper limb surgery, there was similar quality of pain relief with ropivacaine and bupivacaine in a trial conducted among patients who had interscalene block prior to major open surgeries to their shoulders (Borgeat *et al.,* 2001). However, the authors observed that the hand strength returned more expeditiously and the degree of paraesthesia at the finger level was less in patients receiving 0.2% ropivacaine than in those receiving 0.15% bupivacaine (Borgeat *et al.,* 2001). At 24 hours after the performance of interscalene block, the hand strength (the primary endpoint) was reduced

by 48% in 0.2% ropivacaine recipients and 66% in bupivacaine recipients (p value <0.05) (Borgeat *et al.,* 2001). Furthermore, the hand strength was completely recovered for subjects in ropivacaine arm at 6 hours following the cessation of ropivacaine infusion. In bupivacaine group, however, there was a protracted recovery of hand strength since it was still reduced by 25% after the end of bupivacaine administration and the difference was significant when comparison was made with the ropivacaine group (Borgeat *et al.,* 2001). Nevertheless, the results of this study should be taken with a pinch of salt due to the controversial use of the non-validated bulb-grip device test as a measurement tool for motor strength by the authors.

In another study conducted locally by Mageswaran and Choy (2010), subjects undergoing elective or orthopaedic upper limb surgery were randomized into receiving either 0.5% ropivacaine or 0.5% levobupivacaine via infraclavicular brachial plexus block. The mean onset for sensory and motor block were significantly higher in 0.5% ropivacaine recipients than 0.5 levobupivacaine recipients (sensory block: 13.5 minutes vs 11.1 minutes (p value = 0.003), motor block: 19.0 minutes vs 17.1 minutes (p value = 0.013). However, no statistically-significant difference was found with regard to the analgesic efficacy at 6 hours after the surgery. Again, the findings of this study should not be taken at face value and hence careful consideration should be exercised before recognising the validty of such results since the number of participants allocated in each intervention group was small (n = 24 per group). Hence, further studies are required to gain further information on the exact benefits of ropivacaine over other anaesthetic agents such as bupivacaine for upper limb surgeries.

2.3 PARECOXIB: PHARMACOLOGICAL PROPERTIES

The management of moderate-to-severe acute pain involves a prudent utilisation of opioids, local anaesthetics, and non-steroidal anti-inflammatory drugs (NSAIDs) (Carr

and Goudas 1999). NSAIDs is a group of drugs that function as cyclo-oxygenase (COX) inhibitor, an enzyme that is critical for prostaglandins production (Jain 2000). The unselective NSAIDs indiscriminately hamper the function of COX-1 and COX-2 (Jain 2000).

COX-1 has “housekeeping” functions which include preserving renal perfusion and protecting the gastric mucosal layer against ulceration (Emery 1999). It is constitutively expressed and has critical roles in the production of prostaglandin in the gastric mucosal layer, platelets and renal blood vessels (Fosslien 1998). On the contrary, the blockade of the inducible isoform COX-2 synthesis is believed to be chiefly accounted for the NSAIDs' analgesic and anti-inflammatory effects (Bolten 1997, Needleman and Isakson 1998).

The development of COX-2-specific oral NSAIDs (e.g. celecoxib and rofecoxib) has resulted in a class of theraputic agent that provides effective relief of mild-to-moderate pain without the gastrointestinal and anti-platelet adverse effects (Jain 2000). However, in cases of postoperative nausea and vomiting or where the oral route of administration is deemed unsuitable postoperatively, the use of orally-administered NSAIDs is hence ill-suited (Carr and Goudas 1999). At present, there are very few NSAIDs that are available in parenteral form with ketorolac (Toradol®) is the sole exception. Nevertheless, due to being a non-selective COX inhibitor, ketorolac is associated with gastrointestinal ulceration, deterioration of kidney function and a susceptibilty to raised incidence of perioperative bleeding (McArdle 1999). Besides, ketorolac is also contraindicated postoperatively since it may interfere with the wound healing process which may result in serious bleeding and other life-threatening post-surgical complications.

Parecoxib (Dynastat®) is a COX-2 specific inhibitor which can also be administered as an IV or intramuscular injection. It is a prodrug of valdecoxib which was chemically designed to overcome the poor solubility of valdecoxib in aqueous solution so that it can be administered parenterally (Amabile and Spencer 2004). Structurally, it has a sulphonamide moiety. Parecoxib is broken down by carboxylesterase in the liver into its active form, valdecoxib (Amabile and Spencer 2004). Valdecoxib, however, is metabolized via oxidative process which is catalysed by CYP3A4 and slightly by CYP2C9 (Amabile and Spencer 2004).

There are two postulated mechanisms on how parecoxib modulates nociception. Firstly, the blockade of prostaglandin H_2 and E_2 ,which are subtypes of prostaglandin that are synthesised from arachidonic acid, results in the modulation and diminishment of nociception by the reduction of the sensory neuron's electrical excitability and bradykinin-associated hyperalgesia (Jain 2000, Amabile and Spencer 2004). Secondly, parecoxib may also directly act on the inhibitory or excitatory neurone's amino acid sites (Jain 2000). In this subchapter, we shall focus our discussion on the pharmacological properties of parecoxib to rationalise its use as an adjunct to ropivacaine for BPB.

2.3.1 Absoprtion, Distribution, Metabolism and Elimination (ADME)

In normal and healthy individuals, the maximum plasma concentration (C_{max}) of valdecoxib (the active metabolite of parecoxib) was found 73% lower after the administration of 20 mg of IM parecoxib (1 – 1.25 mg/L) than following IV administration (3.8-4.7 mg/L) (Gajraj, 2007). The time to C_{max} (t_{max}) was approximately 5 minutes after IV administration and 20 minutes after intramuscular administration (Gajraj 2007). However, the total exposure to valdecoxib (the active form of parecoxib) based on the area under the plasma concentration-curve (AUC_{24h}) and the magnitude of C_{max} for valdecoxib were independent of the routes of administration (Gajraj 2007).

Nevertheless, t_{max} is shorter for valdecoxib after 20 mg of parecoxib was administered intravenously (30 minutes) than following IM parecoxib administration (1-2.5 hours) (Gajraj 2007).

Parecoxib was also quickly biotransformed to valdecoxib following IV administration of 50 mg parecoxib in twelve (n=12) normal individuals (Grossman *et al.,* 2000). Grossman and colleagues (2000) established that the $t_{1/2}$ was 0.69 hours and the peak plasma concentration (C_{max}) of valdecoxib following the administration of a single IV dose of 50 mg parecoxib was 1.02mg/L and this was recorded 0.6 hours following parecoxib administration (Ng *et al.,* 2004). If parecoxib is given in a multiple dose regime (e.g. 50mg twice daily), the C_{max} of valdecoxib was higher (1.40 mg/L on day 10) with the mean valdecoxib plasma concentrations at steady-state ($C_{av,ss}$) were attained on the 7^{th} day. The area under the concentration-time curve from time 0 to infinity (AUC_{∞}) for valdecoxib following a single dose of IV parecoxib was 7.80 mg/L per hour and with multiple doses, the area under the plasma-concentration time curve at 12 hours (AUC_{12h}) was 8.16 mg/L per hour on the 10^{th} day. The $t_{1/2}$ for valdecoxib was 7.88 hours and valdecoxib was the primary compound recovered in the urine within the span of 48 hours following parecoxib administration (Ng *et al.*, 2004).

Besides, the mean AUC_{24} and mean C_{max} of valdecoxib was shown to proportionately raise with the parecoxib dose (range: 1 to 100 mg) administered as a solitary IV dose in 356 patients following dental surgery (the AUC_{24} is between 0.15 to 13.61 mg/L per hour; C_{max}: 0.026 to 2.16 mg/L) (Daniels *et al.,* 2000). Using 20mg dose of parecoxib given intravenously, the authors established that the mean AUC_{24h} and C_{max} were 2.62 mg/L per hour and 0.45 mg/L, respectively. Besides, the t_{max} remained stable (0.5 to 0.9 hours) across all range of IV parecoxib doses (Daniels *et al.,*2000).

Parecoxib, in the dose between 1 and 40 mg, is also swiftly biotransformed when it is intramuscularly administered. In a study of 56 normal individuals, the $t_{1/2}$ of parecoxib ranged between 0.25 and 0.58 hours (Karim *et al.,* 2000). The C_{max} of valdecoxib was attained at 1.1 to 3.5 hours after parecoxib was administered and the C_{max} and AUC_{∞} of valdecoxib had been found to raise dose-proportionately as the amount of parecoxib doses increases. The values for C_{max} and AUC_{∞} were not unfortunately disclosed by the authors. Besides, the mean C_{max} (0.027 to 0.39 mg / L per hour) of valdecoxib were also found to raise in a dose-dependent fashion when parecoxib (dose range: 1 to 20mg) was administered as a solitary IM injection to 353 patients with postoperative dental pain (Karim *et al.,* 2000). The median t_{max} was attained at 1.6 hours post IM parecoxib injection. The authors subsequently concluded that the alteration in the plasma concentration of valdecoxib is associated with the analgesic duration and onset (Karim *et al.,* 2000).

2.3.2 Potential drug interactions

To evaluate the potential drug interactions between parecoxib and pharmacological agents metabolized by CYP3A4, an intravenous infusion of midazolam (a commonly-used probe for investigating CYP3A4-mediated drug-drug interactions) dosed at 0.07mg/kg over 5 minutes was given to 12 healthy normal and salubrious subjects at 1 hour following intravenous administration of parecoxib (40mg) or placebo in a double-blind RCT conducted in a crossover fashion (Ibrahim *et al.,* 2000a). The plasma midazolam concentration-time curves were similar for volunteers who had been parecoxib-pretreated and those who were in the placebo group. In addition, $C_{max,}$ systemic clearance and $t_{1/2}$ for midazolam did not differ significantly between those who were pretreated with parecoxib and the individuals who were in the placebo group. Furthermore, in another double-blind and crossover RCT, 40 mg of IV parecoxib

administered to 12 healthy individuals did not significantly alter the plasma concentration-time curve, C_{max} , the systemic parecoxib clearance and $t_{1/2}$ of intravenous propofol 2mg/kh when comparison was made with placebo recipients (Ibrahim *et al.,* 2000b).

Apart from that, Parecoxib has also been found to have several other significant drug interactions. Compared with placebo, parecoxib (given as 40 mg twice daily for 3 days followed by a single dose on day 4) did not significantly affect the anti-platelet effect of aspirin in response to various aggregants at most time-points (Noveck *et al.,* 2000). Platelet aggregation was, on the other hand, lowered in response to arachidonate, ADP or collagen in this well-controlled trial.

Besides, in another open-label single centre RCT, eighteen (n=18) normal healthy fasted study participants were given a bolus 4000U unfractionated heparin (UFH) injection who were then received a heparin infusion at a starting dose of 10 to 14U/kg for a minimum duration of 36 hours. The heparin dose was altered to attain an activated partial thromboplastin time (aPTT) between 1.5 and 3.0 times the normal baseline value. During this period (which is also known as treatment period 1), the aPTT, prothrombin time (PT) and platelet counts were routinely monitored until 24 hours had passed after the UFH infusion was ceased. Following a 2-day washout period, the treatment period 2 started during which the study participants (n=18) received an IV infusion of 40 mg parecoxib twice daily for six consecutive days and a UFH infusion was coadministered with parecoxib on day 5 given at the same dose as in treatment period 1 (Noveck *et al.,* 2001). The results indicate that there were no statistically significant differences in terms of the aPTT, platelet counts and PT between those who received both parecoxib and heparin in treatment period II and the recipients of heparin alone during treatment period

I (Noveck *et al.,* 2001). Hence, parecoxib can be safely coadministed with UFH without affecting any coagulation parameters.

2.3.3 Tolerability and adverse effects

Several adverse events are associated with the intravenously-administered parecoxib (20 or 40mg, single dose) compared with intravenous ketorolac (30mg, single dose), single-dose IV morphine sulphate (4mg) or placebo were found in a multi-centre double-blind placebo-controlled clinical trial involving 202 female patients with moderate to severe pain following abdominal hysterectomy or myomectomy (Langland *et al.*, 2000). The most common adverse events occurring in 10% or more patients irrespective of treatment are nausea, abdominal pain, headache, abdominal fullness, dizziness, back pain, fever, hypoactive bowel sounds, vomiting, tachycardia, somnolence, abnormal breath sounds and pruritus. Most adverse events were mild or moderate in severity and no statistical significant differences with regard to the proportions of adverse events were reported among the intervention groups. Surprisingly, Langland and coworkers (2000) found that parecoxib and ketorolac had greater efficacy in controlling moderate-to-severe pain than a single-dose morphine sulphate among patinets who had undergine abdominal hysterectomies or myomectomies.

In another double-blind placebo-controlled single-centre RCT, 55 patients who underwent abdominal hysterectomies or myomectomies were reandomised into one of the following intervention arms; normal saline placebo (n=18), 20 mg IV parecoxib (n=19) and 40 mg IV parecoxib (n=18) (Tang *et al.,* 2002). The incidence of adverse events reported by these patients were as follows: vomiting 11% (IV 20 mg parecoxib), 0% (IV 40 mg parecoxib) and 6% (saline placebo); pruritus 21% (IV 20 mg parecoxib), 17% (40 mg IV parecoxib) and 28% (saline placebo); and pyrexia 0% (IV 20 mg parecoxib), 11% (IV 40 mg parecoxib) and17% (saline placebo). No other serious adverse

events were reported by Tang and colleague (2002). Besides, there were also no parecoxib-related adverse events when 20 mg or 40 mg IV parecoxib was administered in a double-blind RCT involving 72 female patients experiencing pain following gynaecological surgeries (Kenaan *et al.,* 2001).

With respect to pain control following orthopaedic surgery, Malan *et al.,,*(2003) established that parecoxib, when used concomitantly with PCA morphine, reduced the need for PCA morphine and decreased the time for patients on PCA morphine. Besides, Malan and colleagues (2003) also demonstrated that both IV 20 mg (group 2) or 40 mg parecoxib (group 3) were well-tolerated amongst all adult patients who had primary or revised total hip arthroplasty (n=175), with less number of subjects experiencing vomiting, nausea pruritus, tachycardia and pyrexia compared to the placebo group (group 1) (Malan *et al.,* 2003). Apart from that, a significantly less number of subjects receiving 40 mg parecoxib reported pyrexia ($p<0.01$) and/or emesis ($p<0.05$) compared to placebo (Malan *et al.,* 2003). This evidence hence further confirms the excellent safety profile of parecoxib compared to other pain-control medications.

2.3.4 Pharmacodynamic profiles

As a prodrug, parecoxib undergoes a full and swift bioconversion to valdecoxib which is its pharmacologically-active metabolite. The dose of valdecoxib needed to block the activity of COX-2 by half is 0.005μmol / L and this is much greater higher than the half maximal inhibitory dose for COX-1 activity which is 140 μmol/L (Talley *et al.,* 2000).

With respect to its analgesic effect, paracoxib's efficacy has been demonstrated in patients with postoperative pain following third molar extraction, gynaecological and orthorthopaedic surgery (Barden *et al.*, 2003; Martinez *et al.*, 2007; Mohamad *et al.*, 2014). The analgesic activity of IV parecoxib can also be conspicuously observed in a

murine model of acute inflammation and pain brought about by carrageenan (Talley *et al.,* 2000). Talley and co-workers (2000) demonstrated that the IV parecoxib dosed at 30 mg/kg produced a quick onset of action, resulting in a total reduction of nociceptive sensitivity (hyperalgesia) within 1 hour following its administration (Talley *et al.,* 2000). The authors also established that a parecoxib dose of 5mg/kg was required to create analgesic effects in half of the rats in their murine model. Besides, they also showed that a parecoxib dose of 30 mg/kg produce equivalent clinical end-points as ketorolac administered in the same dose (Talley *et al.,* 2000).

With regard to its gastrointestinal side effects, Hubbard *et al.* (2000) established, in a double-blind RCT, that normal elderly individuals (aged between 65 and 75 years old) who were administered with 40 mg IV parecoxib twice daily for 7 days (n=31) had significantly less susceptibility to gastrointestinal ulceration than those who received 15 mg IV ketorolac group 4 times a day for 5 days after which they were given placebo for 2 days (n=31) (0 vs 23% , $p<0.05$). Moreover, the number of new cases of gastrointestinal lesions (both erosions and ulcers) was also significantly less in parecoxib group. Based upon endoscopic assessment, Hubbard and colleagues (2000) discovered that there were no significant differences in regard to parecoxib-associated gastrointestinal adverse events between the parecoxcib and placebo groups (Hubbard *et al.,* 2000). It was also established that parecoxib did not inhibit arachidonate-induced platelet aggregation when comparison was made with ketorolac (Noveck *et al.,* 2004). In this small open-label, single centre, two-treatment period RCT (n = 18), the authors also found that there was non-significant alteration of platelet function from baseline when 40 mg parecoxib was administered twice daily for 6 consecutive days with an attendant 4000U of unfractionated heparin (UFH) given as a bolus on the 5th day which was then followed by a UFH infusion with an initial dose of 10-14U/kg for 36 hours. This proves that

parecoxib does not cause overt bleeding even when it is concomitantly used with UFH. This proves the excellent safety profile of parecoxib compared to other NSAIDs such as ketorolac (Noveck *et al.*, 2004).

2.4 THE ROLE OF PARECOXIB AS AN ADJUNCT TO ROPIVACAINE IN BRACHIAL PLEXUS BLOCK (BPB)

Thus far, there are only two RCTs which investigated the effect of parecoxib as an adjunct to ropivacaine in BPB setting. Liu *et al.* (2013) conducted a randomized controlled trial (RCT) from January 2009 to November 2010 with 150 Chinese patients scheduled for elective forearm surgery, using a multiple-nerve stimulation technique. Patients were allotted randomly into one of these 3 groups: Group A (n = 50) subjects received single-agent 0.25%% ropivacaine for the axillary BPB; Group B (n = 50) received 0.25% ropivacaine and 20 mg of adjunct parecoxib on the axillary BPB; and subjects in Group C (n = 50) received only 20 mg IV parecoxib. The authors documented the sensory and motor blockade duration, and the highest pain score in a 24-hour period following elective forearm surgery.

The results indicated that parecoxib, when used as an adjunct to ropivacaine, prolonged the motor and sensory block times. However, in those who only received the IV parecoxib injection (Group C), such prolongation in sensory and motor block was not observed. Liu and co-workers (2013) also found lower mean pain intensity scores in Group B than the Groups A and C subjects. According to the authors, 20 mg parecoxib given as an adjunct had significantly lengthened the motor (mean motor block duration: 371 minutes (group A) vs 509 minutes (group B); mean difference = 138 minutes; $p < 0.001$) and sensory (mean sensory block duration: 439 minutes (group A vs 543 minutes (group B); mean difference = 104 minutes; $p = 0.001$) block times when comparisons were made with group A. However there were no significant differences

with respect to the durations of sensory (mean sensory block duration: 439 minutes (group A) vs 457 minutes (group C); mean difference: 18 minutes; p value = 0.300) and motor (mean motor block duration: 371 minutes (group A) vs 414 minutes (group C); mean difference: 43 minutes; p value = 0.800) blockades between group A and C. Besides, the authors also established that the primary block effectiveness was similar in all three groups (96% for group A, B and C). The authors eventually concluded that adjunct parecoxib significantly lengthened the duration of axillary brachial plexus blockade and lessened postoperative pain in subjects who underwent orthopaedic surgeries to their forearms. However, the authors' findings are still inconclusive due to the small sample sizes employed in their trial and the much lower concentration of ropivacaine (0.25% ropivacaine) that they used in their trial.

There was also another recent study conducted by Cherif and coworkers (2014) in Tunisia. They recruited 118 patients who underwent infraclavicular BPB prior to upper limb surgeries. The patients were randomized into 3 intervention arms; 1) bupivacaine and parecoxib (n=44) (group P), 2) bupivacaine and dexamethasone (n=40) (group D) and 3) bupivacaine and saline (n=34) (group C, placebo controls). The authors established that parecoxib had significantly hastened the time to onset of motor and sensory blockades compared to dexamethasone and saline placebo (mean onset of sensory block: 77.82 seconds (group P) vs 383.45 seconds (group D) vs 302.94 seconds (groupd C), p value <0.05;mean onset of motor block: 120.45 seconds (group P) vs 440.5 seconds (group D) vs 316.24 seconds (group C), p value <0.05). However, dexamethasone was found to enhance the quality of analgesia in comparison with parecoxib and saline placebo (mean Visual Analogue Scale (VAS) score on postoperative day 1: 0.7 (group D) vs 2.68 (group P) vs 2.11 (group C), p <0.05; mean time to first analgesic consumption: 2283 minutes (group D) vs 1248 minutes (group P) vs 1408 minutes (group C) . Nevertheless, the

generalisability of the findings is still implausible due to the small sample size of this study, the lack of details on the randomization method and procedure employed by the researchers and the lack of controls on confounders that would make the findings accidental (spurious) and inauthentic.

Nonethless, the efficacy of parecoxib (Liu *et al.*, 2013; Cherif *et al.,* 2014) had also been substantiated by other safety data for parecoxib obtained from murine models and a non-randomized double-blind cross-over trial. Kim *et al.* (2011) demonstrated that an epidural injection of COX-2 is a beneficial therapeutic alternative in the clincal management of pain due to its excellent neurotoxicity profile based on their murine model. They also hypothesized that parecoxib might be a suitable alternative to corticosteroid for the management of pain associated with herniated discs and other spinal pathologies due to its antinoceptive effect on the peripheral and central nervous systems. However, since this is just a murine model and did neither incorporate nor investigate the possible synergestic effects of ropivacaine and parecoxib on the nociceptive transmission and modulation in humans, the findings are still not sufficiently conclusive to effect the ubiquitous use of parecoxib in BPB setting.

Apart from that, Martin *et al.* (2007) conducted a non-randomized double-blind cross-over trial involving twelve (n=12) normal individuals to investigate the effect of IV parecoxib at a dose of 1mg/kg on the electrophysiologic recordings of nociceptive flexion reflex (RII). The RII reflex is an objective physiologic index of the spinal transmission of nociceptive signals. Their results indicated that parecoxib, when compared to placebo, significantly reduced the RII stimulus response curve, suggesting a diminishment of the spinal nociceptive signal transmission in. The authors concluded that the constitutive COX-2 isoform regulates the spinal nociceptive transmission processes and the effect of IV parecoxib on the spinal nociceptive transmission blockade is

suggestive of there is no causal relationship between its anti-inflammatory and anti-nociceptive properties (Martin *et al.,* 2007). Nevertheless, the validity of the study findings had also suffered from the study's sample size, the absence of control subjects and the improper randomization technique used in this trial.

2.5 THE RATIONALE OF THIS STUDY

There is still a paucity of information concerning the role of parecoxib as an adjunct to ropivacaine in supraclavicular BPB, hence creating a gap in clinical knowledge (also known as clinical equipoise) with respect to the exact role of adjunct parecoxib in supraclavicular BPB setting. The only available details that established the utility of adjunct parecoxib in supraclavicular BPB setting are those gained from the small-sized trial conducted by Liu *et al.,* (2013) which are only corroborated by safety data obtained from the murine model (Kim *et al.,* 2011) and the non-randomized cross-over trial (Martin *et al.,* 2007). Furthermore, the usefulness of adjunct parecoxib was only investigated in axillary BPB setting and hence its practicality in other approaches of BPB, for example supraclavicular BPB, is yet to be properly scrutinised. Therefore, this clearly warrants a new clinical trial to further evaluate the extent of adjunct parecoxib's utility in other clinical setting.

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2.7 CONCEPTUAL FRAMEWORK

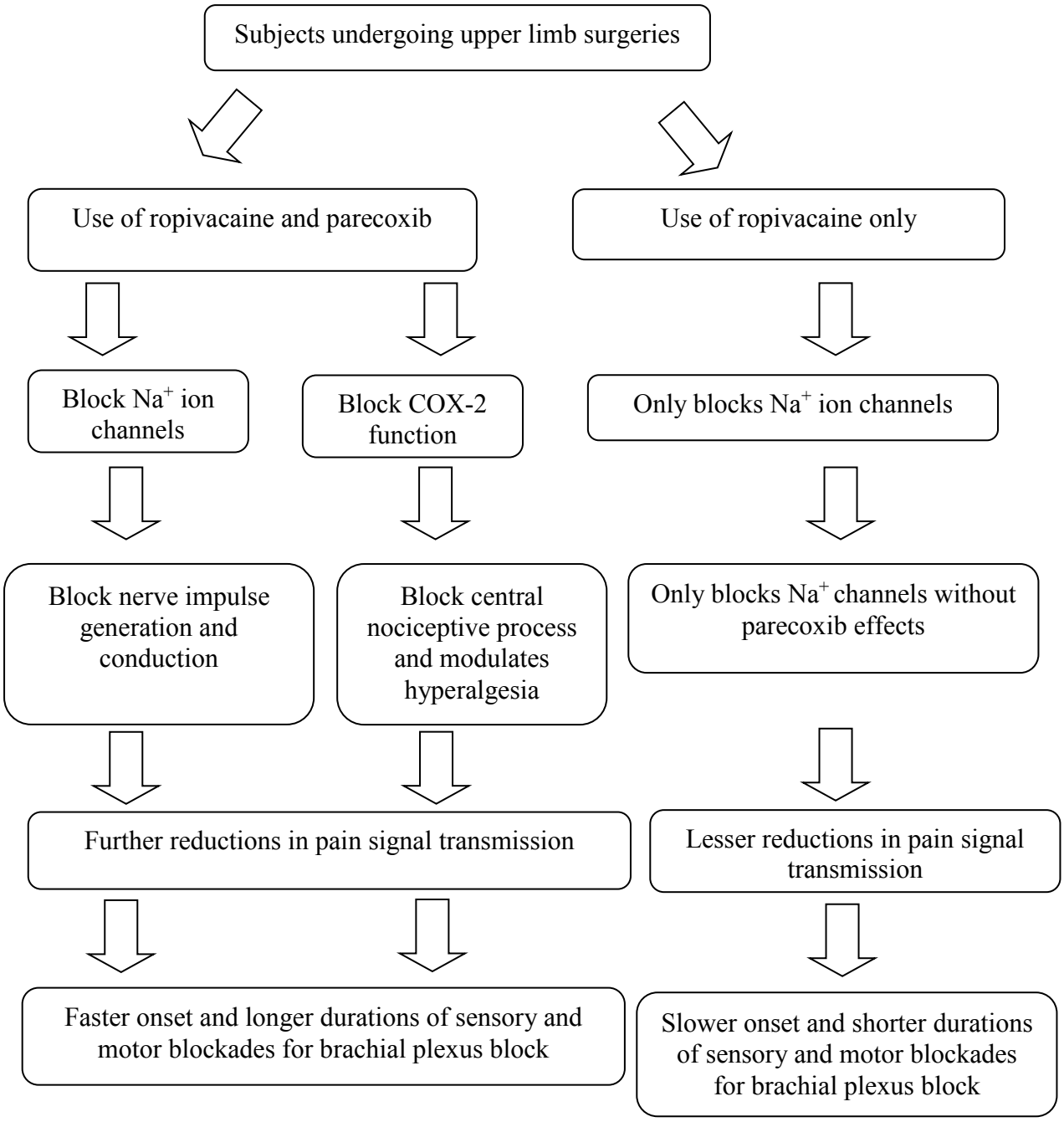


Figure 2.1: The conceptual framework of the synergestic effects of parecoxib and ropivacaine on blocking pain signal transmission resulting in an enhanced onset and durations of sensory and motor blockades in BPB.

SECTION 3

RESEARCH OBJECTIVES

3.1 GENERAL OBJECTIVES:

To investigate the effectiveness of parecoxib 20 mg as an adjunct to ropivacaine 0.75% for ultrasound guided supraclavicular block for upper limb surgery.

3.2 SPECIFIC OBJECTIVES:

1. To compare the onset of the sensory block between 20mg of parecoxib in 0.75% ropivacaine and plain 0.75% ropivacaine.
2. To compare the onset of the motor block between 20mg of parecoxib in 0.75% ropivacaine and plain 0.75% ropivacaine.
3. To compare the degrees of sensory and motor block after 30 min between 20mg of parecoxib in 0.75% ropivacaine and plain 0.75% ropivacaine.
4. To compare the duration of the sensory block between 20mg of parecoxib in 0.75% ropivacaine and plain 0.75% ropivacaine .
5. To compare the duration of the motor block between 20mg of parecoxib in 0.75% ropivacaine and plain 0.75% ropivacaine .

3.3 RESEARCH QUESTIONS

1. Do subjects receiving 20mg of parecoxib in 0.75% ropivacaine significantly differ in terms of the onset of the sensory block when compared to those recipients of single-agent 0.75% ropivacaine?
2. Do recipients of 20mg of parecoxib in 0.75% ropivacaine significantly differ with respect to the onset of the motor block when they are compared with those recipients of single-agent 0.75% ropivacaine?

3. Is there any significant difference between subjects receiving 20mg of parecoxib in 0.75% ropivacaine and single agent 0.75% ropivacaine with regard to the degrees of sensory and motor block?
4. Are those receiving 20mg of parecoxib in 0.75% ropivacaine significantly differ from the recipients of single-agent 0.75% ropivacaine with respect to the duration of sensory block?
5. Is there any significance difference in terms of duration of motor block between the recipients of 20 mg parecoxib in 20% ropivacaine and those receiving single-agent 20% ropivacaine?

3.4 RESEARCH HYPOTHESES

1. **Null hypothesis (H_0):** There is no significant difference in the onset of the sensory block is faster in 20mg of parecoxib in 0.75% ropivacaine in comparison to plain 0.75% ropivacaine.
2. **Null hypothesis (H_0):** There is no significant difference in the onset of the motor block is faster in 20mg of parecoxib in 0.75% ropivacaine in comparison to plain 0.75% ropivacaine.
3. **Null hypothesis (H_0):** There are no significant differences in the degrees of sensory and motor block after 30 min is higher in 20mg of parecoxib in 0.75% ropivacaine in comparison to plain 0.75% ropivacaine
4. **Null hypothesis (H_0):** There is no significant difference in the duration of the sensory block in 20mg of parecoxib in 0.75% ropivacaine in comparison to plain 0.75% ropivacaine
5. **Null hypothesis (H_0):** There is no significant difference in the duration of the motor block in 20mg of parecoxib in 0.75% ropivacaine in comparison to plain 0.75% ropivacaine.

SECTION 4

RESEARCH METHODOLOGY

4.1 STUDY DESIGN

A prospective, single center, two-parallel group, single (observer)-blinded controlled trial involving surgical patients undergoing upper limb surgeries at the HUSM surgical theatres.

4.2 STUDY PERIOD AND PERIOD OF RECRUITMENT

The total study duration is 10 weeks and the period of patient recruitment is from 20th June 2017 till 28th August 2017.

4.3 TRIAL CENTRE

Hospital Universiti Sains Malaysia (HUSM) is the main teaching hospital for the Eastern Coastal states of Peninisular Malaysia. It is situated in Kubang Kerian, Kelantan and handles primary-care referrals from all the states in the eastern region of Peninsular Malaysia (Kelantan, Terengganu and Pahang). Hence, it can be considered as one of the chief tertiary care centres that dispenses a modern specialty care for nearly a third of the whole population in Peninsular Malaysia.

Annually, HUSM accepts almost 2000 surgical cases, of which nearly 19.65 percent are elective or semi-emergency surgical patients that require upper limb procedures (393 cases). This provides the study investigators ample resources for the acquisition of patients that meet the trial criteria which ensures in the accomplishment of the intended sample size.

4.4 REFERENCE AND SOURCE POPULATION

The reference population is all elective or semi-emergency surgical patients who underwent upper-limb surgical procedures and supraclavicular BPB in Kelantan. The source population is all elective or semi-emergency surgical patients receiving upper-

limb surgical procedures and supraclavicular brachial plexus block who resided in Kota Bharu.

4.5 SAMPLING FRAME

All subjects who fulfilled the eligibility criteria (both inclusion and exclusion) and had upper-limb surgical procedures and supraclavicular BPB in the HUSM between 20th June 2017 and 28th August 2017 were included in the sampling frame.

4.6 SAMPLING METHOD

Despite sufficient potential subjects for their recruitment into this trial, convenient sampling had to be used due to the time constraint imposed by the urgency for thesis submission within the tight submission window (early November).

4.7 STUDY SUBJECTS

All patients that fulfilled the eligibility (inclusion and exclusion) criteria and consented for study participation.

4.8 ELIGIBILITY CRITERIA

4.8.1 Inclusion criteria

I) Aged between 18 to 70 years old

II) Subjects with the American Society of Anaesthesiologists (ASA) physical status grade 1 to 2

III) The expected duration of surgery was between 1 and 4 hours.

4.8.2 Exclusion criteria

I) Subjects who refused to brachical plexus block (BPB)

II) Known allergies to parecoxib, other NSAIDS and anaesthetic agents.

III) Pregnancy

IV) History of prior brachial plexus injury

V) History of chronic pain that requires long-term use of analgesic medications

VI) Coagulopathy

VII) Systemic infection or local infection at the site of injection

VII) Known neuropathy for the limb undergoing surgical procedures.

4.9 OPERATIONAL DEFINITIONS OF VARIABLES

a) **Independent variables**

i) **Age:** The age of patients (in years) when BPB was performed. Measured and recorded as a strictly positive continuous variable.

ii) **Gender:** The gender of a subject. Recorded as a categorical variable with 0 = male (the baseline group) and 1 = female.

iii) **Ethnicity:** Subject's racial origin. Recorded as a categorical variable with 0 = Malay (the baseline group), 1 = Chinese, 2 = Indian, 3 = Others (such as Siamese)

iv) **The American Society of Anaesthesiologist (ASA) grades:** Recorded as a categorical variable with 0 = Grade 1 (the baseline group), 1 = Grade 2.

v) **Weight:** The weight of a study participant measured in kilograms measured during he pre-surgical assessment. Recorded as a strictly positive continuous variable.

vi) **Intervention groups:** Recorded as a categorical variable with 0 = 0.75% Ropivacaine only group (the baseline group) and 1 = 0.75% Ropivacaine + adjunct 20 mg parecoxib group.

b**) Dependent (outcome) variables**

i) **Onset of sensory block:** Time required for a decrease of sensation to 30% or less by comparison to the contralateral limbs as a reference (Duma *et al.,* 2005). Measured in minutes and recorded as a numerical variable.

ii) **Onset of motor block**: the time from injection of local anesthetic mixture until a reduction in motor power to grade 3 or 4 ensued (Ammar and Mahmoud, 2012). Measured in minutes and recorded as a numerical variable.

iii) **Sensory block duration:** The time from injection of local anaesthetic mixture to complete recovery from cold and pain sensation as tested by an alcohol swab and pin prick respective in all dermatomes of the brachial plexus (C5-T1). Measured in hours and recorded as a continuous variable

iv) **Motor block duration:** the time from injection to complete recovery of motor function in all nerve dermatomes. Measured in hours and recorded as a continuous variable.

v) **Sensory and motor blockades at 30 minutes:** The presence of complete sensory (grade 2) and motor (grade 4) blockades at 30 minutes following the BPB institution.

c) **Other relevant clinical variables**

i) **Time 1st PCA:** The time taken from the end of the surgery until the delivery of the first PCA morphine. Measured and recorded as a strictly positive numerical variable

ii) **Volume PCA:** The total volume of PCA morphine administered to the patients after surgery until the patient was discharged from the ward. Measured in mls and recorded as a numerical variable.

iii) **PCA demand:** The total frequency of morphine demand over a period of 24 hours. Measured and recorded as a strictly positive numerical count variable.

iv) **Sensory block grades:** This was assessed using the a 3-point scale utilised by Crews *et al.* (2002). There are 3 grades for this variable;

- Grade 0 = normal sensory response
- Grade 1 = reduced sensory perception (partial sensory blockade)
- Grade 2 = no sensation (complete sensory blockade).

Recorded as 0 = normal (baseline group), 1 = reduced , 2 = absent.

v) **Motor block grades:** The scale used by Borgeat, Ekatodramis and Durmont (2001) are employed to grade the magnitude of motor block. This scale has 4 grades:

- Grade 1: ability to flex or extend the forearm
- Grade 2: ability to flex or extend only the wrist and fingers
- Grade 3: ability to flex or extend only the fingers
- Grade 4: inability to move the forearm, wrist, and fingers

Recorded as 0 = Grade 1 (baseline group), 1 = Grade 2, 2 = Grade 3, 3 = Grade 4.

vi) **Surgical sites:** The exact location where surgery to the upper limb was carried out. Recorded as 1 = Arm, 2 = Forearm, 3 = Hand, 4 = Fingers.

vii) **VRS :** The visual rating score (VRS) which was recorded at 1, 2, 4, 12, 24 hours post operatively. Its range is between 0 and 10. Recorded as a strictly-positive numerical variable.

viii) **Preoperative VRS:** The VRS recorded prior to supraclavicular BPB.

4.10 STUDY PROTOCOL

4.10.1 Randomisation method and allocation concealment

After receiving the ethical clearance from USM's Ethics Committee, the patient recruitment for this trial commenced. The study subjects were firstly screened against the eligibility criteria and those who met the criteria, informed consents were acquired from each one of them.

The study participants were then block-randomized using a block size of 4 with a balanced 1:1 allotment ratio without any covariate stratification. This method of randomization, instead of the simple randomization technique, was utilized to ensure that the number of study participants is equal in both intervention groups. In this case, for every block of four study participants, each two of them will be allotted to one intervention arm. The block randomization was performed using permuted block design, with the random numbers generated by a random number generator package in Stata 9.0 (StataCorp, College Station, Texas). This randomization process was performed by an

independent third-party statistician (Mr Muhammad Irfan bin Abdul Jalal, Graduate Statistician (GradStat), the Royal Statistical Society, UK).

To ensure selection bias was prevented, the allocation sequence was kept inside a password-protected STATA 9.0 file which was only accessible to the independent third-party statistician. The sequence of treatment allotment was only revealed after a study participant was properly recruited and subsequently randomized to treatment allotment. To prevent ascertainment and performance bias, the study participants and the independent assessors (2^{nd} medical officer) were shielded from the knowledge of the type of intervention received. However, the intervention was administered by the primary investigator (VG) who was not blinded to the kind of intervention received.

4.10.2 Details of the administered interventions

The premedication was first prescribed in the morning of the surgery. Upon arrival in the OT, all patients were monitored based on the standard anaesthesia monitoring and for relevant clinical parameters (baseline blood pressure (BP), saturation pressure of oxygen (spO_2), electrocardiography (ECG) and heart rate (HR)) which were obtained using the electric B30 monitor (Stimuplex D® plus 50mm, B. Braun, Melsungen, Germany) and documented before the BPB commenced. Subsequently, IV access of at least 20 G size was inserted on the selected hand of study participants.

Intravenous (IV) loading of Ringer's Lactate solution (B. Braun, Melsungen, Germany) 10 ml/kg was administered before performing the block. Brachial plexus block (BPB) was performed in the block corner at the recovery bay. Drugs regime and other standard equipment for BPB was prepared and acquired and these include:

- 5 mls of Lignocaine 2% for skin infiltration
- 20 mls of Ropivacaine (Naropin®, Astrazeneca) 0.75% + 20mg Parecoxib (Dynastat®, Pfizer)(1 mls) ---Group A

- 20mls Ropivacaine 0.75% + 1 ml Normal Saline----Group B.
- Ultra Sonographic machine (Mindray® Version M5, Mindray, Shenzen, China) with high frequency (10-15MHz) linear probe
- 50 to 80mm 22 G insulated peripheral nerve block needle. Vygon, France
- 2% chlorhexidine in 70% isopropyl alcohol solution for skin cleaning

The BPB was implemented by a single operator and assessed by the independent 2nd medical officer in-charge who was blinded and oblivious to the treatment administered. No peripheral nerve stimulator was employed during the procedure. The detailed descriptions of the techniques utilized in the BPB are as follows:

- The block site will be cleaned and draped. The US probe also was draped for the procedure as well.
- SCB technique:
    - Subjects were positioned semi-recumbent with the head turned to the contralateral side with the ipsilateral shoulder slightly elevated with the pillow.
    - An exploratory scan was performed in all patients before the block, by positioning the probe on a coronal oblique plane above the clavicle.
    - Hypoechoic and pulsating supraclavicular artery was then identified, which was lying above the hyper echoic first rib. While maintaining the view of the artery, the probe was then angled until both the first rib and the pleura were also seen simultaneously.
    - After skin preparation and draping, the probe was next placed in the supraclavicular fossa and subcutaneous infiltration will be given on the targeted needle side

- The needle was then inserted from lateral to medial direction in the long axis of the transducer (in-plane technique).
- Nineteen (19) ml of 0.75% ropivacaine and 1 ml of 20 mg of parecoxib (Group I: parecoxib + ropivacaine) or 19 mls of 0.75% alone plus 1 ml of normal saline (Group II: ropivacaine alone) was then injected at the "corner pocket". Adrenaline was not added into any solution.
- The remaining 5 ml was later injected to a point approximately level with the superior/ cephalad aspect of the subclavian artery, but no further than 1 cm lateral to the artery

Block performance-related pain was then evaluated immediately after removing the needle by asking the patient to verbally quantify the level of pain using a score between 0 to 10 (0 meaning no pain, 10 meaning excruciating pain). The study participants were withdrawn from the trial and rescue medications were given if one of the following withdrawal criteria occurred:

- Patient developed local anaesthetic toxicity (seizure)
- Patient developed hemodynamically instability bradycardia/hypotension)
- Patient developed anaphylaxis

The procedures for the assessment of sensory and motor block are as follows:

- Assessment of sensory block:
  - Sensory blockade was assessed every 5 minutes up to 30 minutes following the completion of administration of intervention.
  - Sensory loss was confirmed by the loss to cold sensation using 10 mls cold saline bottle and pinprick sensation using 23G needle in all dermatomes supplied by the brachial plexus (C5-T1).
  - Time zero was defined as the time at which LA was completely injected.

- Sensory block success was defined as complete pin-prick sensory blockade (grade II based on the grading scale employed by Crews *et al.* (2002)) in all dermatomes of the brachial plexus (C5-T1).
- The block was considered incomplete if any supplemental local anesthetic is needed for complete anesthesia.
- The block was considered failed if the desired volume did not provide complete anesthesia or conversion to general anaesthesia was required prior to surgery.
- General anaesthesia was routinely performed with intravenous induction (sedation) agent, short acting opiods and muscle relaxant

- Assessment of motor block:
  - Motor blockade was also evaluated every 5 minutes up to 30 minutes following the completion of administration of intervention.
  - Motor block was assessed by subject's capability of flexing his / her elbow and hand against gravity. This was then graded according to the scale utilised by Borgeat, Ekatodramis and Durmont (2001).
  - Motor block success was considered achieved when the motor power was reduced to grade 3 or more based on the criteria used by Ammar and Mahmoud (2012).
- Intra-surgical assessment:
  - Requirement of block supplementation, surgical wound infiltration and patient requested sedation or general anaesthesia
  - Surgical anaesthesia success was defined as surgery without the requirements of block supplementation, general anesthesia (administered for incomplete block) or surgical site infiltration

- Haemodynamic monitoring was performed at baseline, after LA injection, after 15 min, 30 min, 1 hour of block procedure & after completing surgery.

- Postoperative assessment:
  - Sensory and motor blockade durations were assessed on half-hourly basis (up to 12 hours postoperatively), during the post surgical period.
  - Patient-controlled analgesia (PCA) morphine or IV tramadol was given as rescue analgesia.
  - Pain scores were assessed using the visual rating scale (VRS) (0-10) where pain was evaluated when the patients were resting at 1, 2, 4, 12, 24 hours postoperatively.
  - The duration of analgesia (time interval from the completion of local anesthetic administration until the first need of rescue analgesia in the form of PCA morphine or IV tramadol) and the amount of morphine or tramadol consumed during the postoperative 24 hours were also documented.
  - Any evidence of complications (e.g., bruises/swelling at the block site, chest pain/ breathing difficulty, dysaesthesia/ muscle weakness in the operated extremity not related to the site of operation) were also recorded.
  - Surgeons were alerted to report any neurological problems not related to surgery during the clinical rounds prior to the patients were discharged from the hospital.
  - Anaesthetic preferences (one of the following: 1) the BPB; 2) block under deep sedation; 3) block under GA).
  - Preferred block for future hand operations was then recorded.

4.11 SAMPLE SIZE DETERMINATION

Sample size calculation was performed using Power & Sample Size (PS®) software version 3.1.2 (Dupont and Palmer, Vanderbilt, Nashville, Tenessee, 2014) based on the following outcome parameters:

i) Motor Block Duration –based on Liu et.al, 2013

We are planning a study of a continuous response variable from independent control and experimental subjects with 1 control per experimental subject.In a previous study the response within each subject group was normally distributed with a standard deviation of 139 minutes (Liu *et al.* 2013). If the true difference in the experimental and control means of motor block time is 138 minutes and assuming the attrition (drop-out) rate was 20%, 44 subjects (22 in each intervention arm) were required to reject the null hypothesis that the population means of the experimental and control groups are equal. The type I (α) and type II (β) were fixed at 0.05 and 0.1, respectively and hence the power (1-β) of the study is 0.9.

ii) Sensory Block Duration – based on Liu et.al, 2013

We are planing a study of a continuous response variable from that required 1 control per experimental subject (1:1 control-to-experimental unit ratio). In a previous study, the response within each subject group was normally distributed with standard deviation of 140 minutes (Liu *et al.* 2013). If the true difference in the experimental and control means of sensory block time is 104 minutes and assuming the attrition (drop-out) rate is 20%, we required 39 experimental subjects and 39 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power, 1 - β) of 0.9.The type 1 error probability (α) associated with this test of this null hypothesis is 0.05.

4.12 ETHICAL ISSUES AND CONSENT ACQUIREMENT PROCESS

Since this study involves the use of invasive interventions on human subjects, it therefore requires ethical review of study protocol by the institutional review board. To meet this requirement, an ethical clearance was sought from USM Human Research Ethics Committee, which was obtained on **20th June 2016 (Human Research Ethics Committee (HREC) reference number: USM/JEPeM/16010033**). Besides, this study was also conducted in accordance to the principles of ethics on human research that had enacted by the Declaration of Helsinki during the 18th World Medical Association General Assembly, 1964).

Voluntary written informed consent was acquired from each study participant. They were informed about their rights to withdraw from the study at any stage and for any reason without jeopardizing their subsequent medical care. To protect the confidentiality and anonymity of each study participant, the names of the subjects were not documented in the data collection sheet and each subject received a set of random number produced by the Microsoft Excel random number generator for identification purposes. Apart from that, the data collection sheet were kept by the principal investigator at a secured place and the SPSS file, in which all the research data was stored, was password-protected to prevent any accidental or intentional breach of participant's confidentiality.

To ensure that no subjects were recruited more than the minimum number required to significantly demonstrate the difference in the study outcomes between the 20mg parecoxib + 0.75% ropivacaine and single-agent 0.75% ropivacaine groups, interim analyses were conducted after every 6 subjects recruited. These were done after the number of recruited subjects exceeded 20 subjects per group. Any toxicity or unanticipated harms associated with the study interventions were recorded and reported using JEPeM-USM-FORM 3(G):2014 Adverse Events Report. Opinions from

independent study adjudicators which consist of USM ethical review board members were sought to determine whether the trial should be stopped prematurely due to obvious patterns of benefits or harms observed from the interim analyses. If the trial is deemed to be ended prematurely, the date and reason for such early trial termination should be notified to the JEPeM committee using JEPeM-USM-FORM 3(E) 2015.

4.13 STATISTICAL ANALYSIS

All analysis was implemented using the Statistical Package for Social Science (SPSS) for Windows version 20 IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) and STATA version 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

The data was firstly assessed for any inaccurate data entry and missing data. The data was cross-checked with the information in data collection sheet to optimise accuracy of data entry. Multiple imputation was then utilised as remedial measures to rectify and mitigate the effects of missing data on the accuracy of subsequent analyses. Besides, missing data were treated as missing at random (MAR) based upon Rubin's missing data mechanism (Little and Rubin, 2002).

Numerical data was then descriptively summarised in mean and standard deviation (or median and interquartile range if the data were not normally distributed) whilst frequency and percentage were the descriptive summaries for categorical data. For continuous outcome variable, the normality of each outcome variable was then **subjectively** evaluated by histogram with overlying normal distribution curve, box and whisker plot and stem and leaf diagram. Besides, Shapiro-Wilks (since the sample size is small, i.e. less than 50) was also utilised to provide **objective assessments** of normality assumption. Any significant p-value ($p<0.05$) indicates that the normality (Gaussian) assumption had been violated. These assessments were then further strengthened by the

objective evaluation of the normality assumption using Fisher's coefficient of skewness, whose formula is presented as follows:

Fisher's coefficient of skewness = Skewness / standard error of skewness

Any variable that exhibits a Fisher's coefficient of skewness that is nearly twice as large as the standard error of skewness (1.96 x SE) would indicate the presence extreme skewness (i.e. more than 1.96 or less than -1.96) and as a result, the normality (Gaussian) assumption was assumed to be violated. Besides, the kurtosis (the peakness of the distribution) was also examined using the same cut-off (±1.96) to ensure that the peak of the distribution conformed to the bell-shaped characteristic of the normal (Gaussian) distribution. The final verdict on the normality assumption of a distribution was based upon whether such distribution "passed" both objective and subjective evaluations of its distributional characteristics.

For categorical outcomes, either Pearson χ^2 or Fisher's exact test was used to assess the significance of association between the intervention arms and the the proportions of successful complete sensory block after 30 minutes. For numerical outcomes, either independent t-test (with or without adjustment for the violation of homogeneity of variance assumption) or Mann-Whitney test was used, depending upon whether the normality assumption was violated or not. However, if both normality and homogeneity of variance assumptions were violated, the adjusted independent-t test (corrected for degree of freedom) was used since it controls type I error rate better than the Mann-Whitney U test (Ruxton 2006).

The statistical analysis conducted for each objective clinical outcome are given on the next page:

Table 4.1: The statistical methods used for each clinical outcome

Objective parameters	Statistical analysis
The onset of the sensory block	Independent t / Mann-Whitney test[a]
The onset of the motor block	Independent t / Mann-Whitney test[a]
The degree of sensory and motor block 30 minutes after BPB	Pearson Chi Square / Fisher's Exact test[b]
The duration of sensory block	Independent t / Mann-Whitney test
The duration of motor block	Pearson Chi Square / Fisher's Exact test[b]

[a]Non-parametric analogue of independent-t test. It is used when the normality assumption is violated

[b]Used when the percentage of cells with expected value of less than 5 is more than 20%

The level of significance was set at 0.05 and any p value that was less than 0.05 ($p<0.05$) is considered significant. The analysis was performed in accordance to the intention-to-treat (ITT) principle. A step-by-step summary of statistical methods employed for the analysis of this trial's data is given by figure 4.1 on the next page.

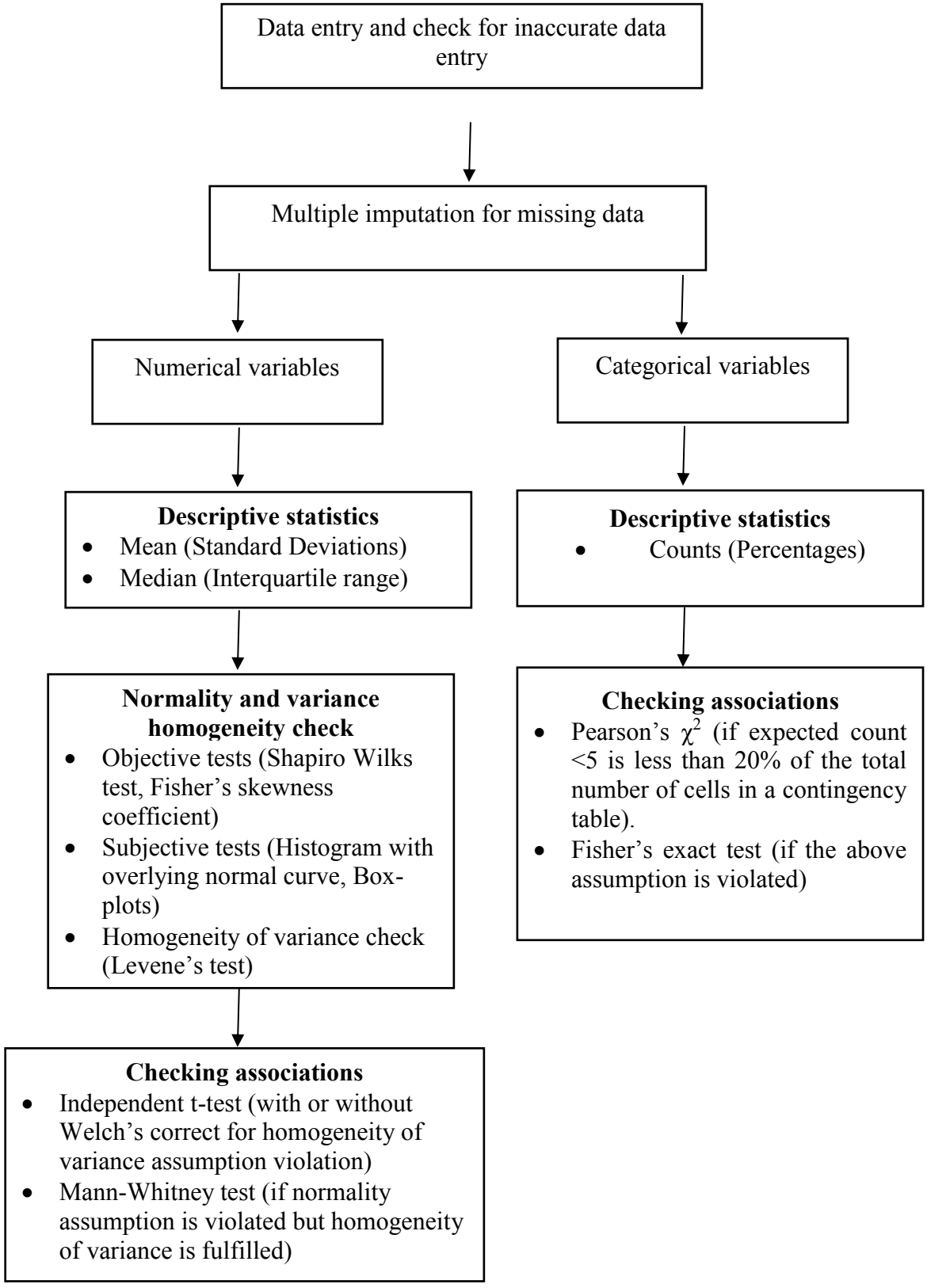


Figure 4.1: The step-by-step summary of the statistical methods used in this trial.

4.14 TRIAL FLOW CHART

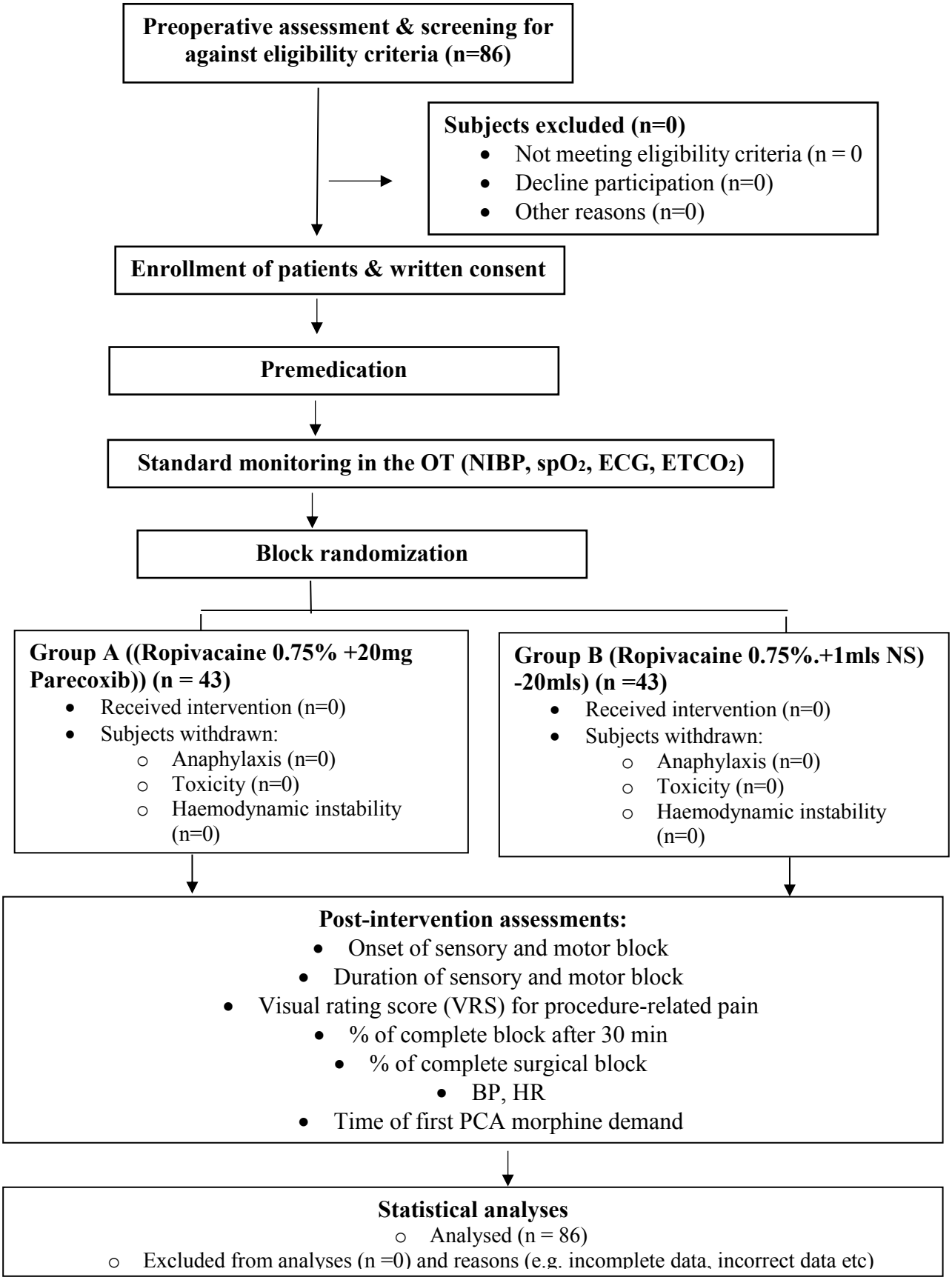


Figure 4.2: The flowchart of this study (prepared according to the CONSORT guideline).

SECTION FIVE

STUDY RESULTS

5.1 THE CLINICO-DEMOGRAPHIC PROFILES OF THE STUDY PARTICIPANTS

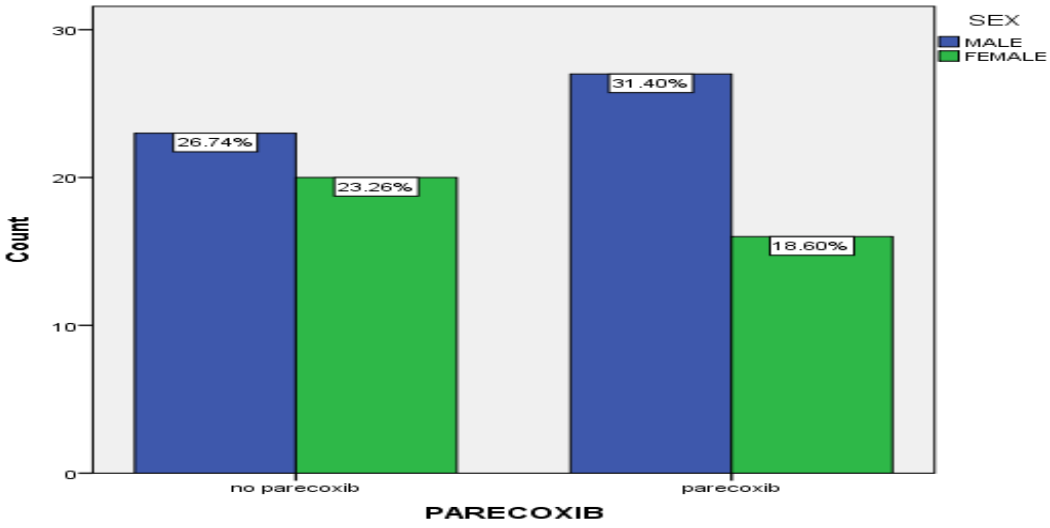
On the whole, 86 study participants were included in the analysis. The mean age and weight of the participants are similar between the two groups of interventions. Apart from that, both intervention groups exhibit similar patterns of VRS pain score, volumes of local anaesthetics received, supplemental local anaesthetics received and PCA morphine profiles.

With regards to gender and ethnic compositions, both intervention groups, in general, demonstrated similar proportions of females, males and each ethnic groups. Furthermore, both intervention arms have also relatively the same proportions of participants for each ASA grade. Nevertheless, with respect to the specific surgical sites, more study participants in the ropivacaine group had surgeries to their arms whilst more patients in the combined parecoxib-and-ropivacaine group had surgeries to their forearms. Besides, there are also two missing data in this group. However, it can be safely said that proportions of surgical sites are roughly similar in both groups. For further information, refer to table 5.1 and figures 5.1-5.3.

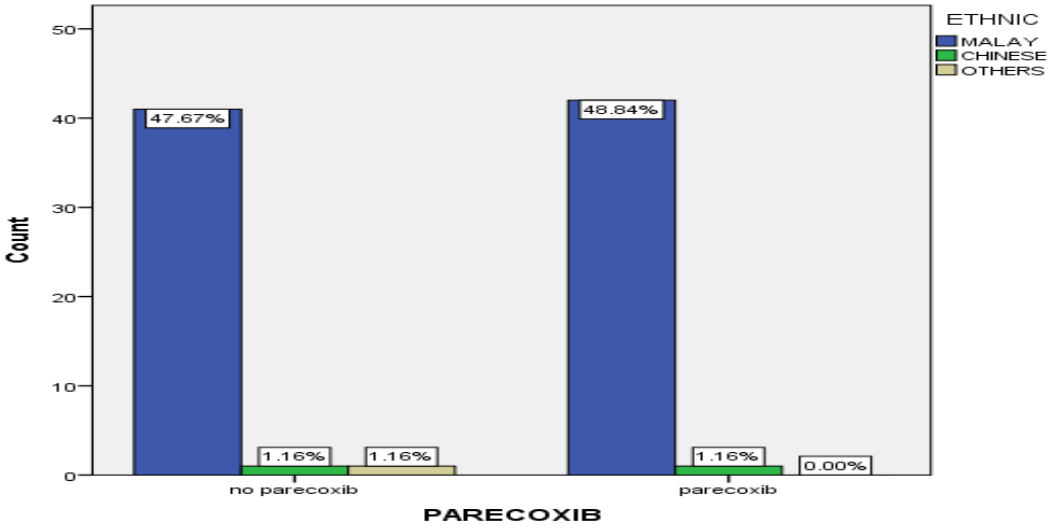
Table 5.1: The clinico-demographic characteristics of study participants (n = 86)

Parameters	Parecoxib + Ropivacaine (n=43) Mean (SD)	n(%)	Ropivacaine (n=43) Mean (SD)	n(%)
Age	43.8 (13.7) 47.5 (26)[a]		46.3 (12.6) 51.0 (21.0)[a]	
Weight (kg)	60.8 (7.6) 60.0 (13.0)[a]		61.6 (7.6) 60.0 (12.0)[a]	
VRS pain score	1.0 (0)		1.0 (0)	
LA volume	20.0 (0)		20.0 (0)	
Supplement LA volume	0.0 (0)		0.0 (0)	
Time to 1st PCA morphine (hours)	0.0 (0)		0.0 (0)	
PCA Morphine demand within 24 hours (counts)	0.0 (0)		0.0 (0)	
PCA Morphine given within 24 hours (counts)	0.0 (0)		0.0 (0)	
Gender				
Female		16 (37.2)		20 (46.5)
Male		27 (62.8)		23 (53.5)
Ethnicity				
Malay		42 (97.7)		41 (95.3)
Chinese		1 (2.3)		1 (2.35)
Others		0 (0)		1 (2.35)
Surgical sites				
Forearm		14 (32.5)		8 (18.6)
Arm		21 (48.9)		31 (72.1)
Hand		0 (0)		1 (2.3)
Fingers		6 (14.0)		3 (7.0)
Missing		2 (4.6)		0 (0)
ASA grades				
I		7 (16.3)		6 (14.0)
II		36 (83.7)		37 (86.0)
Preoperative VRS score	0.0 (0.0)		0.0 (0.0)	

[a]Median (Interquartile range)

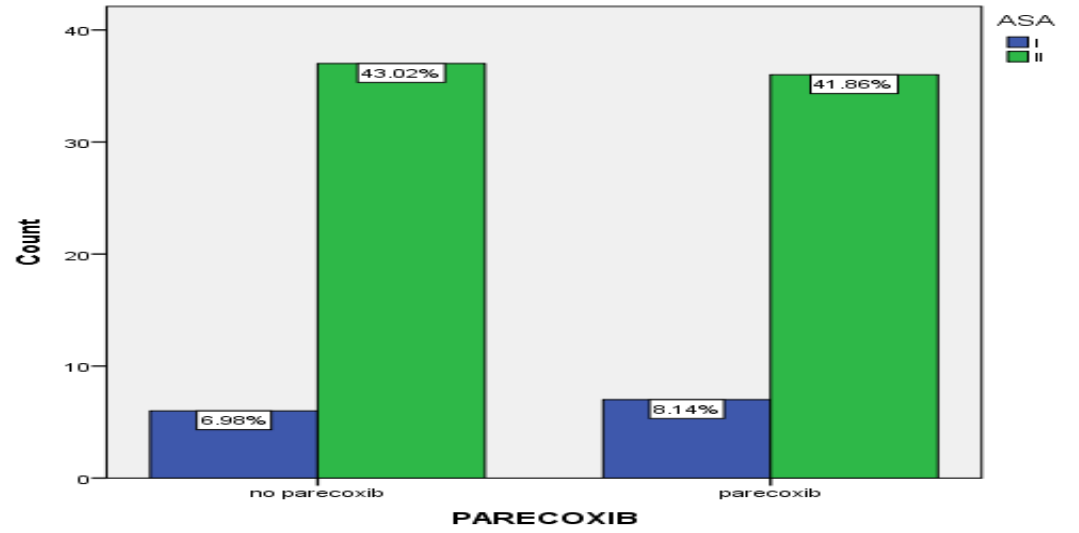


a) Gender

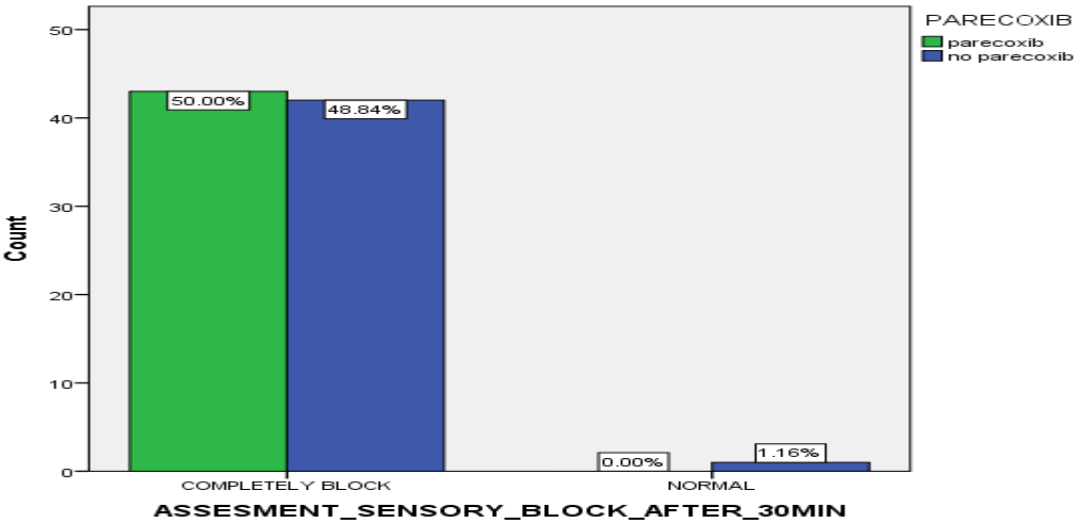


b) Ethnicity

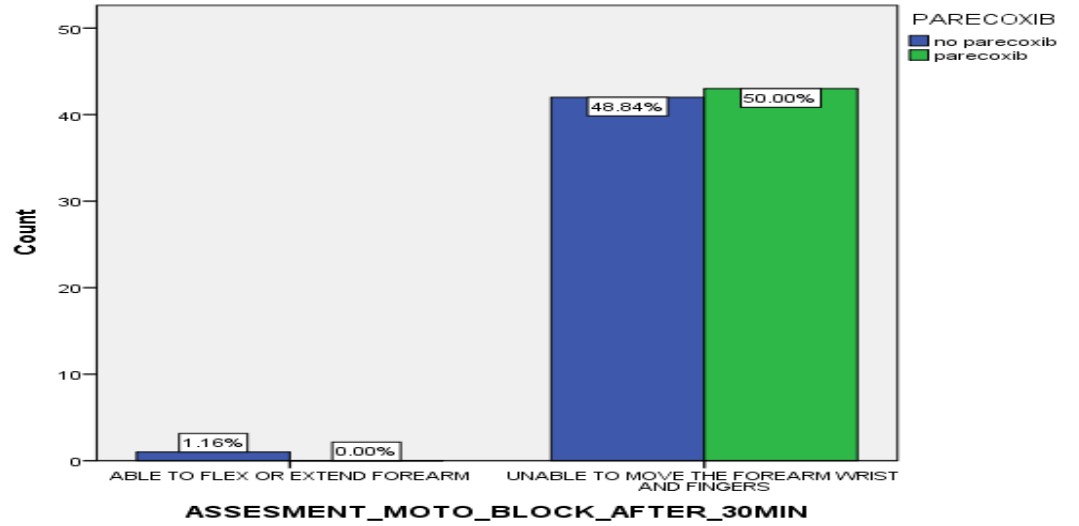
Figure 5.1 (a-b): The proportions and percentages of subjects in each intervention arm, as stratified by gender and ethnicity of subjects



a) ASA grades



b) Sensory block



c) Motor block

Figure 5.2 (a-c): The proportions and percentages of ASA grades, sensory and motor block status at 30 minutes post BPB as stratified by the intervention arms.

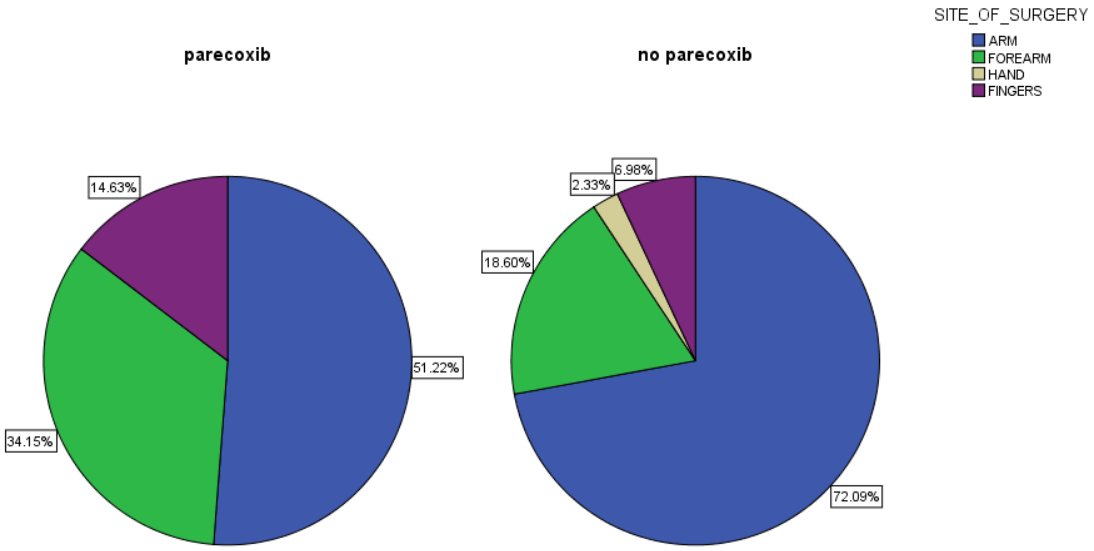


Figure 5.3: Pie charts detailing the percentages of subjects in each intervention arm as stratified by the surgical sites.

5.2 THE STATISTICAL EVALUATIONS OF THE NORMALITY AND HOMOGENEITY OF VARIANCES ASSUMPTIONS FOR CONTINUOUS OUTCOME VARIABLES

Based on the results presented in table 5.2 and figures 5.4 – 5.9, it can be conspicuously observed that all continuous outcome variables have violated the normality (Gaussian) assumptions. This claim is corroborated by the significant Shapiro-Wilks test results for the all outcome variables and the large values for the a significant proportion of Fisher's coefficients of skewness. Besides, based on the inspection of figures 5.4 – 5.9, all of the histograms with the overlying distribution curves do not conform to the bell-shaped characteristic of normal distributions and exhibit extreme skewness with or without "peaked" (leptokurtic) or flat (platykurtic) at the symmetrical point. This fact is further augmented by the uneven lengths of box parts of the box plots when comparisons were made with their whiskers. All these are tell-tale signs of distributions that have violated the characteristics of normal distribution curves.

On the other hand, the homogeneity of variances assumption is deemed fulfilled for the majority of continuous outcome variables since the p values for the Levene's tests are not significant. However, for motor block duration, the p value is significant, indicating that the homogeneity of variances assumption is not tenable. We can conclude for this variable, the variances are inhomogeneous between the two intervention groups (i.e there is a heteroscedasticity in the variances).

From these results, we conclude that the appropriate statistical test is Mann Whitney test for all continuous outcome variables, except for motor block duration (in this case, the Welch's version of the independent t-test is the most suitable alternative).

Table 5.2: The objective statistical tests for the evaluation of the assumption of normality

Parameters	Shapiro-Wilks test		Fisher's Skewness Coefficients	
	Par+Ropi[b]	Ropivacaine	Par+Ropi[b]	Ropivacaine
Age	<0.001	<0.001	1.04	-2.58
Weight	0.019	0.003	1.56	-0.31
Sensory block onset	<0.001	0.001	2.61	2.70
Motor block onset	0.001	<0.001	-1.01	-0.84
Sensory block duration	0.001	0.001	1.62	0.13
Motor block duration	<0.001	<0.001	0.69[a]	-1.29

[a]Kurtosis (peakness of the distribution) indicates normality assumption is violated.
[b]Parecoxib + Ropivacaine

Table 5.3: The results of Levene's tests for assessing the homogeneity of variances assumption

Parameters	F statistics	p values
Age	1.239	0.269
Weight	0.064	0.801
Sensory block onset	0.003	0.957
Motor block onset	2.000	0.161
Sensory block duration	0.517	0.474
Motor block duration	7.564	**0.007**

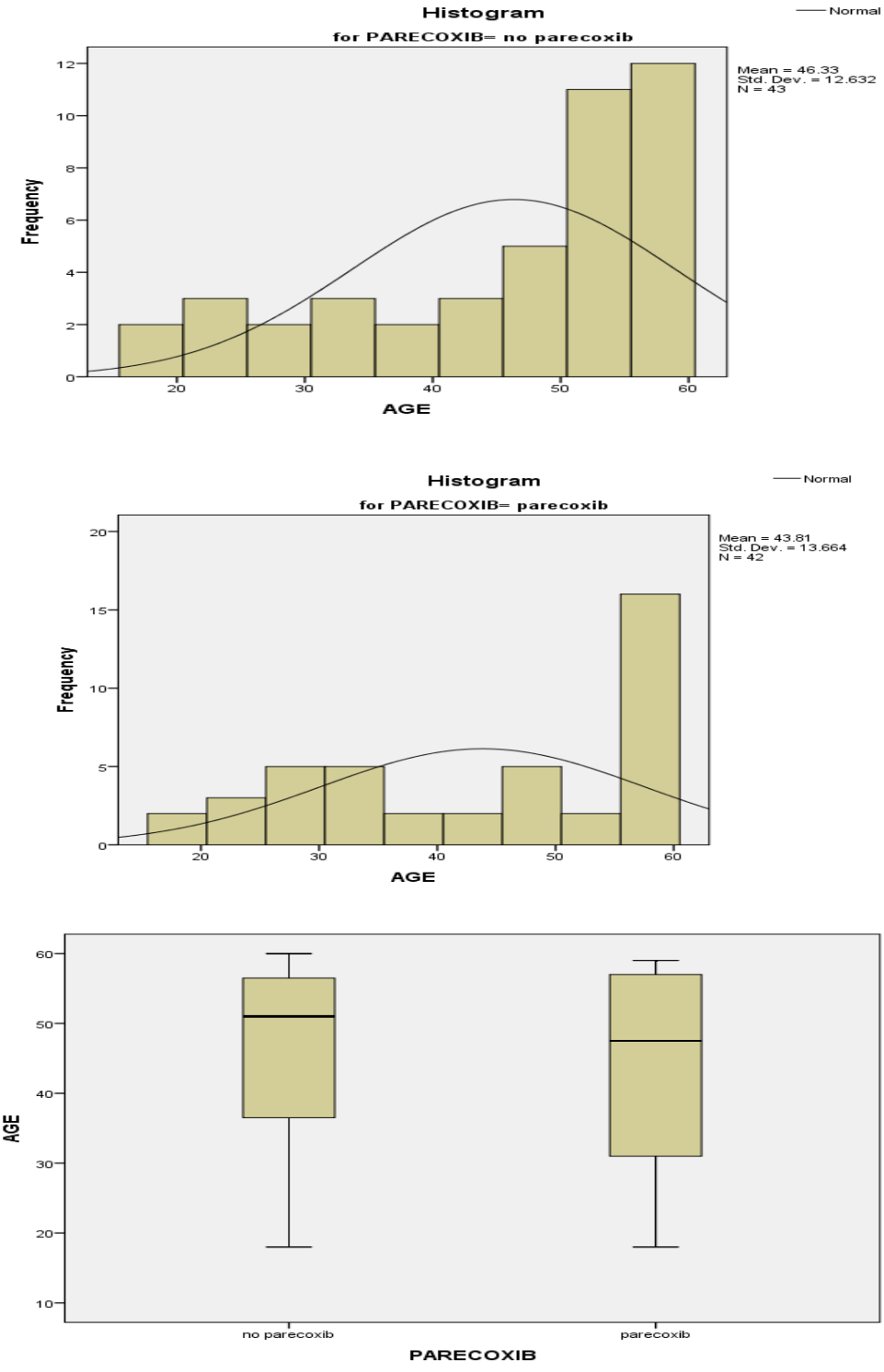


Figure 5.4: The histograms (with the overlying distribution curves) and box plots representing the characteristics of distribution for age.

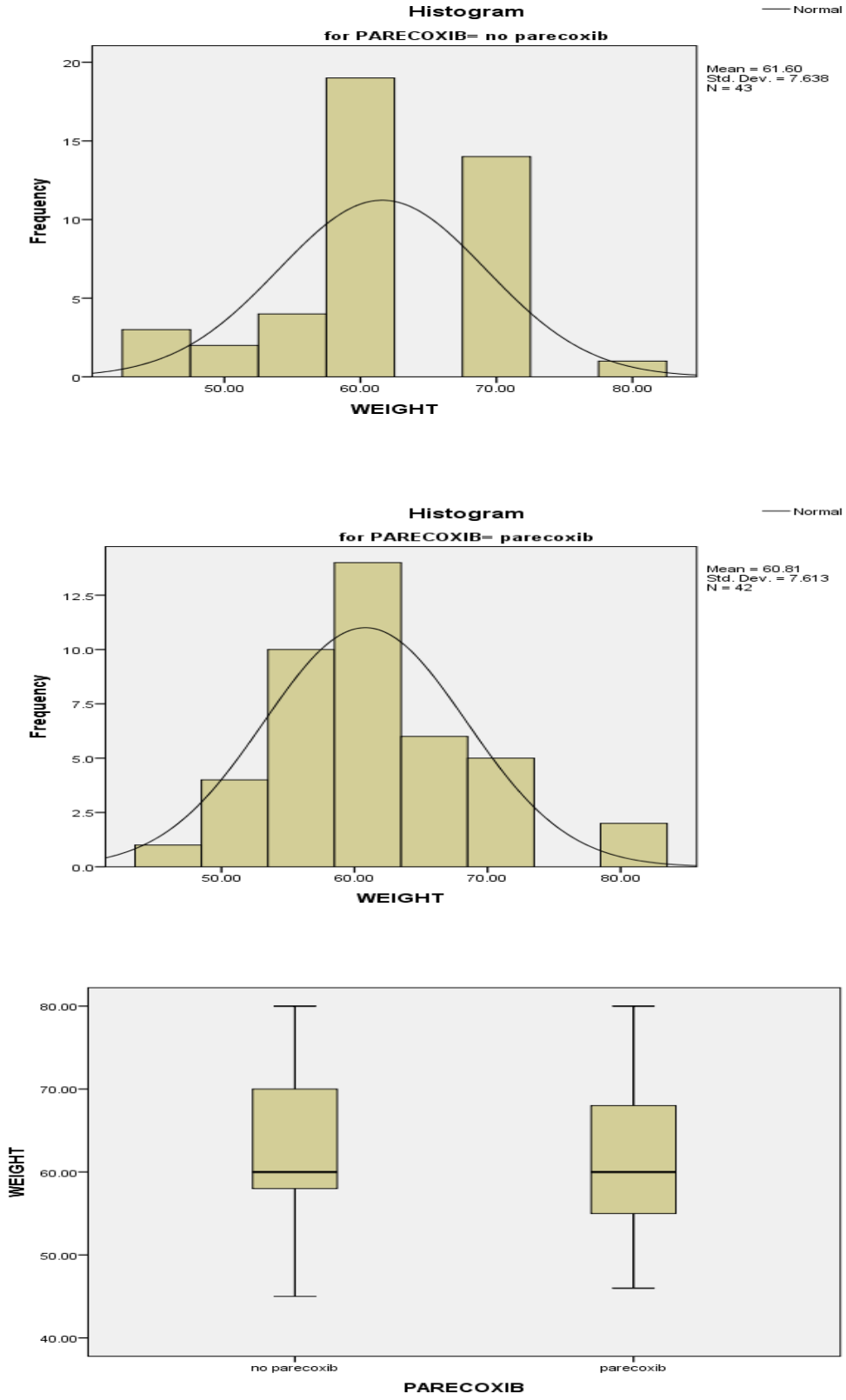


Figure 5.5: The histograms (and the overlying distribution curve) and box plots representing the distribution of weights of patients.

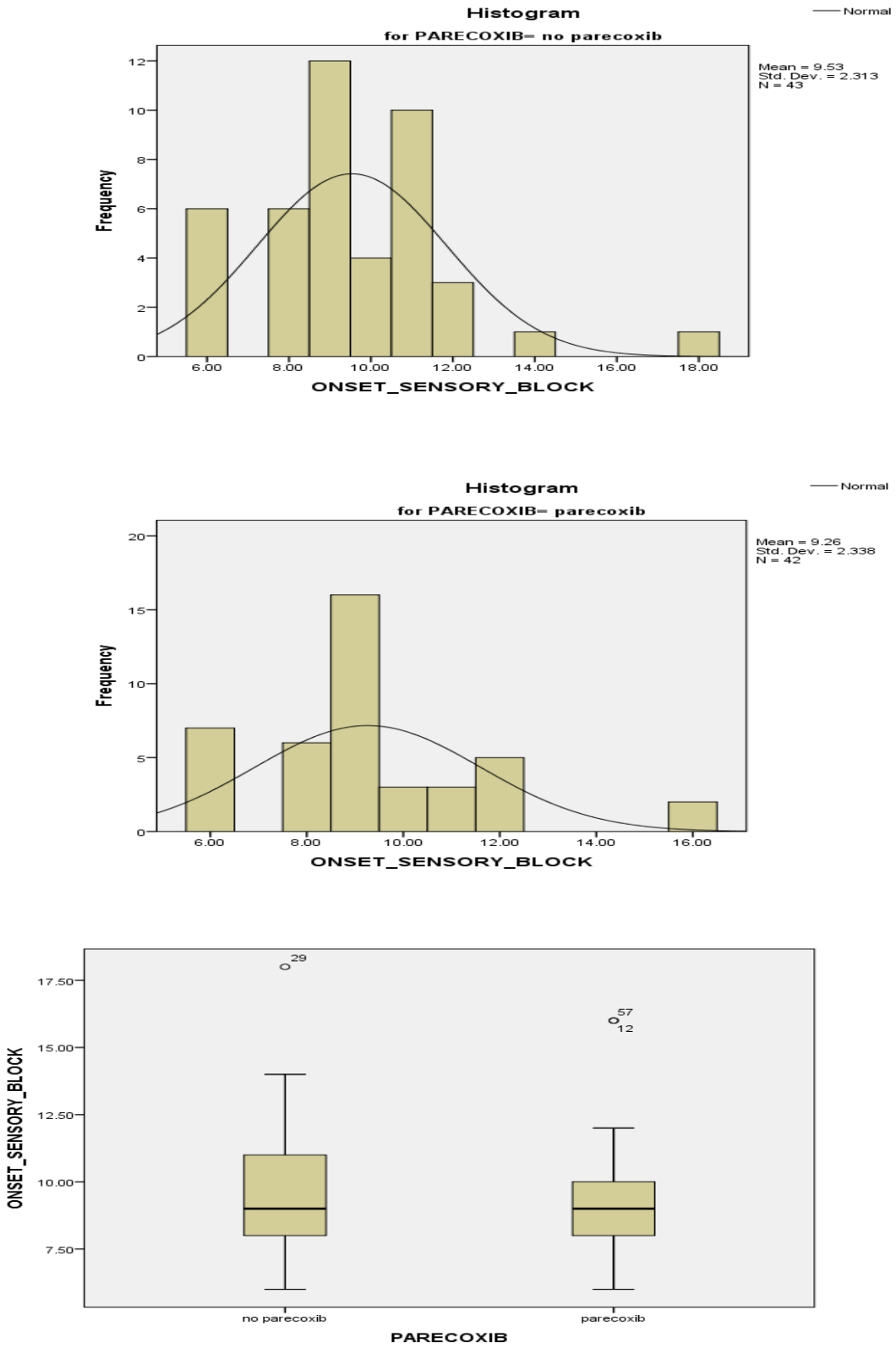


Figure 5.6: The histograms (with the overlying distribution curves) and box plot of the time of onset of sensory block as stratified by the intervention arms. The circles and numbers represent outliers and outlier's ID.

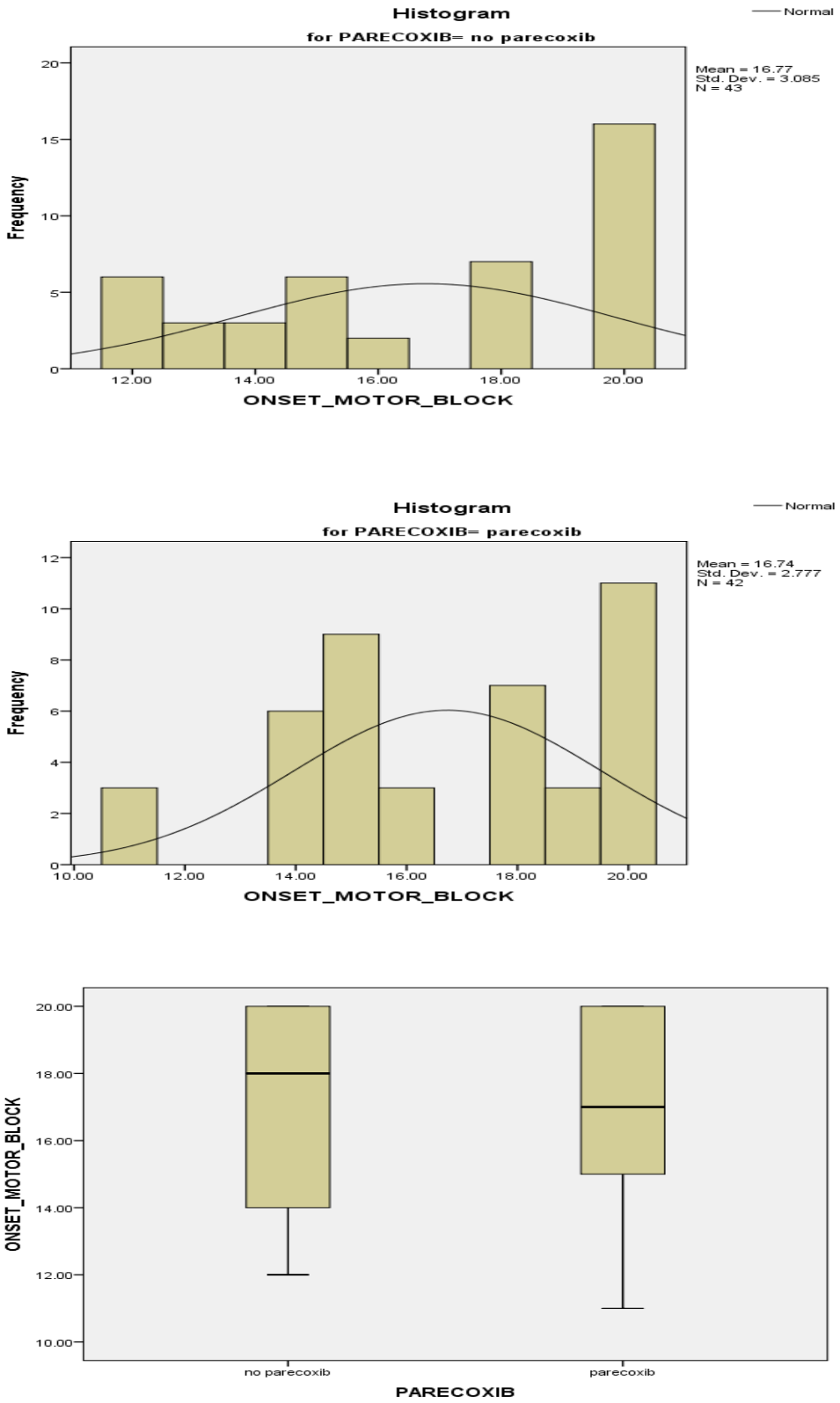


Figure 5.7: The histograms (with overlying distribution curves) and box plots representing the time of onset of motor block as stratified by the intervention groups.

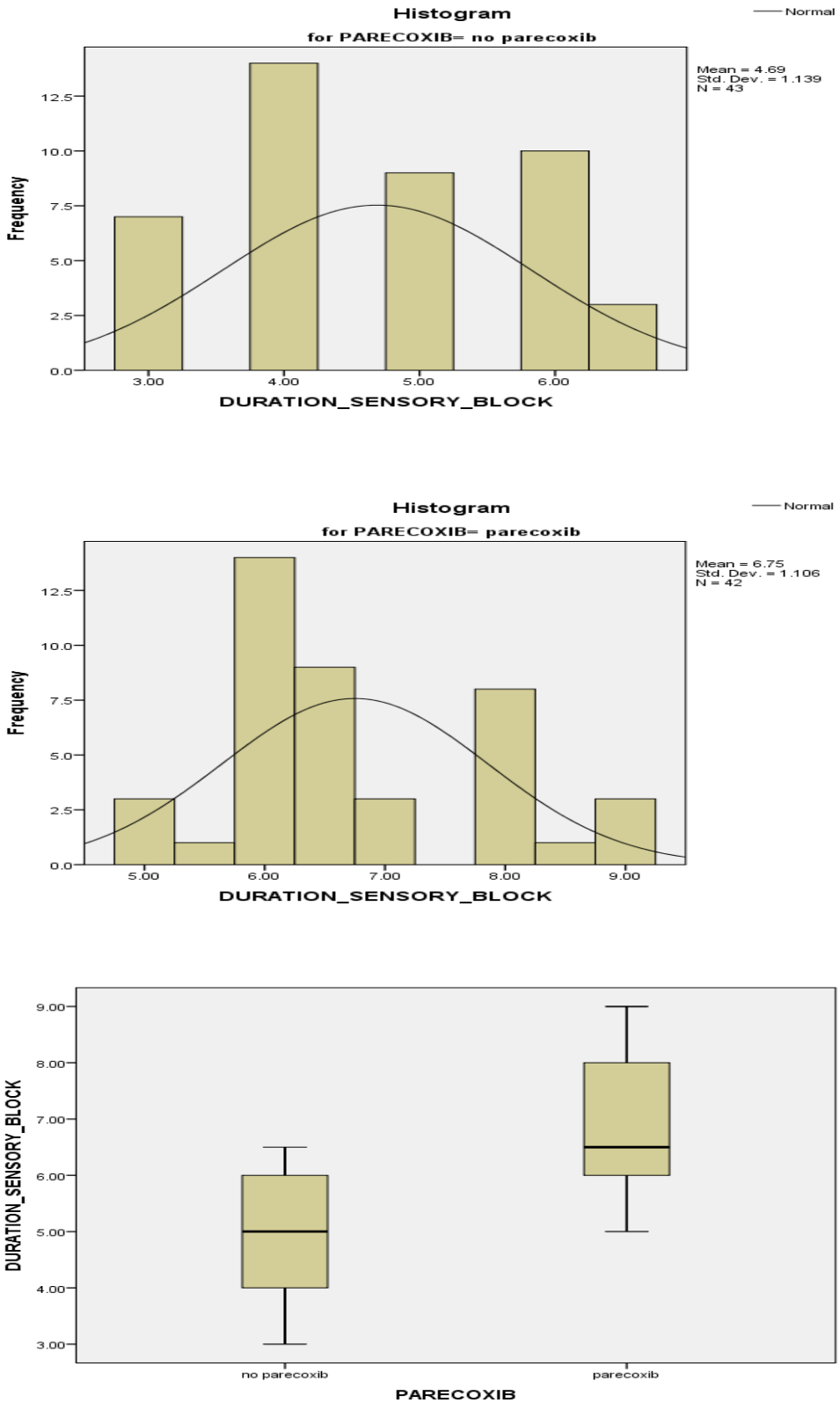


Figure 5.8: The histograms (with the overlying distribution curves) and box plots for the duration of sensory block as stratified by the intervention groups.

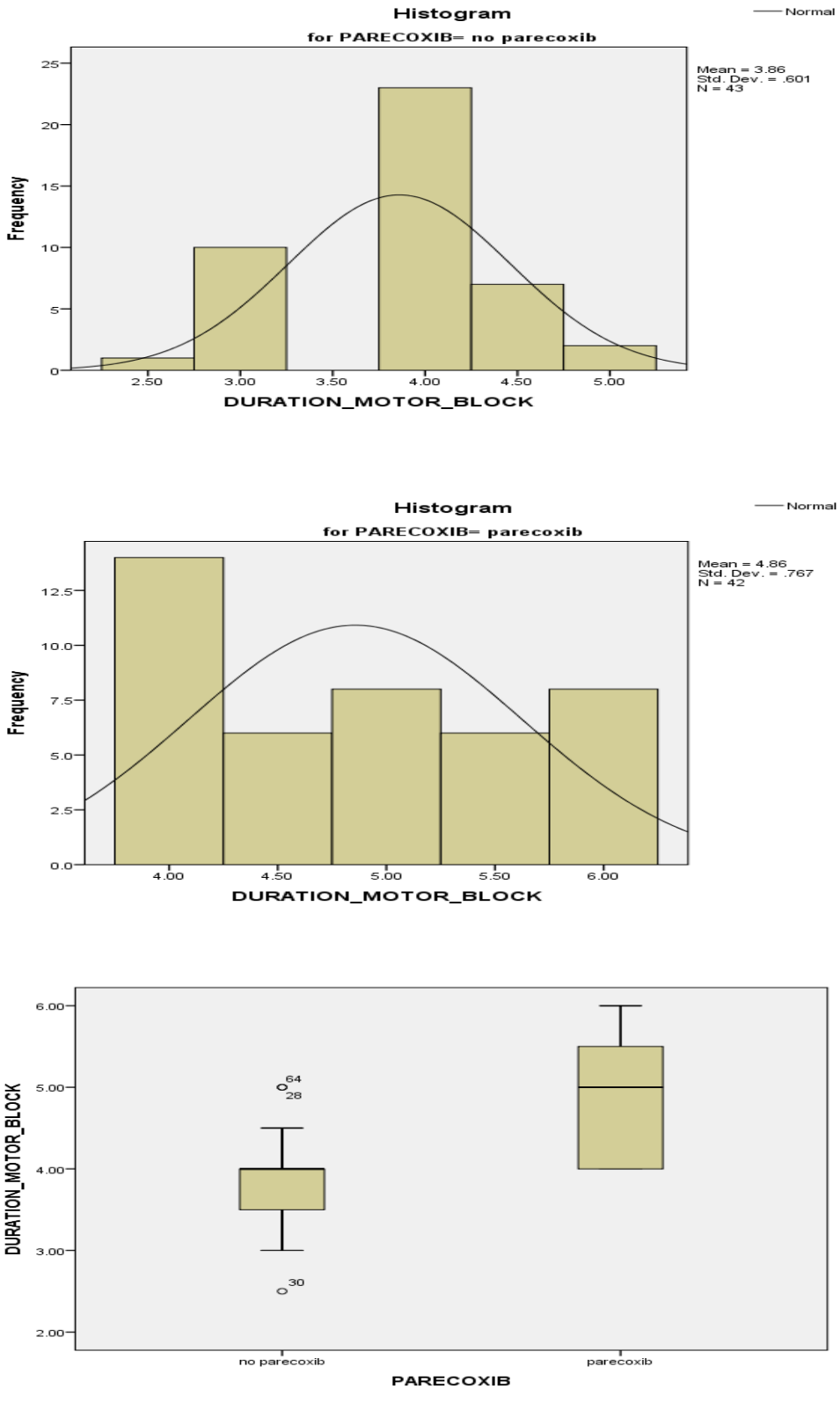


Figure 5.9: The histograms (with the overlying distribution curves) and box plot representing the duration of motor block as stratified by the intervention groups. The circles and numbers indicate outliers and outlier's ID, respectively.

5.3 THE ASSOCIATIONS BETWEEN THE INTERVENTION ARMS AND CLINICAL OUTCOMES

5.3.1 The onset of sensory and motor block

From table 5.4, there are no significant differences between the two intervention arms with respect to the sensory and motor block onsets. These are corroborated by the small median differences in both clinical outcomes when comparisons are made between these two groups.

5.3.2 The degrees of sensory and motor block

Based on inspection of table 5.5, there are no significant differences with regard to the degrees of sensory and motor block at 30 minutes following supraclavicular BPB between the two intervention arms (p values of 1 for both outcome parameters). The odds ratio cannot even be computed because there are cells with 0 count.

5.3.3 The durations of sensory and motor block

There are significant differences in terms of the durations of sensory and motor block between the intervention arms and the differences are 1.5 hours and almost 1 hour, respectively (table 5.4). The evidence against null hypothesis can be considered very strong since the p values are less than 0.001 for both clinical outcomes. Hence, the null hypothesis of no significant difference can be safely rejected.

5.3.4 Other clinical parameters

For other clinical parameters, there is no single significant difference observed between the intervention groups. Hence, both groups exhibit fairly balanced effects of confounders.

Table 5.4: The differences between the intervention arms in terms of sensory and motor block onset and durations and other clinical parameters (n=86).

Outcomes	Intervention arms		Median differences*	Mann-Whitney U statistics	p values
	Parecoxib + Ropivacaine Median (IQR)	Ropivacaine only Median (IQR)			
Sensory block onset (minutes)	9.00 (2.25)	9.00 (3.00)	0	861.00	0.577
Motor block onset (minutes)	17.00 (5.00)	18.00 (6.00)	-1	900.50	0.832
Sensory block duration (hours)	6.50 (2.0)	5.0 (2.00)	1.50	199.00	**<0.001**
Motor block duration (hours)	4.84 (0.77)[a]	3.86 (0.60)[a]	0.97 (0.68, 1.27)[b]	6.561 (79.342)[c]	**<0.001**
Age (years)	47.5 (26)	51.0 (21.0)	-3.5	838.00	0.455
Weight (kg)	60.0 (13.0)	60.0 (12.0)	0	809.50	0.399

*Parecoxib and Ropivacaine group minus Ropivacaine only group, [a]Mean (SD), [b]Mean difference (95% CI), [c]Independent t-test for unequal variance (degree of freedom)

Table 5.5: The associations between the intervention arms in terms of the degrees of sensory and motor blockade at 30 minutes following supraclavicular brachial plexus block and other clinical parameters (n=86).

Outcomes	Intervention arms		Odds ratio (95% CI)	χ^2 statistics (df)	p values
	Parecoxib + Ropivacaine n (%)	Ropivacaine only n (%)			
Degree of sensory block			-[a]	Not applicable	1.000
Complete block	43 (100)	42 (97.7)			
Normal sensation	0 (0)	1 (2.3)			
Degree of motor block			-[a]	Not applicable	1.000
Flex / extend forearm (grade I)	0 (0)	1 (2.3)			
No upper limb movement (grade IV)	43 (100)	42 (97.7)			
Gender			Not applicable	0.764 (1)	0.382
Female	16 (37.2)	20 (46.5)			
Male	27 (62.8)	23 (53.5)			
Ethnicity			Not applicable	Not applicable	1.000
Malay	42 (97.7)	41 (95.3)			
Chinese	1 (2.3)	1 (2.35)			
Others	0 (0)	1 (2.35)			

[a]Cannot be computed due to the presence of 0 cell count

Table 5.5, continued

ASA grades	7 (16.3)	6 (14.0)	Not applicable	0.091 (1)	0.763
I	36 (83.7)	37 (86.0)			
II					
Sites of surgery					
Forearm	14 (32.5)	8 (18.6)	Not applicable	Not applicable	0.102
Arm	21 (48.9)	31 (72.1)			
Hand	0 (0)	1 (2.3)			
Fingers	6 (14.0)	3 (7.0)			
Missing	2 (4.6)	0 (0)			

5.4 THE ADVERSE EVENTS ASSOCIATED WITH ROPIVACAINE AND / OR PARECOXIB

No subjects reported any significant and serious side effects associated with ropivacaine and parecoxib. The signs and symptoms of side effects that are commonly associated with ropivacaine administration such as CNS (seizures, peri-oral numbness, paraesthesia, dysaesthesia, tremor, dizziness) and cardiovascular toxicities (hypotension, bradycardia and arrythmias) were not reported by any study participant in both intervention groups. Besides, no significant side effects related to parecoxib administration (gastrointestinal bleeding, anaphylaxis reactions such as swelling, rash and breathing difficulties, jaundice, abnormal liver function tests etc.) were experienced by the study participants.

The trial was not stopped prematurely and lasted for the whole duration as planned.

SECTION SIX

DISCUSSION

6.1 THE ANTI-NOCICEPTIVE EFFECTS OF PARECOXIB IN SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK

In this study, our primary finding is that synergistic combination of ropivacaine and parecoxib only prolonged the duration of sensory and motor blockades, not the onset of sensory and motor block. This proves that COX-2 inhibitors act centrally and that the spinal transmission of nociceptive signals is affected by constitutively-expressed COX-2 in the central nervous system. More generally, our results indicate that the anti-inflammatory and antinociceptive effects of COX-2 inhibitors are not necessarily related since the dosage we used in this study was well below the dose required for anti-inflammatory induction. However, the discrepancy between our findings and Liu *et al.* (2013) in terms of the onset of sensory and motor blockades can be attributed to the higher concentration of ropivacaine (0.75%) compared to one used by Liu *et al.* (2013) (0.25% ropivacaine). As a result, Liu *et a.* (2013) reported a significant difference with regard to the onset of sensory and motor blockades between 0.25% ropivacaine + parecoxib recipients and those who received 0.25 % ropivacaine only. Therefore, our finding adds to the current knowledge by demonstrating the attenuation of 20 mg parecoxib's effect when it is used as an adjunct to a higher concentration of ropivacaine. Besides, we also generalised the findings and conclusion made by Liu *et al.* (2013), who only recruited subjects who were recipients of axillary brachial plexus blockade, by demonstrating that the benefits of adjunct parecoxib can also be extended to patients undergoing BPB via supraclavicular approach as well. We also sucessfully managed to control the confounding effects of preoperative (baseline) pain scores since both intervention groups

exhibited identical mean visual rating scores (VRS). Consequently, the validity of our findings is more bona fide than the ones asserted by Liu *et al.* (2013).

The prolongation of sensory and motor blockades upon the addition of 20 mg parecoxib to ropivacaine is still not well-understood. There are several explanations that can be put forward to expound these findings. Firstly, the inhibition of COX-2's action will result in a decrease in the production of prostacyclin (a potent vasodilator), whilst conserving the synthesis of the vasoconstrictive thromboxane A_2. Consequently, parecoxib prolonged the duration of anaesthetic action in a similar fashion like the vasoconstrictive effect produced by adjunct epinephrine mixed with LA agents for infiltrative anaesthesia (Newton *et al.*, 2004). Next, the action of ropivacaine on sodium channels might be altered by the addition of parecoxib. Butterworth IV and Strichartz (1990) had hypothesized that there were a multitude of LA's mechanisms of actions for spinal and epidural analgesia and one of them was via the reduction of prostacylin and prostaglandin production, resulting in a modulated effect of LA on sodium channel bloackade. Thirdly, the inhibitory effect of parecoxib on COX-2 may also decrease the production of prostanoid centrally, hence reducing the effects of peripheral inflammation and the ensuant mechanical hypersensitivity (Samad *et al.*, 2001).

NSAIDSs have long been considered to have effects on the CNS via COX inhibition, as numerous experimental models over the past 15 years have established. The findings that both COX isoforms are expressed in the CNS and the fact that central nociceptive transmission and pain hypersensitivity secondary to mechanical inflammation are modulated by COX-2 following peripheral inflammation lend further support to this notion (Choi *et al.*, 2009; Vardeh *et al.,* 2009). These observations question the classical perception that NSAIDs's antinociceptive effect was solely attributed to preventing the sensitization of nociceptor (Sinatra 2002). Nevertheless, the peripheral and

central modes of NSAID actions should not be regarded as mutually independent but as complementary and possibly synergistic. Furthermore, the fact that COX-2 is also constitutively expressed in the CNS hints towards its role in modulating pain induced by even the normal physiological processes (Burian and Geisslinger, 2005; Martin *et al.*, 2007).

Nevertheless, the arguments about the roles of COX-2 enzymes in central pain modulation in both normal physiological and pathological settings were far from conclusive since they chiefly relied upon the findings obtained from animal models, not from experiments or trials involving human subjects. Thus far, the central effects of COX-2-specific inhibitors in humans was solely investigated in the setting of primary and secondary hyperalgesia caused by sunburn injury due to exposure to an ultraviolet-B (UVB) radiation, the application of electrical stimulation transdermally and skin sensitization via capsaicin exposure (Sycha *et al.,* 2005; Koppert *et al.*, 2004; Burns *et al.*, 2006). However, the generalisability of the findings obtained from these experimental models is still restrictive due to their ancillary methods used to evaluate the intervention's central analgesic effects. Moreover, the findings were also heavily biased since the experimental results obtained were contingent upon the types of experimental pain model used by the researchers. This may hence cause the negative results reported by Burns and coworkers (2006).

The primary issue that prevents the researchers from gaining a concrete evidence and thus conclusively confirming the authenticity of COX-2-specific inhibitor's central antihyperalgesic effect is that in the majority of pain states induced by inflammatory causes, a mixture of peripheral and central sensitization materalises. As a result, it is indeed laborious to distinguish the peripheral from spinal components of the antihyperalgesic effects attributed to COX-2-selective inhibitor. The effect of antidromic

electrical stimulation on peripheral sensitization had been negated by the prior work of Schmeltz *et al.* (1996). In fact, Klede *et al.* (2003) had assuringly established, using an anaesthetic strip experiment, that in the setting of electrically-induced mechanical hyperalgesia, the origin of such hyperalgesic state is centrally located, not peripherally located. The unvarying pain scores obtained prior to and following the exposure to the electrical stimuli and the absence of clinically and statistically meaningful decrease in axon reflex erythema, which has a peripheral hyperalgesic component, further corroborate the belief that COX inhibitors' peripheral effects did not result in evident antihyperalgesic effect (Koppert *et al.*, 2004).

The central release of prostaglandins which results in the creation of hyperalgesic state is a fact that has been agreed upon by the scientific community (Vanegas and Schaible, 2001). Nevertheless, the involvement of disparate molecular and cellular mechanisms in the production of the central hyperalgesic effects induced by prostaglandins is still yet to be wholly comprehended. Baba *et al.* (2001) demonstrated that PGE_2 has the ability to precisely depolarize the neurons located at spinal dorsal horns through the EP_2 receptors. Furthermore, the blockade of glycinergic neural signal transmission of the inhibitory neurons by PGE_2 through blocking the glycine receptor that posesses α3 subunit could also be one of the critical mechanisms of inflammatory hyperalgesia (Zeilhofer, 2005). Hence, it is highly likely that the addition of parecoxib may remove the blockade to the α3 glycine receptor and hence prolonging the duration of sensory and motor blockade by improving the glycinergic neural signal transmission.

6.2 THE MECHANISMS OF ANTI-NOCICEPTIVE EFFECTS OF PARECOXIB

In an *in vitro* study by Mitchell *et al.* (1994), the authors, using preparations of broken cells and cyclooxygenase enzymes that had been purified, demonstrated that acetylsalicylic acid (ASA*) was only twice more potent than salicylate in terms of COX-

2 inhibition despite both having identical analgesic profile. The authors then hypothesized that the analgesic activities of both ASA and salicylate might be attributed to their predominant action on COX-2 rather than COX-1 since ASA has much superior COX-1 inhibitory action (i.e. 100 times more potent) to salicylate whilst both of them having equianalgesic capacity. Nevertheless, due to the *in vivo* nature of this experiment, the findings should be treated with caution when extrapolating and correlating the results to other *in vivo* experimental models and clinical studies.

It is a well-known fact that prostaglandin E2 (PGE_2) has the capacity to sensitize the peripheral nerve endings to pain (Warner and Mitchell 2004). This is substantiated by Svenson and Yaksh (2002) who had explicated in their excellent review article that the COX-2 enzyme could be indigenously found in the dorsal and ventral grey matter of the spine, dorsal root ganglia and even in the glial cell such as astrocytes. Apart from that, Beiche *et al.* (1998) also confirmed the presence of COX-2 using immunohistochemical techniques in the neurons that are located in the whole layers of spinal cord's lamina, especially in its outermost superficial layer. The presence of constitutive COX-2 in the neuronal cells of all lamina of the spinal cord may explain for the acute antinociceptive effect of the intrathecal administration of COX-2 inhibitors. Furthermore, Pinardi *et al.* (2005), together with the observations made Samad *et al.* (2001) and Seybold *et al.* (2001), further endorsed the conclusion drawn from the other studies that the COX-2-induced prostanoid at the spinal level may result in the perpetuation of hyperalgesic state. These perhaps partly expound the abolition of hyperalgesic state induced by the substance P and the NMDA-mediated nociceptive transmission via cycloxygenase inhibition (Malmberg and Yaksh 1992) and carrageenan-induced thermal hyperalgesia by the COX-2-specific inhibitor that was intrathecally administered (Yaksh *et al.,* 2001). In addition, Warner and Mitchell (2004) also stated that the induction of COX-2 expression and hence

PGE_2 synthesis by the injured cells may in turn result in the neuronal hyperexcitability that will cause pain hypersensitivity in the neighbouring uninjured cells. Moreover, Ossipov *et al.* (2004) also established the presence of μ-opioid receptors in the same locality (i.e. the outermost laminae of the spinal cord's dorsal laminae) as COX-2 inhibitor. All these facts lend further support to the hypothesis that the combination of analgesic or anaesthetic agents with divergent mechanistic profiles may be more effective in attenuating acute pain and prolonging the effects of anaesthetic agents (Phillips and Currier 2004). The results of these prior research hence corroborated the outcomes of our study that the addition of parecoxib to other anaesthetic agents may further reduce the sensitization of nerve ending to pain and, in general, reinforce the duration of sensory and motor blockades.

Based on the findings obtained from their murine model of abdominal constriction, Abacioglu and coworkers (2000) has advocated that the components of the L-arginine / nitric oxide (NO) / cGMP cascade may be involved in the transmission of nociceptive processes both peripherally and centrally by either a direct effect on the nociceptors per se or by the involvement of other related pathways of nociceptive processes induced by NO (Abacioglu *et al.*, 2000). Nitric oxide (NO) is involed in the antinociceptive activity of morphine and the intrathecal administration of morphine modulates spinal antinociception by interacting with the NO-glutamate cascade. In contrast, the activity of COX-2 may be stimulated by NO (Dudhgaonkar *et al.*, 2004), which in turn seems to be modulated by morphine administered intrathecally. In addition, COX-2 and inducible NO synthase are both frequently and simultaneously co-regulated (Simmons *et al.,* 2004).

6.3 PARECOXIB-ASSOCIATED TOXICITY AND ADVERSE EVENTS IN BRACHIAL PLEXUS BLOCKS

It is also crucial to establish whether injecting parecoxib directly into the brachial plexus resulted in neurotoxicity. We found that no recipients of parecoxib during the brachial plexus block reported any evidence of neurotoxicity. Our findings corroborated the findings of Liu *et al.* (2013) and Kim *et al.* (2011).

Liu *et al.* (2013) followed up the patients for two months after surgery and they found out no single episode of paraesthesia was reported by the study participants. As a result, the authors believed that their study provides the first direct evidence that parecoxib can be safely tolerated when injected into the peripheral nerve or spinal cord. Besides, the neurotoxicity of parecoxib administered into the epidural space was investigated and no behavioural or histological changes attributed to the neurotoxicity in the spinal cords of rats were observed following the administration of parecoxib.

The fact that there is a low incidence of toxicity associated with parecoxib when used for brachial plexus block may popularise its use. Besides, due to its opiod-sparing effect, Kim *et al.* (2011) has recommended that parecoxib can be safely combined and administered intrathecally with other opioid such as morphine. Hence, the potentially-fatal side effects of opioids such as death, respiratory depression and thrombosis can be avoided. Apart from that, it is also worth mentioned that since parecoxib only acts on enzyme system and not on receptors, the risks of tolerance, resistance and addiction will be smaller than drugs of opioids class (Wang *et al.* 1995).

6.4 LIMITATIONS OF THE STUDY

The first limitation of this study is the small size employed in this trial. As a result, the power of the study might be affected, resulting in the failure of rejecting the null hypothesis. However, we have already meticulously calculated the sample size of this

study based on the findings of Liu *et al.* (2013) and the total subject obtained is presumably sufficient to provide at least 90% power in rejecting the null hypothesis. Nevertheless, the effect size demonstrated by the findings Liu *et al.* (2013) may be much larger than ours and as a result, they required a much smaller sample size to confidently reject the null hypothesis. It is highly recommended that a larger sample size should be employed if future researchers would endeavour to verify our findings.

The second limitation of our study is much more subtle. It is highly recommended that the future statistical analysis of a trial data should be done within the Bayesian framework, not solely within the frequentist setting. In this trial, the use of p values as the decision rule to determine whether a null hypothesis should be rejected or not may lead to incorrect conclusion since p value on itself is not the probability of a null (or studied) hypothesis is true (Wasserstein and Lazar, 2016) . P value is actually just an assertion on the compatibility of our findings (or data) are with the hypothesis prespecified before the p value is obtained and assumed to be true (Wasserstein and Lazar, 2016). Besides, p value is also not a measure of effect size since a large p value does not mean that effect size is small and clinically negligible and a small p value represents a large and clinically-relevant effect size (Wasserstein and Lazar, 2016). Apart from that, p value is also not a measure whether a null hypothesis should be accepted or rejected since a small p value is not indicative of an evidence against null hypothesis or vice versa. This is because there are many other competing hypotheses that may be more compatible with the data than the tested null hypothesis (Wasserstein and Lazar, 2016). In fact, a borderline p value, for instance p equals 0.049, is just a weak against the null hypothesis and is usually lumped together with any p value that is less than 0.05 (Greenland *et al.,* 2016). As a result of this statistical fallacy associated with the misinterpretation of p value, the number of positive-but-irreproducibe findings in trials will start to rise (Halsey *et al.*, 2015).

Another drawback of p value is we cannot incorporate the prior information obtained from the results previous trial (i.e. from Liu *et al.,* (2013)) with the findings of our study to alter our belief on the validity of tested hypotheses. Bayesian statistics provides a better tool to address the shortcomings of the frequentist school of statistics (Spiegelhalter *et al.*, 2004). In the Bayesian school of thought, the information contained in our findings is represented by the likelihood of our data and the prior information (i.e. the results obtained from Liu *et al.*, (2013)) is conveyed by the prior distribution. Our conclusion on whether to accept a statistical hypothesis will then depend on our posterior belief which is an updated prior after mathematically combining it with the likelihood of the data in this fashion:

Prior X Likelihood = Posterior

However, Bayesian statistics suffered from several drawbacks which hamper its ubiquitous use by the scientific community. The obvious disadvantage of using Bayesian statistics is, however, the intractable posterior distribution obtained which results in statistical methods that computationally intensive. To compute the posterior distribution that represents the researcher's belief after "seeing" the information in the data and integrating it with the prior belief is arduous especially for multi-dimensional cases. The only way to solve this problem is to resort to statistical simulation using the Markov Chain Monte Carlo (MCMC) method which requires a state-of-the-art computer.

The third limitation of our study is the enrollment criteria we used to screen the patients. we excluded the definite pain-related main factors (eg, psychiatric anxiety and alcohol abuse) but did not limit other factors that also might affect pain sensation (eg, age and sex). If we had stricter enrollment criteria such as restricting the study to one certain type of surgical procedure or just in females or males, the findings of our study will be more cogent. Fourthly, we also did not evaluate the pain threshold of the study

participants since we are not in possesion of any valid apparatus that can establish the threshold of heat or pressure-induced pain in humans accurately. We did evaluate the preoperative VRS as a surrogate measure for the pain threshold of each study participant but we believe this is not an accurate measure of the participants' pain tolerance. Finally, we only employed a single dose of parecoxib (i.e. 20 mg parecoxib) and consequently we were not being able to evaluate the association between different doses of parecoxib and the trend in the duration and onset of sensory and motor blockade. However, we did ascertained that the inclusion of 20 mg parecoxib to ropivacaine increased the duration of motor and sensory blockades.

SECTION SEVEN

CONCLUSION

All in all, our conclusively demonstrated that the addition of parecoxib to ropivacaine prolonged the duration of sensory and motor blockades, but not their onset. Several mechanisms have been proposed that may explain the differential effects of parecoxib on both onset and duration of the blockades. Besides, we also discussed about a few limitations of our study and recommended several remedies to improve the designs and analyses of future trials addressing the same research question. Contigent upon the findings of future studies, a 20 mg adjunct parecoxib will provide better anaesthetic effects than a single 0.75% ropivacaine in patients undergoing upper limb surgeries.

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CASE REPORT FORM (CRF)

CASE NO	GROUP: SCB / ICB

DATA COLLECTION SHEET:

EFFECT OF PARECOXIB 20MG AS AN ADJUNCT IN 0.75% ROPIVACAINE TO ULTRASOUND GUIDED SUPRACLAVICULAR BLOCK FOR UPPER LIMB SURGERY

PRE OP SCREENING:

INCLUSION CRITERIA	TICK (√)	EXCLUSION CRITERIA	(X)
Adult (age 18 to 60)		Patient refusal for BPB	
ASA I to II		Known case of allergic to parecoxib and local anesthesia	
Expected duration of surgery 1-4 hours		History of previous brachial plexus injury	
		Pregnancy	
		History of chronic pain, those that using chronic analgesic medication	
		Coagulapathy	
		Systemic infection or local infection at site of injection	
		History of Ischaemic Heart Disease.	
		History of Renal failure	
		History of Atopy	

CASE NO:

BACKGROUND DATA

Date: _____

Full Surgical Procedure:

SITE OF SURGERY	CODING	TICK (√)
Arm	1	
Forearm	2	
Hand	3	
Fingers	4	

R/N: _____

Age: _____ Sex: M/F Ethnicity: M / C /I /Others

ASA: I / II

If ASA II, state the disease/s_____

Height: _____ cm Weight: _____ kg

BLOCK TECHNIQUE

- Size of the needle: 50 / 80/ 100 mm
- Depth of skin to superior part of the artery: _____ cm
- VRS of procedure-related pain (1 to 10): _____
- Volume of LA given: _____ ml
- Supplement volume of LA given: _____ ml
- Time of completing LA injection: _____
- Time of sensory block onset (reduce sensation ≤ 25% from contralateral side): _____
- Onset of sensory block: _____ min
- Time of motor block onset (reduce motor power ≤ 25% from contralateral side): _____
- Onset of motor block: _____ min
- Assessment of sensory block after 30 min:

SENSORY BLOCK	TICK (√)
2 (Normal)	
1 (partial block/ reduced)	
0 (Complete block/ absent)	

- Assessment of motor block after 30 min:

GRADE	TICK (√)
1 (able to flex or extend the forearm)	
2 (able to flex or extend only the wrist and fingers)	
3 (able to flex or extend only the fingers)	
4 (unable to move the forearm, wrist, and fingers)	

QUALITY OF OPERATIVE CONDITIONS

QUALITY OF OP	**Please tick (√)**
4 (Excellent/ No complaint from patient)	
3 (Good/ Minor complaint with no need for the supplemental analgesics)	
2 (Moderate/ Complaint that required supplemental analgesia)	
1(Unsuccessful/ Patient given general anaesthesia)	

SITE REQUIRED SUPPLEMENT BLOCK

PATCHY BLOCK SITE	**Please tick (√)**
Ulnar	
Median	
Musculocutaneous	
Radial	

POST OP ASSESSMENT

- Time of complete motor function recovery:
- Time of complete cold & pin-prick sensation recovery:
- Duration of sensory block: _____ min

  Duration of motor block: _____ min
- Time of 1st PCA demand: _____
- Total of PCA Morphine demand over 24 hours: _____
- Total of PCA Morphine delivery over 24 hours: _____

CASE NO:

COMPLICATIONS (ASSESSMENT AFTER 48 H):

COMPLICATIONS	Please tick (√)
Bruises/swelling at the block site	
Chest pain/ breathing difficulty	
Dysaesthesia	
Muscle weakness	
Seizures	
Bradycardia	
Hypotension	
Others:	

ANAESTHETIC PREFERENCES FOR FUTURE HAND OPERATIONS:

ANAEST TECH PREFERENCE	Please tick (√)
Same block	
Block under deep sedation	
Block under GA	

.

PATIENT INFORMATION AND CONSENT FORMS (ENGLISH VERSION)

RESEARCH INFORMATION

Research Title:

THE EFFECT OF PARECOXIB 20 MG AS AN ADJUNCT IN 0.75% ROPIVACAINE TO ULTRASOUND GUIDED SUPRACLAVICULAR BLOCK FOR UPPER LIMB SURGERY.

Researchers:

1. Dr Wan Mohd Nazaruddin bin Wan Hassan (Anaesthetist and Senior Lecturer , Department of Anaesthesiolgy and Intensive Care Unit, HUSM),

2. Dr Vivekananda Gunasekaran (Medical Officer Anaesthesiolgy, Master Candidate, USM), No.MPM 44220

Introduction

You are invited to take part voluntarily in a research study the comparison of perineural parecoxib in 0.75% ropivacaine and plain ropivacaine 0.75% in ultrasound guided supraclavicular brachial plexus block for upper limb surgery.

Generally, brachial plexus is a bunch of nerves derived from spinal cord from multiple levels into the nerves branches peripherally. It provides movement of the upper limb muscles (motor) and also supply the dermatomes (sensory). It can be blocked at certain levels throughout its route. For this study, we interested to block the plexus at the level of supraclavicular.

It is important to know that this study will benefit both the patient and the doctor:

i. **Patient's peace of mind from any risk from general anesthesia; free from interruption of unwanted pain post-operatively; can take orally after the operation; can have an early hospital discharge after the operation; and can communicate with the surgeon during the surgery.**
ii. **Doctor (surgeon) can fully focus on the operation since there is no unintentional arm movement after the brachial plexus block; the vasodilatation effect of brachial plexus block will provide a good surgical field to the surgeon hence optimum surgery outcome.**

This study is supervised by Dr Wan Mohd Nazaruddin bin Wan Hassan (Anaesthetist and Senior Lecturer , Department of Anaesthesiolgy and Intensive Care Unit, HUSM),

The supraclavicular brachial plexus block will be performed by the researcher, Dr Vivekananda Gunasekaran (M.Med. Anesthesiology, HUSM) and other medical officers who had skills and previledge in performing brachial plexus block.

Before agreeing to participate in this research study, it is important that you read and understand this form. It describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at anytime. If you participate, you will receive a copy of this form to keep for your records.

Your participation in this study is only during your scheduled elective or emergency surgery for upper limbs surgery. Up to 86 patients will be participating.

Purpose of the Study

The purpose of this study is to determine the effect of adding parecoxib 20 mg in 0.75% ropivacaine in comparison to plain ropivacaine 0.75% in ultrasound guided supraclavicular block.Are of interest is concentrated mainly at onset of anaesthesia as well as duration of the block wheereby the patient remains pain free.

Qualification to Participate

The doctor in charge of this study or a member of the study staff has discussed with you the requirements for participation in this study. It is important that you are completely truthful with the doctor and staff about you health history. You should not participate in this study if you do not meet all qualifications.

Some of the requirements **to be in this study are:**

- **You are between the ages of 18 and 65 years old**
- **You are scheduled for elective or emegency for upper limbs surgery**
- **You must be consented for brachial plexus block (supraclavicular approach)**

You cannot **participate in this study if:**

- **You refuse to cooperate or to participate in this study**
- **You are allergy to parecoxib and ropivacaine.**
- **You are pregnant or suspected pregnant or breastfeeding**
- **You had history of brachial plexus injury**
- **You had history of chronic pain that using regular chronic analgesic**
- **You have coagulapathy**
- **You had systemic infection or local infection at site of injection**
- **You have serious chronic heart disease, lungs disease and liver disease**
- **You had nerve disease involving the limbs that going for surgery**
- **You had join this study before and did not complete the study**

Study Procedures

Patients are recruited from Operation Theatre (OT) List, scheduled for upper limbs surgery provided by Orthopedic or Plastic and Reconstructive Surgery Department, HUSM

No premedication will be prescribed in the morning of the surgery and patients will be randomized using simple randomization technique in the morning of the surgery

Block randomization technique
Two cards written either Group A (parecoxib 20 mg (1ml)+ropivacaine 0.75%(19 ml)) or Group B (ropivacaine 0.75% 19 ml + 1 ml NS) will be put inside the opaque envelope (allocation concealment)

A card will be picked up each time by either anaesthesia nurse or second medical officer incharge in the OT

Upon arrival in the OT, patients will be brought to the Recovery Room for the procedure.

All patients will be monitored based on standard anaesthesia monitoring (non invasive BP, pulse oxymetry (spO2), electrocardiography (ECG)

Baseline BP, and HR will be documented before the procedures.

IV excess at least 20 G will be inserted on the other hand

IV loading of Ringer's Lactate solution 10 ml/kg will be given before performing the block.

BPB will be performed in the bock corner at the recovery bay.

Drugs regime for BPB will be prepared, which is:

5 ml of Lignocaine 2% for skin infiltration

19 mls ropivacaine 0.75% +parecoxib 20 mg (1ml)

Other standard equipments will be used for the block:

Ultra Sonographic machine Mindray Version M5, Manufactured in China with high frequency (10-15MHz) linear probe

50 to 80mm 22 G insulated peripheral nerve block needle. Vygon, France

2% chlorhexidine in 70% isopropyl alcohol solution for skin cleaning

Block will be performed by a single operator and 2nd medical officer incharge will be blinded assessor. The technique will not use peripheral nerve stimulator.

The block site will be cleaned and draped. The US probe also will be draped for the procedure.

SCB technique will be as below:

Subjects are in the semi-recumbent position with the head turned to the contralateral side and the ipsilateral shoulder slightly elevated with the pillow.

An exploratory scan will be performed in all patients before the block, by positioning the probe in a coronal oblique plane above the clavicle.

Hypo echoic and pulsating supraclavicular artery will be identified, which is lying above the hyper echoic first rib.

While maintaining the view of the artery, the probe is then angled until both the first rib and the pleura are also seen simultaneously.

After skin preparation and draping, the probe will be placed in the supraclavicular fossa and subcutaneous infiltration will be given on the targeted needle side

The needle will be inserted from lateral to medial direction in the long axis of the transducer (in-plane technique)

15 ml of the LA will be injected at the "corner pocket" , an approximately 1 cm^2 area bounded medially by the subclavian artery and inferiorly by the first rib

The remaining 5 ml will be injected to a point approximately level with the superior/ cephalad aspect of the subclavian artery, but no further than 1 cm lateral to the artery.

Risks

Based on the study done by Dr Vincent W.S. Chan et al. (2003), ultrasound guidance for brachial plexus block can potentially improve success and complication rates. In his study, the block was successful after one attempt in 95% of the cases and one well known complication, air in the outer layer of the lungs or *pneumothorax*, did not occur.

However, the complications of supraclavicular brachial plexus block still can occur (e.g.: hematoma, intravascular injection, pneumothorax) but less because the operator is expert and routinely done the procedure**. The procedure will be stopped if any complication should develop and if needed, patient will be observed in "PACU" or "ICU". To prevent the complications, all the safety measures will be complied.**

If there is any new important information discovered during the period of study which could change the consent and to be continue involved in the study, you will be informed as soon as possible.

Reporting Health Experiences.

If you have any injury, bad effect, or any other unusual health experience during or after this study, make sure that you immediately tell the nurse or Dr Vivekananda Gunasekaran 0174384585**. You can call at anytime, day or night, to report such health experiences.**

Other Treatments

You do not have to take part in this study to be treated for your illness or condition. Other treatments and therapies for your condition are available, including your current therapy. The study doctor can discuss these treatments and treat you.

Participation in the Study

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop participation in the study at anytime, without a penalty or loss of benefits to which you are otherwise entitled. Your participation also may be stopped by the study doctor or sponsor without your consent.

If you stop being part of this study, the study doctor or one of the staff members will talk to you about many medical issues regarding the stopping of your participation.

Possible Benefits

Study drug and study procedures will be provided at no cost to you. You may receive information about your health from any physical examination and laboratory tests to be done in this study.

Although this drug (ropivacaine 0.75% and parecoxib) is commonly used as part of anesthetic treatment, there is no guarantee that you will receive any medical benefit.

Investigator's Payment

The study doctors are not receiving any form of payment from any private sponsor.

Questions

If you have any question about this study or your rights, please contact;

Dr Vivekananda Gunasekaran
Department of Anaethesiology
USM Health Campus.
Tel: 0174384585 (HP)

If you have any questions Regarding the Ethical Approval, please contact;

Mr Bazlan Hafidz Mukrim
Secretary of Research Ethics Committee (Human)
Clinical Science Research Platform
USM Health Campus
No. Tel: 09-767 2354/ 09-767 2362
Email : bazlan@usm.my/jepem@usm.my

Confidentiality

Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law.

Your original medical records may be reviewed by the Ethical Review Board for this study, and regulatory authorities for the purpose of verifying clinical trial procedures and/or data. Your medical information may be held and processed on a computer.

By signing this consent form, you authorize the record review, information storage and data transfer described above.

Signatures

To be entered into the study, you or a legal representative must sign and data the signature page.

Patient Information and Consent Form
(Signature Page)

Research Title:

THE EFFECT OF PARECOXIB 20 MG AS AN ADJUNCT IN 0.75% ROPIVACAINE TO ULTRASOUND GUIDED SUPRACLAVICULAR BLOCK FOR UPPER LIMB SURGERY.

Researchers:

1. Dr Wan Mohd Nazaruddin bin Wan Hassan (Anaesthetist and Senior Lecturer , Department of Anaesthesiolgy and Intensive Care Unit, HUSM),

2. Dr Vivekananda Gunasekaran (Medical Officer Anaesthesiolgy, Master Candidate, USM), No.MPM 44220

To become a part this study, you or your legal representative must sign this page. By signing this page, I am confirming the following:

I have read all of the information in this Patient Information and Consent Form including any information regarding the risk in this study and I have had time to think about it.

All of my questions have been answered to my satisfaction.

I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.

I may freely choose to stop being a part of this study at anytime.

I have received a copy of this Patient Information and Consent Form to keep for myself.

Patient Name **(Print or type)** Number	Patient Initials **and**
Patient I.C **No. (New)**	Patient I.C **No. (Old)**
Signature of Patient **or Legal Representative**	Date **(dd/MM/yy) (Add time if applicable)**

Name of Individual
Conducting Consent Discussion (Print or Type)

Signature of Individual
Conducting Consent Discussion

Date **(dd/MM/yy)**

Name & Signature of Witness

Date **(dd/MM/yy)**

Note: **i)** **All subject/patients who are involved in this study will not be covered by insurance.**

PATIENT INFORMATION AND CONSENT FORMS (MALAY VERSION)

LAMPIRAN A

MAKLUMAT KAJIAN

Tajuk Kajian:

KESAN PENGGUNAAN PARECOXIB SEBANYAK 20 MG SEBAGAI AGEN TAMBAHAN KE DALAM 0.75% ROPIVACAINE MENGGUNAKAN TEKNIK ULTRASOUND UNTUK PEMBIUSAN SUPRAKLAVIKULAR BAGI PEMBEDAHAN TANGAN DAN LENGAN.

Nama Penyelidik:

3. Dr W Mohd Nazaruddin bin W Hassan (Pakar Bius Neuro dan Pensyarah, Jabatan Anestesiologi dan Unit Rawatan Rapi, HUSM),

4. Dr Vivekananda Gunasekaran (Medical Officer Anestesiologi,Master Candidate USM No.MPM 44220

Pengenalan

Anda dipelawa untuk menyertai satu penyelidikan secara sukarela untuk menentukan sama ada penambahan ubat Parecoxib ke dalam Ropivacaine 0.75% semasa pembiusan saraf (supraklavikular) dapat mempercapatkan kesan pembiusan dan juga manambahkan durasi tahan sakit.(pain free duration)

Pada umumnya, otot pergerakan dan deria rasa anggota tangan kanan dan kiri dikawal oleh cabang dari saraf tunjang yang dikenali sebagai *Brachial Plexus* yang berpunca dari leher dan berterusan di bawah tulang bahu sehinggalah ke jari jemari. Oleh itu, fungsi saraf *Brachial Plexus* boleh disekat di sepanjang unjurannya dari leher ke jari jemari. Untuk kajian ini, kami lebih berminat untuk menyekat fungsi saraf *Brachial Plexus* di paras atas tulang bahu (supraklavikular).

Pentingnya kajian ini dapat dikongsi bersama oleh pesakit dan doktor dari segi:

i. Keselesaan pesakit yang tidak perlu risau risiko pembiusan penuh; tidak perlu risau masalah sakit sebaik sahaja selepas pembedahan; boleh makan dan minum selepas pembedahan; boleh segera pulang ke rumah selepas pembedahan; dan berinteraksi dengan doktor sewaktu pembedahan;
ii. Doktor bedah dapat memberi tumpuan yang penuh pada bahagian yang perlu dibedah kerana anggota tak dapat bergerak selepas pembiusan; hasilnya pembedahan lebih optimum.

Kajian ini akan diseliai oleh Dr W Nazaruddin b W Hassan (Pakar Bius Neuro dan Pensyarah, Jabatan Anestesiologi HUSM).
Manakala teknik pembiusan akan dijalankan oleh Dr Vivekananda Gunasekaran (M.Med. Anestesiologi HUSM) dan pegawai perubatan yang ada privilegde dan kemahiran melakukan pembiusan brachial plexus.

Sebelum anda bersetuju untuk menyertai kajian penyelidikan ini, adalah penting anda membaca dan memahami borang ini. Ia menghuraikan tujuan, prosedur, manfaat, risiko, ketidakselesan dan langkah berjaga-jaga kajian ini. Ia juga menghuraikan prosedur alternatif yang terdapat untuk anda dan hak anda untuk menarik diri dari kajian ini pada bila-bila masa. Sekiranya anda

menyertai kajian ini, anda akan menerima satu salinan borang ini untuk disimpan sebagai rekod anda.

Penyertaan anda di dalam kajian ini adalah sewaktu anda dijadualkan untuk pembedahan kecemasan atau elektif. Seramai 86 pesakit akan menyertai kajian ini.

Tujuan Kajian

Kajian ini bertujuan untuk mengetahui kesan dan manfaat dengan penambahan Parecoxib ke dalam Ropivacaine 0.75% dan membandingkannya dengan teknik yang menggunakan Ropivacaine 0.75% sahaja.Perkara yang akan dibandingkan adalah jagka masa keberkesanan pembiusan dan juga jangka masa yang diambil selepas pembedehan untuk pesakit kembali seperti sediakala contohnya mampu untuk menggerakkan tangan.

Kelayakan Penyertaan

Doktor yang bertanggungjawab dalam kajian ini atau salah seorang kakitangan kajian telah membincangkan kelayakan untuk menyertai kajian ini dengan anda. Adalah penting anda berterus terang dengan doktor dan kakitangan tersebut tentang sejarah kesihatan anda. Anda tidak seharusnya menyertai kajian ini sekiranya anda tidak memenuhi semua syarat kelayakan.

Beberapa keperluan **untuk menyertai kajian ini adalah –**

- **Anda mesti berumur diantara 18 – 65 tahun.**
- **Anda dijadualkan untuk pembedahan tangan atau lengan samada elektif atau kecemasan**
- **Anda mesti memberikan kebenaran bertulis untuk pembiusan Brachial Plexus (Supraklavikular)**

Anda tidak boleh **menyertai kajian ini sekiranya –**

- **Anda tidak mahu memberikan kerjasama atau tidak mahu mengikuti kajian ini.**
- **Anda alergik pada ubat dexmedetomidine dan ropivacaine.**
- **Anda mengandung atau suspek hamil atau sedang menyusukan anak**
- **Anda ada sejarah kecederaan pada brachial plexus.**
- **Anda ada sejarah sakit kronik yang menggunakan ubat tahan sakit yang kronik**
- **Anda menghidapi " coagulapathy"**
- **Anda menghidapi jangkitan kuman sistemik atau lokal tempat injeksi**
- **Menghidap penyakit jantung kronik, masalah paru-paru dan penyakit hati kronik.**
- **Anda menghidap penyakit saraf yang menglibatkan tangan yang ingin dibedah**
- **Anda telah mengikuti kajian ini sebelum ini atau tidak memenuhi kriteria kajian**

Prosedur-prosedur Kajian

1. Pesakit yang dijadualkan untuk pembedahan tangan atau lengan di bawah seliaan Jabatan Orthopedik atau Bedah Plastik dan Rekonstruktif HUSM akan dipilih untuk menyertai kajian.

2. **Premedikasi untuk sedasi tidak diberikan sebelum prosedur dijalankan.**

3. **Pesakit akan dipilih secara rawak menggunakan teknik rawak berblok pada pagi pembedahan**

4. **Teknik rawak berblok:**
    a. **Dua kad bertulis kumpulan A (Parecoxib +Ropivacaine 0.75%) atau kumpulan B (Ropivacaine 0.75%) akan disimpan dalam sampul surat**

b. **Satu kad akan dipilih samada oleh jururawat anesthesia atau pegawai perubatan kedua bertugas dalam wad bedah**

5. **Pesakit dibawa ke Ruang Pemulihan untuk prosedur. Tanda-tanda vital diambil dan direkod (tekanan darah, kadar denyutan nadi, EKG, SpO2).**

6. **Kanulasi saluran darah melalui intravena dibuat pada lengan yang tidak dioperasi menggunakan Branula bersaiz 20G.**

7. **Pembiusan *brachial plexus* secara supraklavikular dilakukan oleh penyelidik (Dr Vivekanada Gunasekaran)atau pegawai perubatan yang ada *priviledge* dan dibantu oleh seorang lagi pegawai perubatan sebagai pemerhati bebas.**

8. **Selepas kulit dibersih dengan ubat pencegah kuman untuk sterilisasi, ubat lidocaine 2% sebanyak 2 ml disuntik di kulit untuk pembiusan setempat.**

9. **Dengan menggunakan ultrasound (USG), brachial plexus dikenalpasti dan jarum bersaiz 22G, 50 mm dimasukkan**

10. **Ubat Parecoxib 20 mg (1 ml) dan anestetik lokal Ropivacaine 0.75% dimasukkan sebanyak 19 ml dalam 2 lokasi berlainan pada sarung plexus (*posterior and anterior pocket*) untuk biius supraklavikular.**

11. **Selepas prosedur selesai, setelah pesakit sudah berasa kebas dan tidak boleh menggerakkan lengan, pesakit ditolak ke Dewan Bedah untuk dioperasi.**

12. **Jika pesakit mengalami komplikasi dari pembiusan, tindakan resusitasi (ubat, intubasi) akan dilakukan dan terkecuali dari kajian.**

Risiko

Berdasarkan kajian yang dilakukan oleh Dr Vincent W.S. Chan et al. (2003), pembiusan brachial plexus yang dilakukan dengan menggunakan ultrasound mampu mengurangkan kadar kegagalan prosedur dan menurunkan kadar komplikasi. Dalam kajian beliau, kadar sukses pembiusan brachial plexus dengan hanya sekali suntik adalah 95% dan salah satu komplikasi yang boleh berlaku iaitu udara di selaput luar paru-paru atau *pneumothorax*, tidak berlaku.

Namun, risiko terjadinya komplikasi pembiusan brachial plexus teknik supraklavikular masih ada (contoh: injeksi ke dalam pembuluh darah, perdarahan setempat, *pneumothorax*) tetapi sangat kurang kerana prosedur ini dilakukan oleh doktor yang mahir serta selalu melakukannya. **Jika berlaku sebarang komplikasi yang tidak diingini, dan jika perlu, pesakit akan ditempatkan di "PACU" (Post-op Anesthesia Care Unit) atau "ICU" (Intensive Care Unit). Semua langkah keselamatan diikuti dengan teliti untuk mencegah sebarang komplikasi.**

Jika apa-apa maklumat penting yang baru dijumpai semasa kajian ini yang mungkin mengubah persetujuan and untuk terus menyertai kajian ini, anda akan diberitahu secepat mungkin.

Melaporkan Pengalaman Kesihatan

Jika anda mengalami apa-apa kecederaan, kesan buruk, atau apa-apa pengalaman kesihatan yang luarbiasa semasa kajian ini, pastikan anda memberitahu jururawat atau Dr Vivekanada Gunasekaran di 0174384585 **secepat mungkin. Anda boleh membuat panggilan pada bila-bila masa, siang atau malam, untuk melaporkan pengalaman sedemikian.**

Rawatan Lain

Anda tidak perlu mengambil bahagian dalam kajian ini untuk rawatan bagi penyakit atau keadaan anda. Terdapat rawatan dan terapi lain untuk keadaan anda, termasuk rawatan anda yang kini. Doktor kajian boleh membincangkan rawatan dan terapi ini dengan anda.

Penyertaan Dalam Kajian

Penyertaan anda dalam kajian ini adalah secara sukarela. Anda boleh menolak penyertaan dalam kajian ini atau anda boleh menamatkan penyertaan anda dalam kajian ini pada bila-bila masa, tanpa sebarang hukuman atau kehilangan sebarang manfaat yang sepatutnya diperolehi oleh anda.

Jika anda berhenti menyertai kajian ini, doktor kajian atau salah seorang kakitangan akan berbincang dengan anda mengenai apa-apa isu perubatan berkenaan dengan pemberhentian penyertaan anda.

Kemungkinan Manfaat

Ubat dan prosedur kajian akan diberikan kepada anda tanpa kos. Anda mungkin menerima maklumat tentang kesihatan anda dari apa-apa pemeriksaan fizikal dan ujian makmal yang bakal dilakukan dalam kajian ini.

Walaupun ubat ini (Ropivacaine dan Parecoxib) merupakan ubat yang sering digunapakai dalam bidang anestesia, tidak ada jaminan bahawa anda akan menerima apa-apa manfaat perubatan.

Bayaran Doktor (Penyelidikan)

Doktor kajian tidak menerima bayaran daripada mana-mana pihak penaja swasta.

Soalan

Sekiranya anda mempunyai sebarang soalan mengenai prosedur kajian ini atau hak-hak anda, sila hubungi;

Dr Vivekananda Gunasekaran
Pegawai Perubatan Bius,
Jabatan Anestesiologi dan Rawatan Rapi
Universiti Sains Malaysia
Tel: 0174384585 (HP)

Sekiranya anda mempunyai sebarang soalan berkaitan kelulusan Etika kajian ini, sila hubungi;

Encik Bazlan Hafidz Mukrim
Setiausaha Jawatankuasa Etika Penyelidikan (Manusia) USM
Pelantar Penyelidikan Sains Klinikal, USM Kampus Kesihatan.
No. Tel: 09-767 2354 / 09-767 2362
Email : bazlan@usm.my/jepem@usm.my

Kerahsiaan

Maklumat perubatan anda akan dirahsiakan oleh doktor dan kakitangan kajian dan tidak akan dedahkan secara umum melainkan jika ia dikehendaki oleh undang-undang.

Rekod perubatan anda yang asal mungkin akan dilihat oleh Lembaga Etika kajian ini dan pihak berkuasa regulatori untuk tujuan mengesahkan prosedur dan/atau data kajian klinikal. Maklumat perubatan anda mungkin akan disimpan dalam komputer dan diproses dengannya.

Dengan menandatangani borang persetujuan ini, anda membenarkan penelitian rekod, penyimpanan maklumat dan pemindahan data seperti yang dihuraikan di atas.

Tandatangan

Untuk dimasukkan ke dalam kajian ini, anda atau wakil sah anda mesti menandatangani serta mencatatkan tarikh halaman tandatangan (Lihat LAMPIRAN 1**).**

Borang Keizinan Pesakit
(Halaman Tandatangan)

Tajuk Kajian:

KESAN PENGGUNAAN PARECOXIB SEBANYAK 20 MG SEBAGAI AGEN TAMBAHAN KE DALAM 0.75% ROPIVACAINE MENGGUNAKAN TEKNIK ULTRASOUND UNTUK PEMBIUSAN SUPRAKLAVIKULAR BAGI PEMBEDAHAN TANGAN DAN LENGAN.

Nama Penyelidik:

1. Dr W Mohd Nazaruddin bin W Hassan (Pakar Bius Neuro dan Pensyarah, Jabatan Anestesiologi dan Unit Rawatan Rapi, HUSM),

5. Dr Vivekananda Gunasekaran (Medical Officer Anestesiologi,Master Candidate USM

No.MPM 442200

Untuk menyertai kajian ini, anda atau wakil sah anda mesti menandatangani mukasurat ini.Dengan menandatangani mukasurat ini, saya mengesahkan yang berikut:

- **Saya telah membaca semua maklumat dalam Borang Maklumat dan Keizinan Pesakit ini** termasuk apa-apa maklumat berkaitan risiko yang ada dalam kajian **dan saya telah pun diberi masa yang mencukupi untuk mempertimbangkan maklumat tersebut.**
- **Semua soalan-soalan saya telah dijawab dengan memuaskan.**
- **Saya, secara sukarela, bersetuju menyertai kajian penyelidikan ini, mematuhi segala prosedur kajian dan memberi maklumat yang diperlukan kepada doktor, para jururawat dan juga kakitangan lain yang berkaitan apabila diminta.**
- **Saya boleh menamatkan penyertaan saya dalam kajian ini pada bila-bila masa.**
- **Saya telah pun menerima satu salinan Borang Maklumat dan Keizinan Pesakit untuk simpanan peribadi saya.**

Nama Pesakit **(Dicetak atau Ditaip)**	Nama Singkatan & No. Pesakit
No. Kad Pengenalan Pesakit **(Baru)**	No. K/P **(Lama)**
Tandatangan Pesakit atau Wakil Sah	**Tarikh** (dd/MM/yy) (Masa jika perlu)
Nama & Tandatangan Individu **yang Mengendalikan**	Tarikh **(dd/MM/yy)**

Perbincangan Keizinan (Dicetak atau Ditaip)

_____ _____

Nama Saksi dan Tandatangan Tarikh **(dd/MM/yy)**

Nota: **i) Semua subjek/pesakit yang mengambil bahagian dalam projek penyelidikan ini tidak dilindungi insuran.**