A PROSPECTIVE STUDY OF ANALGESIA EFFICACY AND PLASMA ROPIVACAINE CONCENTRATION AFTER PECS II BLOCK IN PATIENT UNDERGOING MASTECTOMY

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DISSERTATION SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS IN ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY
UNIVERSITY OF MALAYA
KUALA LUMPUR

2017

UNIVERSITY OF MALAYA
ORIGINAL LITERARY WORK DECLARATION

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ABSTRACT

Background and Objective: The introduction of novel ultrasound guided Pecs block has changed the choice for providing anaesthesia and/or analgesia to the upper part of the anterior chest wall. This technique was later adapted (PECS II block) to provide better coverage for more extensive procedures, especially involving the axilla. We would like to conduct a prospective descriptive study to measure the safety level of Ropivacaine and the analgesic efficacy for PECS II block using 30ml Ropivacaine 0.5%.

Method: After obtaining approval from the UMMC Medical Research Ethics Committee (20165-2443) and written informed general anaesthesia (GA) and regional block consent, adult female patients undergoing unilateral mastectomy with axillary clearance were prospectively enrolled. PECS II block was performed with ultrasound guidance before induction of anaesthesia, and chronological blood samples were obtained by aspiration from a large bore venous cannula specifically placed in the antecubital fossa. All participants received a total dose of Ropivacaine not more than 3mg/kg, which is diluted with 0.9% saline to constitute 30ml of Ropivacaine 0.5% solution concentration. Venous blood was sampled from the blood taking canulla at 10, 20, 30, 45, 60, 90, and 120 minutes after Ropivacaine administration. Plasma Ropivacaine concentration was measured with liquid chromatography- tandem mass spectrometry method at the Pharmacology department, Medical Faculty, University Malaya.

Results: There were 6 patients who successfully completed this study protocol; they were aged between 52 and 71 (mean 63) years old. The weight of the patients is between 54 and 70kg (mean 63kg). Total Ropivacaine used for every patient was fixed at 150mg. In our study, there were no signs of CVS or CNS toxicity seen in the patients during the study period. The mean peak venous plasma concentration (C_{max}) was 2.12 μg/ml (SD 0.41, range 1.80-2.61). The median time point of maximum concentration

(T_{max}) of Ropivacaine occurred at 37.5min (range 20-60 min). The highest individual venous plasma concentration (C_{max}) was 2.61 µg/ml occurred at 45 min.

Conclusion: This study demonstrates that the use of 150mg Ropivacaine in the unilateral PECS II block in adult females is safe without exceeding the toxic level. There were no patients reported to have signs of CNS and CVS toxicity.

ABSTRAK

Latar Belakang dan Objektif: Pengenalan ultrasound novel berpandu Pecs blok telah berubah pilihan untuk menyediakan anestesia dan / atau analgesia untuk bahagian atas dinding dada. Teknik ini kemudiannya disesuaikan (Pecs II blok) untuk menyediakan liputan yang lebih baik untuk prosedur yang lebih luas, terutamanya yang melibatkan bahagian ketiak. Kami ingin menjalankan kajian deskriptif bakal untuk mengukur tahap keselamatan Ropivacaine dan keberkesanan analgesik untuk Pecs II blok menggunakan 30ml Ropivacaine 0.5%.

Kaedah: Selepas mendapat kelulusan daripada Jawatankuasa Etika Penyelidikan Perubatan PPUM (20165-2443) dan kebenaran bertulis dimaklumkan bius umum (GA) dan blok stempat, pesakit dewasa wanita menjalani mastektomi satu belah dengan pelepasan axillary telah didaftar secara aktif. Pecs II blok dilakukan dengan bimbingan ultrasound sebelum induksi anestesia, dan sampel darah kronologi diperolehi dengan aspirasi dari kanula bore vena besar diletakkan secara khusus dalam lekuk antecubital. Semua peserta menerima sejumlah dos Ropivacaine tidak lebih daripada 3mg / kg, yang dicairkan dengan 0.9% masin untuk membentuk 30ml Ropivacaine 0.5% kepekatan larutan. Darah vena telah disampel daripada canulla pengambilan darah pada 10, 20, 30, 45, 60, 90, dan 120 minit selepas diberi Ropivacaine. Kepekatan plasma Ropivacaine diukur dengan seiring chromatography- kaedah spektrometri jisim cecair di Jabatan Farmakologi, Fakulti Perubatan, Universiti Malaya.

Keputusan: Terdapat 6 pesakit yang berjaya menamatkan protokol kajian ini; mereka adalah berusia antara 52 dan 71 (min 63) tahun. Berat daripada pesakit adalah antara 54 dan 70 kg (min 63kg). Jumlah Ropivacaine digunakan untuk setiap pesakit telah ditetapkan pada 150mg. Dalam kajian kami, tidak ada tanda-tanda system kardiovasular atau ketoksikan system saraf dilihat dalam pesakit sepanjang tempoh kajian. Puncak

kepekatan plasma vena (Cmax) adalah 2.12 μg/ml (SD 0.41, julat 1.80-2.61). Titik masa median kepekatan maksimum (Tmax) daripada Ropivacaine berlaku di 37.5min (julat 20-60 min). Kepekatan individu plasma (Cmax) adalah 2.61 μg / ml berlaku pada 45 min.

Kesimpulan: Kajian ini menunjukkan bahawa penggunaan 150mg Ropivacaine dalam Pecs II blok pada wanita dewasa adalah selamat tanpa melebihi tahap toksik. Tiada pesakit dilaporkan mempunyai tanda-tanda ketoksikan sistem saraf and sistem kardiovascular.

ACKNOWLEDGEMENT

I would first like to thank my thesis advisor Associate Professor Dr Mohd Shahnaz Bin Hasan of the Department of Anaesthesiology, University of Malaya Medical Center. The door to A/Prof. Shahnaz office was always open whenever I ran into a trouble spot or had a question about my research or writing. He consistently allowed this paper to be my own work, but steered me in the right the direction whenever he thought I needed it.

I would also like to thank the experts who were involved in the validation survey for this research project: Dr Azrin Mohd Azidin (Consultant Anaesthesiologist, Hospital Kuala Lumpur), Dr. Beh Zhi Yuen (Anaesthesiologist, Hospital Kuala Lumpur). Without their passionate participation and input, the validation survey could not have been successfully conducted.

I would also like to acknowledge Professor Gracie Ong Siok Yan (Professor in Department of Anaesthsiology, Univerversity Malaya Medical Center) who provided insight and expertise that greatly assisted the research.

Finally, I must express my very profound gratitude to my parents and to my spouse, for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Dr Khaw Soon Keong

TABLE OF CONTENT

LIST OF TABLES

LIST OF SYMBOLS AND ABBREVIATIONS

BMI – Body Mass Index

C_{max} - maximum venous plasma concentration

HKL – Hospital Kuala Lumpur

LAST - Local Anaesthetic Systemic Toxicity

LCMS – tandem mass liquid chromatography

PECS Block – Pectoral nerve block

QLB - Quadratus Lumborum Block

RSB - Rectus Sheath Block

TAP - Transversus Abdominis Plane Block

T_{max} - time point of maximum concentration of Ropivacaine occurred

TPVB – Thoracic paravertebral block

UMMC – university Malaya Medical Center

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

Regional anaesthesia techniques are common modalities used to provide analgesia following both upper and lower extremity surgeries. It is also often used for truncal procedures for the same purpose. A relatively new truncal block, first described in 2012 by Blanco, called the pectoralis nerve block (PECS I and II block) has been used successfully for breast surgery. Despite its description and success in clinical practice, the extent of systemic absorption of local anaesthetics from this truncal plane block has not been described to date.

To our knowledge, there has been no published data on chronological ropivacaine concentration after PECS II block. Therefore, we would like to conduct a prospective descriptive study to measure the safety level of Ropivacaine and the analgesic efficacy for PECS II block using 30ml Ropivacaine 0.5%, as well as to determine the maximum venous plasma concentration (Cmax) and time point of that maximum after the start of injection (Tmax).

Primary outcome:

To measure the chronological changes in venous concentration of Ropivacaine after PECS II block, in which the calculation for the time point of maximum concentration of Ropivacaine occurred (T_{max}) and maximum venous plasma concentration (C_{max}) are mandatory. This would determine whether the peak plasma Ropivacaine concentration level is within the safety level allowed. The venous threshold value of systemic toxicity is 2.2 μg/ml. The result of this study might change future recommended dosing regimen for PECS II block practice using Ropivacaine.

Secondary Outcome

To describe the quality of sensory blockade in terms of dermatological extent and block duration of the analgesic effect.

CHAPTER 2: LITERATURE REVIEW

In the past, thoracic epidural analgesia[1] was the gold standard regional technique for breast surgery while thoracic paravertebral blocks (TPVBs)[2] were the alternative approach. However, both techniques were associated with serious complications, though rare such as pneumothorax, total spinal anaesthesia and inadvertent intravascular puncture. TPVB is generally performed before general anesthesia for surgery, and not all anesthesiologists feel comfortable doing the block. Paravertebral block always has the risk of iatrogenic pneumothorax and nerve injury. Additionally, it cannot be performed in the supine position.

The introduction of novel ultrasound guided Pecs block has changed the choice for providing anaesthesia and/or analgesia to the upper part of the anterior chest wall. [3, 4] This block is easy to perform and avoids complications associated with neuraxial techniques or TPVBs. Pecs block has recently been given Grade A recommendation with the support of level of evidences Ib to III studies.[5] To date, no report of complications after US-guided Pecs blocks has been reported.[6]

Pecs Block was first described by Blanco in 2011.[3] This ultrasound-guided inter-fascial plane block involved placing local anaesthetic (LA) in the plane between the pectoralis major and minor muscles, adjacent to the pectoral branch of the thoracoacromial artery ("Pecs" or "PECS I" block) with 0.4 ml/kg levobupivacaine 0.25%. This block is particularly useful for patients who have breast expanders placed during reconstructive breast cancer surgery or sub pectoral prostheses.

This technique was later adapted (PECS II block) [4] to provide better coverage for more extensive procedures, especially involving the axilla. The first injection is a PECS I block with 10 ml of LA. The second injection of LA is performed more laterally in the plane between the pectoralis minor and serratus anterior muscles at the level of the third and fourth ribs with 20ml LA. Bashandy and Abbas recently reported that

PECS II block was able to reduce intraoperative fentanyl requirement, postoperative pain, postoperative morphine consumption, as well as postoperative nausea and vomiting (PONV) in patients undergoing BCS. [7]

Dr Blanco had used Levobupivacaine as the local anaesthetics (LAs) of choice in his studies.[3, 4] However, Ropivacaine is the preferred LAs in regional anaesthesia with its better safety profile [8], vasoconstrictive effect and preferential more sensory block. Several studies have evaluated the measurement the maximum time to peak concentration (Tmax) and the maximum concentration of Ropivacaine (Cmax) after regional blocks such as intercostal blocks [9], transverse abdominis plane block [10, 11], quadratus lumborum block [12], and scalp block [13]. The above blocks were evaluated, with intercostals block and scalp block found to have the shortest time to reach Tmax, at 11 minutes[9] and 15 minutes[13] respectively.

Knudsen and colleagues had shown that ropivacaine has a higher tolerated dose for central nervous system (CNS) symptoms and less pronounced cardiovascular changes as compared to bupivacaine; the maximum tolerated plasma comcentration plasma concentration of ropivacaine is 2.2µg/ml.[8] Having said that, several studies revealed that despite having higher plasma ropivacaine measured of more than 2.2µg/ml, the subject does not experience significant CNS and CVS symptoms.[9-11, 13]

In this study, we will use venous plasma ropivacaine level for sampling and measurement as this method is less invasive. In a study by Behnke, there is no significant difference for measuring arterial and central mixed venous plasma ropivacaine concentration after 5 minutes time course.[9]

CHAPTER 3: MATERIAL AND METHODOLOGY

After obtaining ethics committee approval (University of Malaya Medical Center, Kuala Lumpur, Malaysia) and written informed general anaesthesia (GA) and block consent, adult female patients undergoing unilateral mastectomy with axillary clearance were prospectively enrolled.

Inclusion criteria:

- ASA 1, 2 and 3 (without significant liver or renal impairment)
- Age above 18 years old
- Able to give consent
- Body weight > 50kg

Exclusion Criteria:

- Patient's refusal and inability to give consent or cooperation during procedure
- Allergy or sensitivity to local anaesthetics
- BMI>35

All patients recruited received 30ml Ropivacaine 0.5% during PECSII block. Every patient was provided with Oral Paracetamol 1g and Oral Celebrex 200mg on OT call for multimodal analgesia. Upon arrival in the induction room, an 18- or 20-gauge intravenous catheter was placed in the upper limb contralateral to the surgical site. Other site for peripheral intravenous access was chosen if required. Premedication was offered if required during block procedure at the jurisdiction of the operator (Midazolam 1 - 3 mg intravenously and/or Fentanyl 25 - 100 ug intravenously). Supplemental oxygen was given if the patient received sedation (nasal cannulas at 3 L/min) and standard ASA monitoring (non-invasive blood pressure, electrocardiogram, and pulse oximetry) was applied throughout the procedure.

After induction of anaesthesia, blood samples were obtained by aspiration from a large bore venous cannula specifically placed in the antecubital fossa on the contralateral side to the cannula used for administering fluids and medications.

The infraclavicular and axillary area of the operative site were cleaned with chlorhexidine solution. PECS II block was performed by a study investigator (or by a senior trainee experienced in the technique, under the direct supervision of a study investigator). Images were obtained using a Sonosite M-Turbo® ultrasound machine (Sonosite Inc., Bothwell, WA, USA) with an L38x 10-5 MHz 38 mm broadband linear array probe. Blocks were performed with a 150 mm Stimuplex® needle (B-Braun Medical, Bethlehem, PA, USA) using an in-plane approach. The skin point of puncture was infiltrated with 2% lidocaine and once the structures were identified with ultrasound, 10 ml of Ropivacaine (Naropin®, AstraZeneca, London, UK) was injected between the pectoral muscles and 20 ml under Pectoralis minor above the serratus muscle as described by Blanco[4]. Overall, participants received a total dose of Ropivacaine not more than 3mg/kg, which was diluted with 0.9% saline to constitute 30ml of Ropivacaine 0.5% solution concentration.

The duration from the end of the block to start of the surgical incision was recorded. Venous blood was sampled from the blood taking canulla at 10, 20, 30, 45, 60, 90, and 120 minutes after Ropivacaine administration. Signs and symptoms of LA toxicity were also recorded if present.

General anesthesia was induced with fentanyl 1-2 mcg/kg, propofol 2-3 mg/kg and supraglotic airway was used for ventilation. Anaesthesia was maintained with sevoflurane or desflurane with MAC 0.8 – 1.0. IV Morphine total 0.1mg/kg was given intraoperatively.

After recovery from anesthesia, patients were transferred to post-anesthetic care unit (PACU) for the first 2 hours. Pain intensity was measured using VAS (1–10) at rest

and during abduction of the ipsilateral upper limb. Secondary end points were the duration of the block and the extent of dermatomes losing a sensation of pain and cold due to the block. The duration of the block was evaluated by measuring the amount of time that elapsed between completion of the block and the first administration of postoperative rescue analgesia. Rescue analgesia was subcutaneous Morphine 0.1mg/kg, administered upon patient request.

Sensory blocks were unable to be assessed 30 minutes after the blocks as patients had to undergo general anaethesia once the blocks were performed.

Plasma Ropivacaine concentration was measured with liquid chromatography-tandem mass spectrometry method at the Pharmacology department, Medical Faculty, University Malaya.

3.1 Blood processing

Blood samples were collected before drug administration and at various intervals post-drug administration. The samples were centrifuged at 4500 rpm for 10 min to obtain plasma. The plasma samples were transferred into separate cryo-vial tubes, frozen and stored at −20 ◦C for further analysis.

Ropivacaine was extracted from plasma samples using a simple protein precipitation method. 100uL of plasma sample was taken and inserted into clean micro-centrifuge tube. Then, 400uL acetonitrile (100%) was added to precipitate the protein. The sample was vortexed for 20 seconds and centrifuged at 14,800 rpm for 15 minutes to separate the supernatant. Then, 400uL of the supernatant was transferred to a new chromatography glass vial. Total 10uL of the extracted sample was injected into LCMSMS for analysis.

3.2 LCMSMS procedure

The LC/MS/MS system consisted of two LC-20ADXR pumps and coupled to an 8030 triple-quadrupole tandem mass spectrometer (Shimadzu, Kyoto, Japan) with a

turbo ion spray interface. The chromatographic separation was detected using an analytical column Phenomenex, Gemini-NX C18 (150 mm length X 2.1 mm I.D, particle size 5µm) and Phenomenex, Gemini-NX C18 guard column (4mm ID x 2.0mm length). Mobile phase A was 15mM ammonium formate in water with 0.01% formic acid, and mobile phase B consisted of LCMS grade acetonitrile. The initial gradient started from 10% of mobile phase B from 0.01 minute and then went up to 95% to 5 minute and hold for 7 minute. At 7.01 minutes mobile phase B was set to 10% again and hold for another 10 minutes. The flow rate was 0.3 mL/min. The retention times for ropivacaine is 2.87 minutes with mass transitions of m/z 275.00→126.10 and m/z 275.00→84.0.

CHAPTER 4: RESULTS

There were 6 patients who successfully completed this study protocol; they were aged between 52 and 71 (mean 63) years old. The weight of the patients is between 54 and 70kg (mean 63kg). Total Ropivacaine used for every patient was fixed at 150mg, the dose according to weight ranged between 2.14-2.78 mg/kg, with the average of 2.4mg/kg Ropivacaine.

In our study, there were no signs of CVS or CNS toxicity seen in the patients during the study period. Only one patient required post operative rescue SC Morphine for severe pain at 8 hours post op when she initially refused the prescribed analgesia given by nurses. All patients underwent the surgery successfully with standard dose of analgesia prescribed.

The mean peak venous plasma concentration (C_{max}) was 2.12 µg/ml (SD 0.41, range 1.80-2.61). The median time point of maximum concentration (T_{max}) of Ropivacaine occurred at 37.5min (range 20-60 min). The highest individual venous plasma concentration (C_{max}) was 2.61 µg/ml occurred at 45 min.

Table 4.1: Patients' characteristics, average dose of Ropivacaine, Cmax and Tmax

Patient number	Age (years)	Weight (kg)	Height (cm)	BMI	Average Dose (mg/kg)	Cmax (µg/ml)	Tmax (min)	Surgery time (min)
1	63	63	153	26.9	2.38	2.57	20	70
2	64	63	148	28.8	2.38	2.61	45	55
3	71	65	158	26.0	2.31	2.23	30	60
4	69	54	154	22.8	2.78	1.80	30	45
5	52	63	149	28.4	2.38	1.84	60	85
6	57	70	157	28.4	2.14	1.66	60	120

CHAPTER 5: DISCUSSION

The mean peak venous plasma concentration (C_{max}) for the current study was 2.12 µg/ml. This was lower than previously published by Knudsen and colleagues(8) in a study of volunteers receiving titrated intravenous (i.v.) infusions of ropivacaine the revealed the onset of neurological symptoms at a mean total plasma venous concentration of 2.2µg/ml. The dose of local anaesthetic in the current study was standardised at 150mg of Ropivacaine despite weight differences; thus Cmax may have differed if different dosages of local anaesthetics were used, as demonstrated in a study by Behnke (9) for intercostals block with different concentrations.

All patients in the current study did not show signs of toxicity, despite having an individual highest level of 2.61µg/ml at 45 minutes after injection. However, Knudsen's paper represented a different clinical scenario, where i.v. local anaesthetic infusions were titrated in volunteers, without supplemental anaesthetic agents which may reduce the likelihood of neurotoxic symptoms. Knudsen's study measured the onset of minor neurotoxic symptoms, rather than potentially life-threatening toxicity.

In Behnke's study, plasma ropivacaine level after intercostals block with Ropivacaine 1% resulted in Central (mixed)venous plasma concentration that were higher compared with arterial concentration at 2 min after completion of the block. On the other hand, no significant differences were found in further time course. [9] In the current study, the first sample after injection was 10 minutes after injection was ompleted.

In addition to absolute plasma levels, the rate of increase in plasma local anaesthetic concentration was implicated in resulting toxicity. In our study, PECS Block has a Tmax of 37.5 minutes, which was comparable to Ilioinguinal block at 45 minutes [14], Infraclaviclar brachial plexus block at 25minutes [15], TAP block at 30minutes [16], Rectus sheath block at 53minutes [10], and QL block at 35minutes [12]. In contrast, after

Intercostal block [9], scalp block [13] and supraclavicular block [15] showed a shorter Tmax at 10minutes, 15minutes, 13.4minutes respectively. By knowing the Tmax of each block, it served as a caution to anaesthetists giving the block to observe for local anaesthetic systemic toxicity (LAST) system while performing respective blocks. In our study, we were unable to check for cutenous block and LAST because most patients underwent surgery before 37 minutes.

Different anatomical locations display different pharmacokinetic characteristics influencing toxicity. Dosage recommendations should also be technique-specific. For example, different approaches to the brachial plexus result in significantly different Cmax and Tmax of local anaesthetic; supraclavicular approach has higher Cmax than infraclavicular approach 3.3 and 2.55µg/ml respectively; Tmax of 13.4 min, and 25.0min respectively.[15] Having said that Cmax was higher; the mean dosage used in this study was among the highest (3.75mg/kg) compared to other regional blocks conducted. (Table 2) TAP block and plasma ropivcaine level were conducted by different authors with comparable Tmax value but differences in Cmax value of 2.54µg/ml [11] and 1.8µg/ml [10] despite having the same average dose of Ropivacaine. This difference is important as one value is higher than the toxicity level, and the reason for the difference may be due to the methodology. Griffiths used Ropivacaine 3mg/kg that was diluted to 40mls, whereas Murouchi gave a standard dose of 30mls Ropivacaine 0.5%. This may suggest that the total volume of LA given may affect the Cmax value; a higher volume may result in a higher Cmax. Epinephrine might reduce the risk to some extent, because it reduces absorption of injected local anesthetics, decreases Cmax and extends Tmax. (17, 18)

Table 5.1: Summary of previous studies and its result on Cmax and Tmax

Yr	Author	Type of Block	Mean dose (mg/kg)	Cmax (µg/ml) (range)	Tmax (min)
2001	Wulf (14)	Ilioinguinal	-	1.5 (0.7-2.6)	45 (30-60)
2002	Behnke (9)	Intercostal block	-	*0.2% - 1.0 (0.3-2.3) *0.5% - 1.8 (0.5-4.5) *0.75%-2.2 (1.5-5.1) *1.0% - 2.3 (1.6-5.6) *#1.0%-2.2 (1.5-3.6)	10 (5-15) 7.5 (5-20) 10 (5-20) 10 (5-45)
2004	Costello (13)	Scalp block	2.15-4.38	1.5 (0.7-2.5)	15 (15-45)
2007	Rettig (15)	Supraclavicular block Infraclavicular block	3.75 3.75	3.30# 2.55#	13.4 25
2010	Griffiths (11)	TAP block	3	2.54	30
2015	Murouchi (10)	Rectus Sheath block	2.66	1.79#	53
2015	Murouchi (10)	TAP block	3	1.83#	35
2016	Murouchi (12)	QL block	2.8	1.0#	35
	Current Study	PECS Block	2.14-2.78	2.12 (1.66-2.61)	37.5

*Ropivacaine concentration
#Arterial sample

5.1 Limitations

PECS block is a truncal block which utilises the spread of volume to the desired dermatome. However, the dosage that the current investigators used was a fixed dosage and not based on patient's weight. Cmax and sign of toxicity could vary if a higher dosage was used.

One limitation of our study is that the investigators did not have enough time to assess the quality of the block before the induction of anesthesia. In the current study, the peak ropivacaine level occurred at 37.5 min where most patients were already under anaesthesia.

Another limitation of the study is the small sample size. During the course of the study, several breast cancer registries as well as other studies conducted by the primary team involved blood sampling. Not surprisingly, patients were reluctant to participate in the current study due to the need for multiple blood taking. This subsequently made the recruitment of participants challenging. However, if more patients could be recruited for this study, then the Cmax and Tmax could have been more precised.

Lastly, the participants in this study were healthy adult female patients. It is possible that the measured concentrations would be different in males, children or the elderly, or in pregnancy. Other conditions in which plasma concentrations may be unexpectedly increased could include renal or cardiac failure.

5.2: Further study

If weight-based Ropivacaine is used in a 30 ml of LA, different LA concentration may be used which may affect the Cmax and Tmax. In view of the safety profile of Ropivacaine, Cmax which is lower that the toxic level, Tmax resembles the the truncal plane block, bilateral PECS block could also be considered in future studies.

A recently published case report of intraoperative catheter placement for PECS block catheter infusion [19], post operative pain relieve and infusion dose could be an

area to explore. Ultrasound-guided parasternal Pecs block: a new and useful supplement for current Pectoral nerve blocks.[20]

CHAPTER 6: CONCLUSION AND RECOMMENDATION

In conclusion, this study demonstrates that the use of 150mg Ropivacaine in the unilateral PECS II block in adult females is safe without exceeding the toxic level. Further study could look into the safety of post operative Ropivacaine infusion in patient undergoing mastectomy.

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APPENDIX A

Data collection Sheet A Study number: _____

Date:

Name	
RN	
Age	
Race	Malay / Chinese / Indian / Others:_____
Weight (kg)	
Height (cm)	
BMI (kg/m^2)	
ASA	I / II /III
Diagnosis	
Operation	
Time of block completed	
Duration of surgery (stating time start and end)	Start : End :
Duration of Anaesthesia (stating time start and end of anaesthesia)	Start : End :

Data Collection Sheet B

Time from block is completed	Ropivacaine concentration (μg/ml)
0 Min	
10 min	
20 min	
30 min	
45 min	
60 min	
90 min	
120 min	

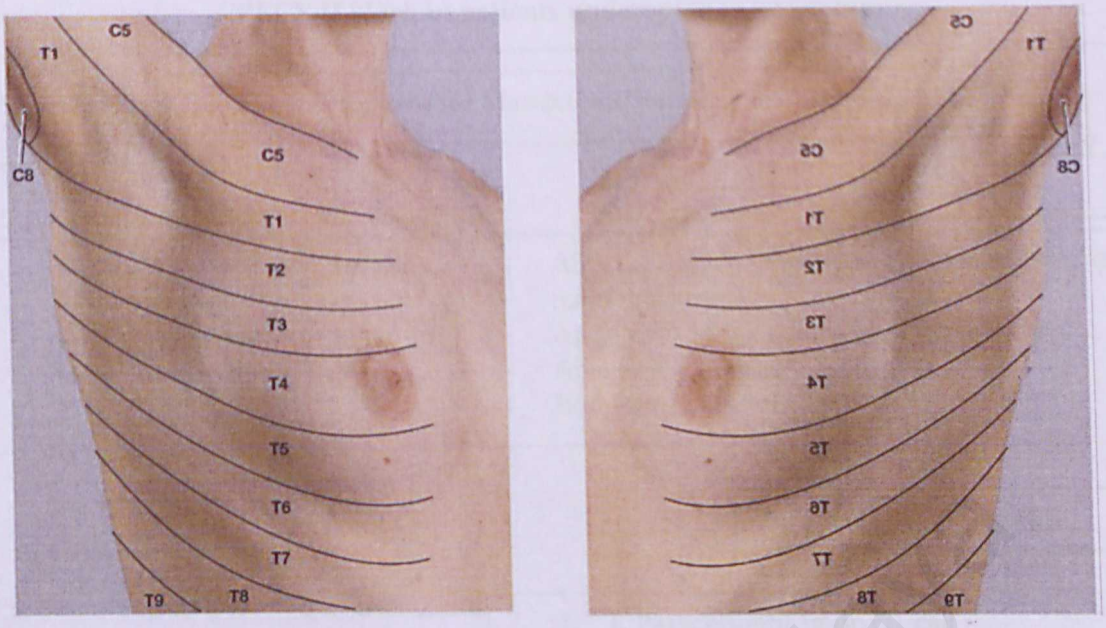
Time point of maximum concentration of Ropivacaine occurred (T_{max}) : _____ min

Maximum venous plasma concentration (C_{max}) : _____ μg/ml

Date and Time for rescue analgesia (SC Morphine 0.1mg/kg):

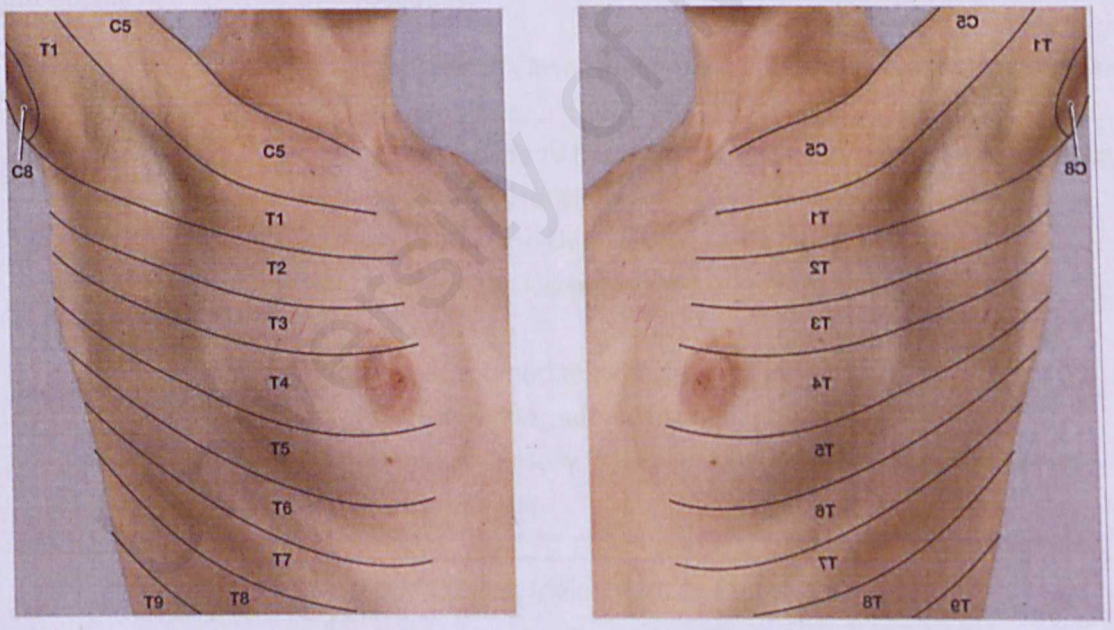
Loss of sensation to **pin prick**:

(Map the area of block)



Loss of sensation to **cold ice pack**:

(Map the area if block)



APPENDIX B

A prospective study of analgesic efficacy and plasma Ropivacaine concentration after PECS II block in patients undergoing mastectomy

Patients for elective Mastectomy with axillary clearance

Exclusion

- Patient's refusal and inability to give consent
- Allergy or hypersensitivity to local anaesthetics
- BMI>35

Inclusion

- ASA 1, 2 and 3 (without significant liver or renal impairment)
- Age above 18 years old
- Able to give consent
- Body weight > 50kg

Enrollment and Consent

Pre-operative :

1. T. Paracetamol 1g on OT call
2. T. Celebrex 200mg on OT call

Intra-operative :

Procedues:

- 18G canulla inserted on cubital fossa, contralateral side with surgery site.
- May provide IV Midazolam 1-3mg, ± IV Fentanyl 25-100mcg per Anaesthetist.
- Injection site clean and drap, LA Lignocaine given.
- PECS II block is performed with Ropivacaine 0.5%, total 30mls.
- Venous blood taken from canulla at 10, 20, 30, 45, 60, 90, 120 min after administration of Rpivacaine.
- Area of sensory blockade is done with cold and pin-prick after 30 min.

Induction and Maintenance of Anaesthesia

- General Anaesthesia with supraglottic airway, IV Fentanyl 1-2 mcg/kg, IV Propofol 2-3mg/kg, Sevoflurane/Desflurane at 0.8-1.0 MAC, IV Morphine 0.1mg/kg.

Post- Operative :

- Routine post Anaesthetic observation in OT Recovery
- Post op oral analgesia : T Paracetamol 1g qid, T. Celebrex 200mg bd
- If pain score >4, or when patient requested for more analgesia:
  Rescue Analgesia is SC Morphine 0.1mg/kg stat, and record time: _____ and date: _____

Issues pertaining to post-operative pain management may contact Dr Khaw SK at 012-8081609.

APPENDIX C

CONSENT BY PATIENT FOR CLINICAL RESEARCH

Version No.: 1
Version Date: 6 May 2016

I,.....IdentityCard No.....
(Name of Patient)
of .....
(Address)
hereby agree to take part in the clinical research (clinical study/questionnaire study/drug trial) specified below:

A prospective study of analgesic efficacy and plasma Ropivacaine concentration after PECS II block in patients undergoing mastectomy

.....

the nature and purpose of which has been explained to me by Dr. .....
(Name & Designation of Doctor)

and interpreted by ..... to the best of his/her ability in
(Name & Designation of Interpreter)

..... language/dialect

I have been told about the nature of the clinical research in terms of methodology, possible adverse effects and complications (as per patient information sheet). After knowing and understanding all the possible advantages and disadvantages of this clinical research, I voluntarily consent of my own free will to participate in the clinical research specified above.

I understand that I can withdraw from this clinical research at any time without assigning any reason whatsoever and in such a situation shall not be denied the benefits of usual treatment by the attending doctors.

Date: ..... Signature or Thumbprint .....
(Patient)

IN THE PRESENCE OF

Name .....

Identity Card No. ..... Signature.....
(Witness for Signature of Patient)

Designation .....

I confirm that I have explained to the patient the nature and purpose of the above-mentioned clinical research.

Date ..... Signature .....
(Attending Doctor)

CONSENT BY PATIENT FOR CLINICAL RESEARCH

R.N.
Name
Sex
Age
Unit

BK-MIS-1117-E02

KEIZINAN OLEH PESAKIT UNTUK PENYELIDIKAN KLINIKAL

Nombor Versi: 1

Tarikh Versi: 6 May 2016

Saya,..... No. Kad Pengenalan .....
(Nama Pesakit)

beralamat.....
(Alamat)

dengan ini bersetuju menyertai dalam penyelidikan klinikal (pengajian klinikal/pengajian soal-selidik/percubaan ubat-ubatan) disebut berikut:

A prospective study of analgesic efficacy and plasma Ropivacaine concentration after PECS II block in patients undergoing mastectomy

.....

yang mana sifat dan tujuannya telah diterangkan kepada saya oleh Dr. .....
(Nama & Jawatan Doktor)

mengikut terjemahan ..... yang telah menterjemahkan
(Nama & Jawatan Penterjemah)
kepada saya dengan sepenuh kemampuan dan kebolehannya di dalam Bahasa /

loghat .....

Saya telah diberitahu bahawa dasar penyelidikan klinikal dalam keadaan methodologi, risiko dan komplikasi (mengikut kertas maklumat pesakit). Selepas mengetahui dan memahami semua kemungkinan kebaikan dan keburukan penyelidikan klinikal ini, saya merelakan/mengizinkan sendiri menyertai penyelidikan klinikal tersebut di atas.

Saya faham bahawa saya boleh menarik diri dari penyelidikan klinikal ini pada bila-bila masa tanpa memberi sebarang alasan dalam situasi ini dan tidak akan dikecualikan dari kemudahan rawatan dari doktor yang merawat.

Tarikh: ..... Tandatangan .....

(Pesakit)

DI HADAPAN

Nama .....

No. K/P..... Tandatangan .....
(Saksi untuk Tandatangan Pesakit)

Jawatan .....

Saya sahkan bahawa saya telah menerangkan kepada pesakit sifat dan tujuan penyelidikan klinikal tersebut di atas.

Tarikh: ..... Tandatangan .....
(Doktor yang merawat)

KEIZINAN OLEH PESAKIT
UNTUK

No. Pend.
Nama
Jantina
Unit

BK-MIS-1117-E02

APPENDIX D

MEDICAL ETHICS COMMITTEE
UNIVERSITY MALAYA MEDICAL CENTRE

PATIENT INFORMATION SHEET

Version No.: 1

Version Date: 6 May 2016

Please read the following information carefully, do not hesitate to discuss any questions you may have with your Doctor/Investigator

1. Study Title:

A prospective study of analgesic efficacy and plasma Ropivacaine concentration after PECS II block in patients undergoing mastectomy

2. Introduction (Scientific basis of the study)

In the past, pain relieve for breast surgery is done by providing local anaesthetics (pain relieve medication) around the spinal cord (eg. thoracic epidural analgesia or paravertebrae block). However, both techniques were associated with serious complications, such as trauma to the lung (pneumothorax), accidental blood vessel injection.

The introduction of using ultrasound guided chest wall block (PECS II block) has changed the choice for providing analgesia to the upper part of the chest wall.

Ropivacaine is a type of local anaesthetic with an established safety profile. We would like to conduct a study to measure the blood safety level of Ropivacaine and the duration of this pain reliever with a specific dose.

3. What is the purpose of this study?

To measure the blood concentration of this pain reliever (Ropivacaine) after PECS II block. This would determine whether the peak plasma Ropivacaine concentration level is within the safety level allowed. We also want to know the spread of this medication over the chest wall providing numbness.

4. **What are the procedures to be carried out?**

- Injection of local anaesthetic over the chest wall guided using an ultrasound machine to ensure precise injection.
- Several Blood taking (approximately 20 ml in total) aspirated from a cannula inserted on an upper limb prior to the surgery, and send for analysis in a lab. The cannula is similar to a cannula inserted for giving intravenous drugs and intravenous drips.
- After the block is performed, we will use 'pin prick' and 'cold pack' technique over the numbness area.
- General Anaesthesia will be provided just before surgery until surgery is completed.

5. **How long will I be involved in this study?**

24-48 hours

6. **Who should not enter the study (exclusion criteria)?**

- Patient refusal for blood taking
- Patient with a body mass index above 35
- Patient with history of allergy to local anaesthetics

7. **How many patients/research subjects will be recruited into this study?**

28 patients

8. **Who will have access to the subjects medical records or research data?**

Investigators and co-investigator for this study

9. **Will the records/data be kept confidential?**

Yes

10. **What will be the benefits of the study to the subject?**

Patient will experience numbness over the location for PECS II block. Indirectly we will also reduce the use of other pain relieve medication such as Morphine which has its own complications such as nausea, vomiting, and allergy.

11. What are the possible drawbacks (side effects, etc.)?

There is no report of complications after ultrasound-guided PECS II block has been reported.

12. Is the investigatory product derived from a source that may be cultural sensitive, eg: bovine or porcine? (If applicable)

No

13. What payments or reimbursement will research subjects receive?

No

14. Can I refuse to take part in the study?

Yes

15. Who should I contact if I have additional questions during the course of the study?

Dr Khaw Soon Keong (012-8081609)

Dr Mohd Shahnaz Hasan (019-2627277)

Dr Azrin Mohd Azidin (019-3657215)

Dr Beh Zhi Yuen (016-2333083)