ANALGESIC EFFICACY OF SYSTEMIC KETAMINE AND LIGNOCAINE FOR PRE-EMPTIVE MULTIMODAL ANALGESIA IN DOGS

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By

UBEDULLAH KAKA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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DEDICATION

My Beloved Parents

Abstract of the thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Doctor of Philosophy

ANALGESIC EFFICACY OF SYSTEMIC KETAMINE AND LIGNOCAINE FOR PRE-EMPTIVE MULTIMODAL ANALGESIA IN DOGS

By

UBEDULLAH KAKA

February 2016

Chairperson : Associate Prof. Chen Hui Cheng, DVSc
Faculty : Veterinary Medicine

Presently, there is no ideal analgesic protocol which is free of side effects to counteract central sensitisation and abolish pain in postoperative period. Opioids being frontline drugs for postoperative pain management possess clinically significant side effects such as respiratory depression, vomiting, bradycardia and vasodilation. Recent findings point towards preemptive multimodal analgesia as the way forward. Ketamine and lignocaine are two potential drugs to be incorporated to an opioid-based protocol, however, research related to their analgesic effects in dogs is limited. This study evaluated the analgesic effects of systemic ketamine and lignocaine for postoperative analgesia in dogs. Treatments were administered in a cross over design with one week wash-out period. Analysis was performed using SAS software package. Data were compared across treatments and time measurement using repeated- measures ANOVA model and paired T test where two treatments were compared. Non parametric tests were used when data were not normally distributed. In experiment one of this study, effects of ketamine and lignocaine on electroencephalography (EEG) with electric noxious stimulus under minimal anaesthesia model were studied. Ketamine at 3 mg/kg intravenous (IV), loading dose (LD) and constant rate infusion (CRI) of 10 and 50 µg/kg/min, and lignocaine at 2 mg/kg followed by 50 and 100 µg/kg/min significantly depressed the median frequency (MF) of EEG, an indicator of nociception. Corresponding serum concentrations at the points of testing that depressed MF were between 1898.41 ± 110.04 and 2100.59 ± 425.48 ng/ml for lignocaine and between 248.71 ± 75 and 641.35 ± 197 ng/ml for ketamine. In experiment two, an algometer was modified, validated and subsequently used to determine mechanical nociceptive thresholds in conscious dogs. In experiment three, ketamine alone at 0.5 mg/kg LD followed by CRI of 30 µg/kg/min and 50 µg/kg/min, and ketamine at 30 µg/kg/min with lignocaine at 2 mg/kg LD followed by 100 µg/kg/min significantly increased the mechanical thresholds during the periods of infusion. Corresponding serum concentrations of ketamine were found to be above 100 ng/ml. Thresholds returned to baseline within 20 minutes following cessation of infusion and serum concentrations were below 100 ng/ml. In experiment four, ketamine and lignocaine in addition to tramadol at 4 mg/kg premedication was evaluated for preemptive multimodal analgesia in dogs undergoing ovariohysterectomy. Results showed that the combination of ketamine-lidocaine-tramadol obtunded intra-operative sympathetic responses better than tramadol alone. The combination also attenuated primary hyperalgesia better than

tramadol in the immediate 8 hours post-surgery, and tended to reduce secondary hyperalgesia during the 72-hour postoperative study period. In conclusion, systemic ketamine and lignocaine possess analgesic effects. Ketamine at serum concentrations of > 100 ng/ml provided analgesia. Ketamine at 0.5 mg/kg LD followed by CRI at 30 or 50 µg/kg/min combined with lignocaine at 2 mg/kg LD followed by 100 µg/kg/min, is safe for preemptive multimodal analgesia in dogs under anaesthesia. Preemptive infusions of ketamine and lignocaine in addition to tramadol augmented analgesia, likely, by attenuating intra-operative nociceptive inputs and reducing central sensitisation.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

KEBERKESANAN ANALGESIK KETAMINE DAN LIGNOCAINE SISTEMIK UNTUK ANALGESIA DAHULUAN BERBILANG MOD PADA ANJING

Oleh

UBEDULLAH KAKA

Februari 2016

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Pada masa ini, tiada protokol analgesik yang bebas daripada kesan sampingan untuk mengatasi pemekaan sistem saraf pusat dan menghapuskan kesakitan selepas pembedahan. Oleh itu, ubat yang berpotensi dan sedia ada perlu dicuba dalam kaedah analgesia dahuluan berbilang mod untuk mencari protokol yang paling sesuai dan dengan kesan sampingan yang minima. Penemuan baru-baru ini menghala ke arah analgesia dahuluan berbilang mod. Ketamine dan lignocaine adalah dua ubat yang berpotensi untuk dimasukkan ke dalam protokol berasaskan opioid, namun kajian kesan analgesik ketamine dan lignocaine pada anjing adalah terhad. Tesis ini bertujuan untuk menilai keberkesanan analgesik ketamine dan lignocaine sistemik untuk analgesia selepas pembedahan pada anjing**.** Dalam bab ketiga tesis, kesan ketamine dan lignocaine pada elektroensefalografi (EEG) dengan penggunaan rangsangan noksius elektrik di bawah model anestesia minima telah dikaji. Ketamine pada dose muatan (LD) 3 mg/kg IV, dan infusi kadar malar (CRI) 10 dan 50 µg/kg/min, serta lignocaine pada 2 mg/kg diikuti 50 dan 100 µg/kg/min didapati menekan kekerapan median (MF) EEG, iaitu satu daripada penunjuk kesakitan. Kepekatan serum semasa MF tertekan adalah di antara 1898.41 ± 110.04 hingga 2100.59 ± 425.48 ng/ml untuk lignocaine, dan 248.71 ± 75 hingga 641.35 ± 197 ng/ml untuk ketamine. Dalam bab keempat and kelima, satu algometer telah diubahsuai, disahkan dan kemudiannya digunakan untuk menentukan nilai ambang nosiseptif mekanikal pada anjing sedar. Ketamine pada 0.5 mg/kg LD diikuti CRI 30 µg/kg/min dan 50 µg/kg/min, serta ketamine pada 50 µg/kg/min dengan tambahan lignocaine 2 mg/kg LD diikuti 100 µg/kg/min, didapati meningkatkan nilai ambang mekanikal dengan ketara semasa tempoh infusi. Kepekatan serum ketamine didapati melebihi 100 ng/ml. Nilai ambang mekanika kembali ke aras awal dalam tempoh 20 minit selepas infusi diberhentikan dan kepekatan serum adalah di bawah 100 ng/ml. Dalam bab keenam, ketamine dan lignocaine sebagai tambahan kepada premedikasi dengan tramadol 4 mg/kg, dinilai untuk analgesia dahuluan berbilang mod pada anjing yang menjalani ovari-histerektomi. Keputusan menunjukkan yang gabungan ketamine-lignocaine-tramadol menyekat respons simpatetik lebih baik daripada penggunaan tramadol sahaja. Gabungan tersebut mengurangkan hiperalgesia primer lebih baik daripada tramadol dalam tempoh 8 jam selepas pembedahan, dan cenderung untuk mengurangkan hiperalgesia sekunder sepanjang tempoh 72 jam pascabedah. Kesimpulannya, ketamine dan lignocaine

sistemik mempunyai kesan-kesan analgesik. Ketamine pada kepekatan serum > 100 ng/ml memberikan kesan analgesia. Ketamine pada 0.5 mg/kg LD diikuti CRI pada 30 atau 50 µg/kg/min, dan digabungkan dengan lignocaine pada 2 mg/kg LD diikuti 100 µg/kg/min, adalah selamat untuk analgesia dahuluan berbilang mod pada anjing yang dibius. Infusi dahuluan ketamine dan lignocaine yang ditambah kepada tramadol meningkatkan kesan analgesia, mungkin melalui pengurangan input nosiseptif dan pemekaan pusat.

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I certify that a Thesis Examination Committee has met on 25 February 2016 to conduct the final examination of Ubedullah on his thesis entitled "Analgesic Efficacy of Systemic Ketamine and Lignocaine for Pre-Emptive Multimodal Analgesia in Dogs" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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LIST OF ABBREVIATIONS

µ	mu
µg	microgram
µL	microliter
1 M	1 molar solution
5HT	5-hydroxytryptamine (serotonin)
ACN	acetonitrile
ACTH	adrenocorticotrophic hormone
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Aβ	A beta
Aδ	A delta
BDNF	brain-derived neurotrophic factor
Ca^{++}	calcium ions
CFA	complete Freund's adjuvant
CH_2Cl_2	methylene chloride
CO^2	carbon dioxide
COX	cyclooxygenase
ECG	electrocardiography
EEG	electroencephalography
ETHAL	end-tidal halothane concentration
FFT	Fast Fourier transformation
G	gravity
H^+	hydrogen ion
HPLC	high performance liquid chromatography
IL-6	Interleukin-6
K^+	potassium ion
KA	kainite
Kg	kilogaram
KH_2PO_4	potassium dihydrogen phosphate
MAC	minimum alveolar concentration
MF	median frequency
Mg	milligram

Ml	milliliter
NaOH	sodium hydroxide
Ng	nanogram
NSAID	nonsteroidal anti-inflammatory drug
Ptot	total power
SEF	spectral edge frequencies
SP	Substance P (neuropeptide)
TNFα	tumor necrosis factor- α
TrkB	tyrosine kinase B
WDR	wide dynamic range
Δ	gamma
K	kappa

LIST OF APPENDICES

BIODATA OF STUDENT

The student was born on 23th January, 1981 in New Saeedabad, a small town in province Sindh, Pakistan. He obtained his early education up to matriculation at his native village and finished higher secondary education from Government Higher Secondary School Bhit Shah. Afterwards, he proceeded to Sindh Agriculture University Tandojam for his DVM and Masters in Surgery. After completion his Master in 2007, he joined Thardeep Rural Development Programme (TRDP) under a Governenment project "Prime Minister's Special Initiatives for Livestock" from February, 2007 to April, 2008. Later he joined a USAID funded project "Conservation of Kamori Goat in Sindh" at Badin District from April 2008 to Feb 2009. He then joined Pakistan Dairy Development Company (PDDC) in Lahore, province of Punjab from Feb 2009 to March 2011 . From April 2011 to Jan 2012 he joined Lasbella University of Agriculture Water and Marine Sciences (LUAWMS), Uthal, in Balochistan province of Pakistan. In February 2012 he moved to Universiti Putra Malaysia for his Doctor of Philosophy (PhD) programme in the field of Anaesthesiology, Department of Clinical Studies, Faculty of Veterinary Medicine under the scholarship from Sindh Agriculture University Tandojam, Sindh, Pakistan. The Author is married to Tabassum Naz in 2008 and is blessed with one daughter Zainab.

LIST OF PUBLICATIONS

Kaka, U., Hui Cheng, C., Meng, G. Y., Fakurazi, S., Kaka, A., Behan, A. A., & Ebrahimi, M. (2015). Electroencephalographic Changes Associated with Antinociceptive Actions of Lignocaine, Ketamine, Meloxicam, and Morphine Administration in Minimally Anaesthetized Dogs. *BioMed Research International, 2015*, 10. doi: 10.1155/2015/305367

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CHAPTER ONE

INTRODUCTION

Pain is a highly complex phenomenon. According to International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1986). Human ability to communicate verbally and physically helps in identifying pain. Since animals are devoid of verbal communication, the task of pain identification is more difficult compared to humans. However, in animals, pain is manifested as a behavioral reaction to an aversive sensory experience associated with actual or potential tissue damage (Cambridge *et al*., 2000). Dogs and cats have similar, if not identical neurotransmitters and neural pathways to those of humans, and likely perceive pain in a similar way (Hellyer *et al*., 2007).

Nociception refers to the process through which noxious stimuli are detected and converted to nerve impulses, conveyed to supraspinal structures through spinal cord where they are further processed and appreciated as pain (IASP Subcommittee on Taxonomy, 1979). The process of nociception takes place in four steps, transduction, transmission, perception and modulation. Transduction is the encoding of noxious stimulus into nociceptive stimulus caused by tissue damage. Transportation of signals from the periphery to the brain is called 'transmission'. Modulation involves the mechanisms of inhibition and excitation along the pathways. Perception is the last step in the process of nociception, which is the sensation of pain (Loveridge and Patel, 2014).

Clinically, pain can be divided into acute and chronic. Acute pain results from an injury and ends with wound healing (Gayner & Muir, 2002). Chronic pain persists beyond the course of acute pain or wound healing (Bonica *et al*., 1993). Surgical pain is one of the most common and typical form of acute pain. Surgery results in a complex cascade of events in the neuroendocrine system, resulting in the release of stress factors, as well as generating the process of nociception along the neural pathways. These changes results in alteration in the function of the nervous system towards various environmental stimuli. This modification in the function takes place centrally (central sensitisation) as well as in the periphery (peripheral sensitisation) (Coderre *et al*., 1993). This sensitisation leads to allodynia, a condition where innocuous stimulus is perceived as noxious causing pain, and hyperalgesia, an exaggerated response to a noxious stimulus (Klede *et al*., 2003). All of these events may contribute to chronic pain if not managed properly.

Preemptive analgesia has been defined as "an antinociceptive treatment that prevents the establishment of altered function of the nervous system from injuries" (Kelly *et al*., 2001a). Practically preemptive analgesia is the injection of analgesic agent before the start of surgical stimulus with the aim of preventing or reducing subsequent pain.

Multimodal analgesia (Kehlet & Dahl, 1993) is a technique in which analgesics with various modes of action such as non-opioid and opioid are mixed with the aim of acting on different pathways and neurotransmitters involved in nociception and hyperalgesia.

Tramadol is a centrally acting synthetic analgesic, which has synergistic opioid and non-opioid modes of action (Raffa *et al*., 1992). Tramadol has insignificant side effects compared to that of other opioids. Lignocaine and ketamine are commonly used as local and general anaesthetics, respectively. Lignocaine and ketamine use for postoperative analgesia may prevent the development of central sensitisation (Muir & Woolf, 2001) during surgical intervention, which augments pain and discomfort in the postoperative period. Lignocaine and ketamine have been reported to supplement general anaesthesia (Muir *et al*., 2003) reducing the amount of inhalant anaesthetics required during anaesthesia, improving cardio respiratory function, and thereby provide safe general anaesthesia, better postoperative comfort, and quicker recovery. The combination of lignocaine and ketamine as a non-opioid adjunct enhances efficacy, potential for drug synergism, decreases drug-related side effects (Woolf & Salter, 2000) and reduces opioid requirement and their side effects in postoperative period (Kehlet & Dahl, 1993).

Problem statement

Though opioids, such as morphine and fentanyl are the front-line analgesics in small animal practice, their perioperative use is often associated with clinically significant side effects, such as respiratory depression (Pattinson, 2008), vomiting (Kukanich et al., 2005), bradycardia and vasodilation (Iizuka et al., 2013) . Presently, there is no any ideal protocol for postoperative analgesia, which is free of side effects. Therefore, it is necessary that the available potential drugs should be tested by the preemptive multimodal analgesia method in order to find the most suitable protocol with least side effects. Mechanism of action of systemic lignocaine and ketamine reveals that these are two potential drugs which can be used for preemptive multimodal analgesia in dogs. However, there is a need to objectively assess the analgesic efficacy of ketamine and lignocaine alone, followed by their combination with opioids to evaluate their effects on postoperative analgesia and central sensitisation. Therefore, this thesis aims to:

1) Determine the antinociceptive actions of systemic lignocaine and ketamine using electroencephalograph (EEG) in dogs under minimal anaesthesia model.
2) Modify and validate an algometry technique on conscious dogs.
3) Correlate analgesic serum levels of ketamine administered alone and in combination with lignocaine, with their effects on mechanical thresholds in conscious dogs.
4) Evaluate the effects of ketamine and lignocaine for preemptive multimodal analgesia with tramadol on postoperative pain and central sensitisation.

It is hypothesised that:

1. Systemic ketamine and lignocaine will affect parameters of EEG related to nociception in dogs under minimal anaesthesia model.
2. Modified algometry technique on conscious dogs would increase mechanical thresholds compared to baseline, if the drug has an analgesic effect
3. Mechanical thresholds on conscious dogs are correlated with serum concentrations of ketamine.
4. Combination of ketamine, lignocaine and tramadol would prevent development of central sensitisation and result in better analgesia compared to tramadol alone in the post operative period.

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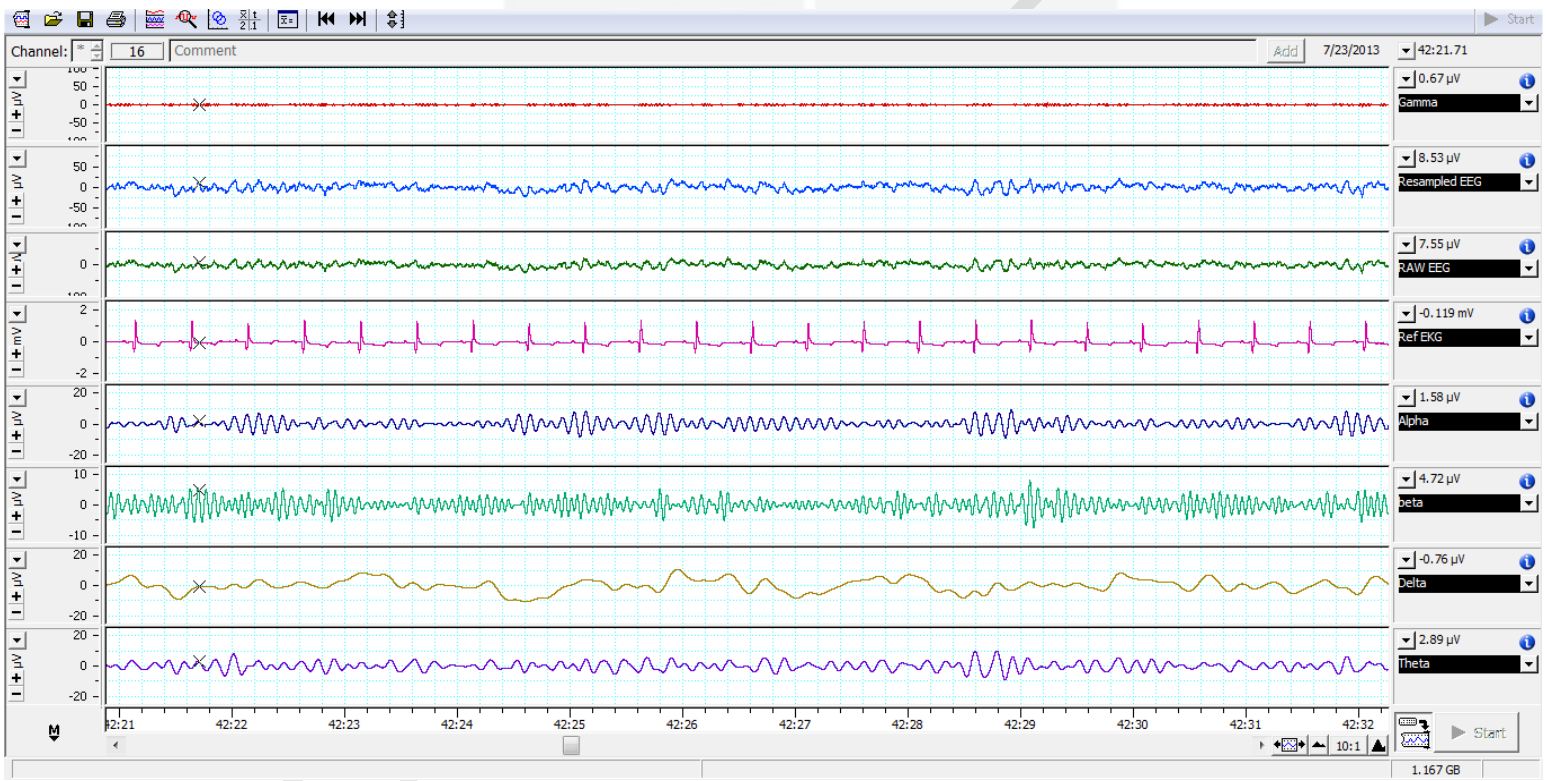
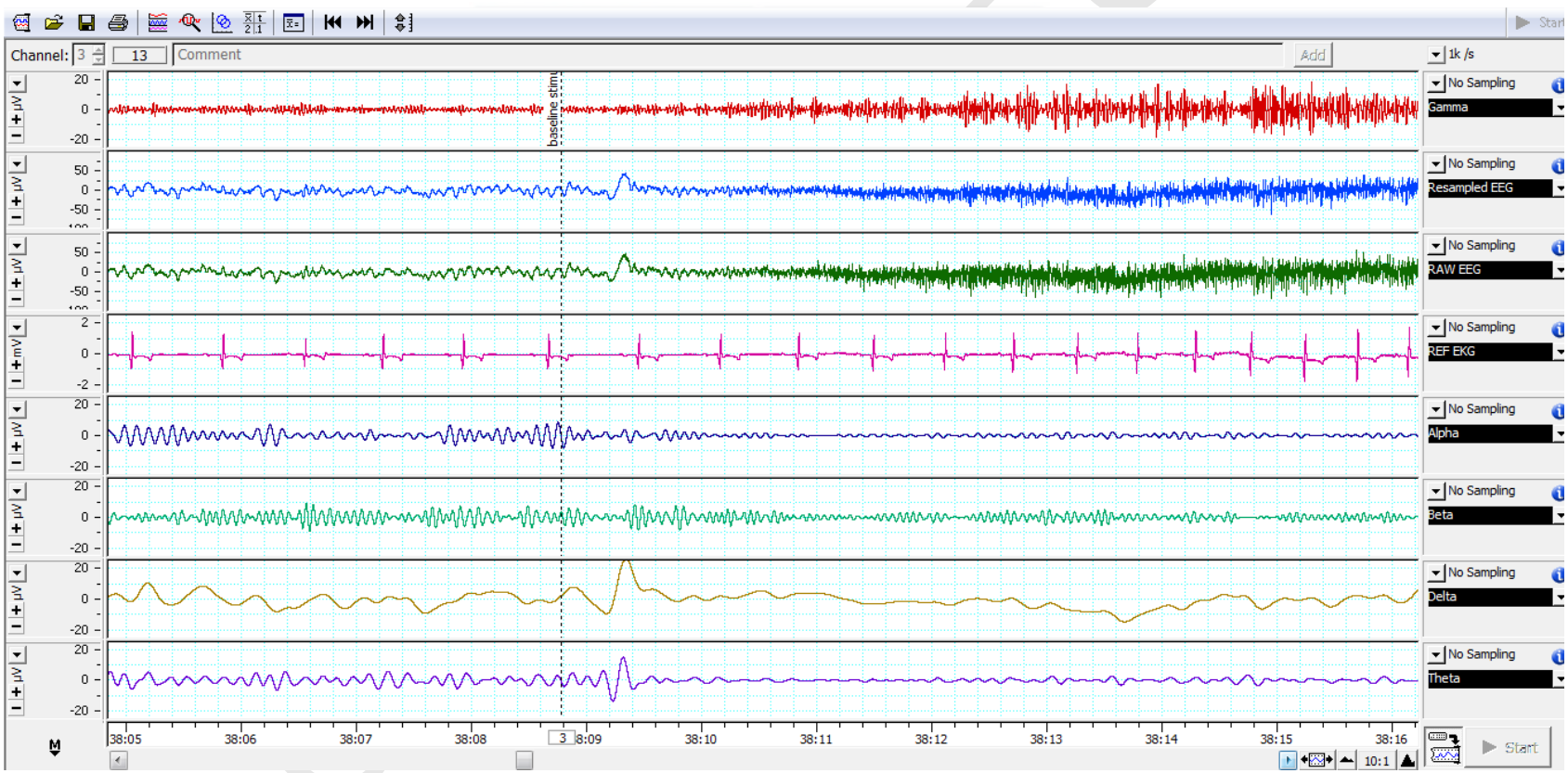
APPENDICES

Appendix A: Electroencephalographic spectrum of minimally anaesthetized dog



Appendix B: Electroencephalographic spectrum before and after stimulus



Appendix C: Short Form of the Glasgow Composite Pain Scale

SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE

Dog's name _____

Hospital Number _____ **Date** / / **Time**

Surgery Yes/No (delete as appropriate)

Procedure or Condition_____

_____

In the sections below please circle the appropriate score in each list and sum these to give the total score.

A. Look at dog in Kennel

Is the dog?

(i)		(ii)	
Quiet	0	Ignoring any wound or painful area	0
Crying or whimpering	1	Looking at wound or painful area	1
Groaning	2	Licking wound or painful area	2
Screaming	3	Rubbing wound or painful area	3
		Chewing wound or painful area	4

In the case of spinal, pelvic or multiple limb fractures, or where assistance is required to aid locomotion do not carry out section **B** and proceed to **C**
Please tick if this is the case ☐ then proceed to C.

B. Put lead on dog and lead out of the kennel.

When the dog rises/walks is it?

(iii)	
Normal	0
Lame	1
Slow or reluctant	2
Stiff	3
It refuses to move	4

C. If it has a wound or painful area including abdomen, apply gentle pressure 2 inches round the site.

Does it?

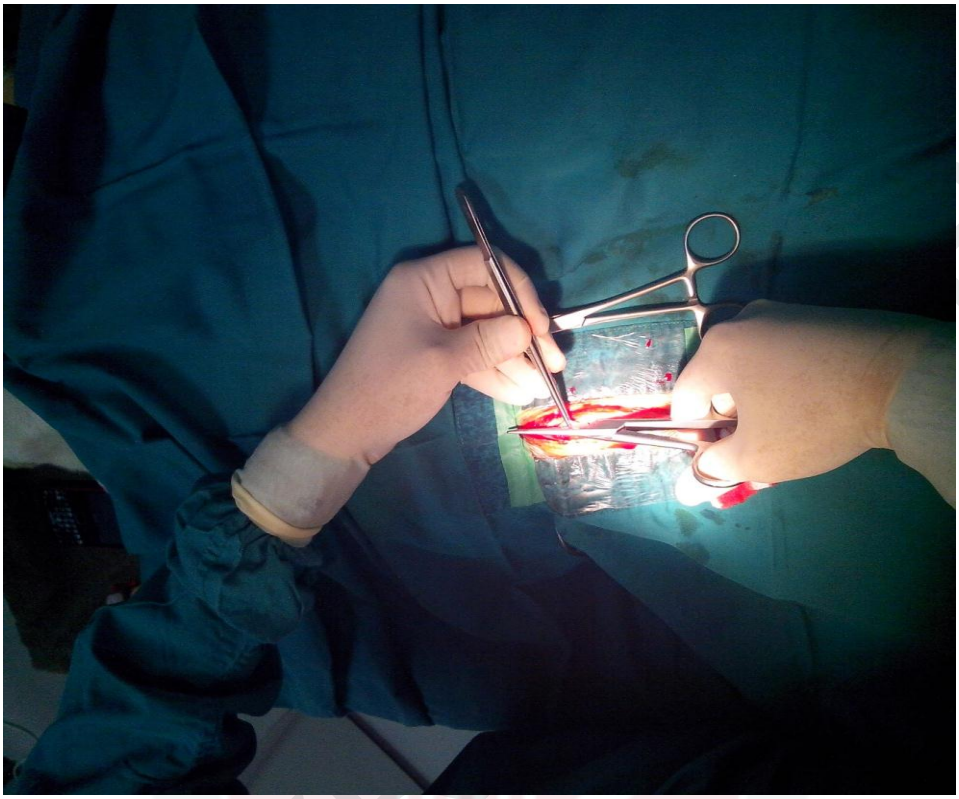
(iv)	
Do nothing	0
Look round	1
Flinch	2
Growl or guard area	3
Snap	4
Cry	5

D. Overall

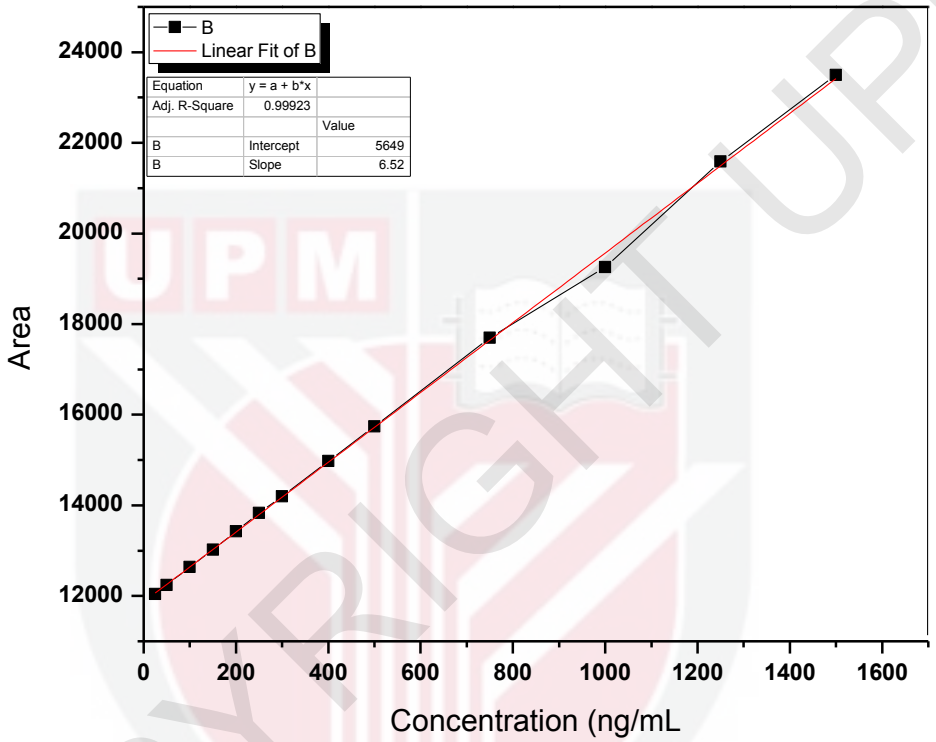
Is the dog? (v)		*Is the dog?* (vi)	
Happy and content or happy and bouncy	0	Comfortable	0
Quiet	1	Unsettled	1
Indifferent or non-responsive to surroundings	2	Restless	2
Nervous or anxious or fearful	3	Hunched or tense	3
Depressed or non-responsive to stimulation	4	Rigid	4

Total Score (i+ii+iii+iv+v+vi) = _____

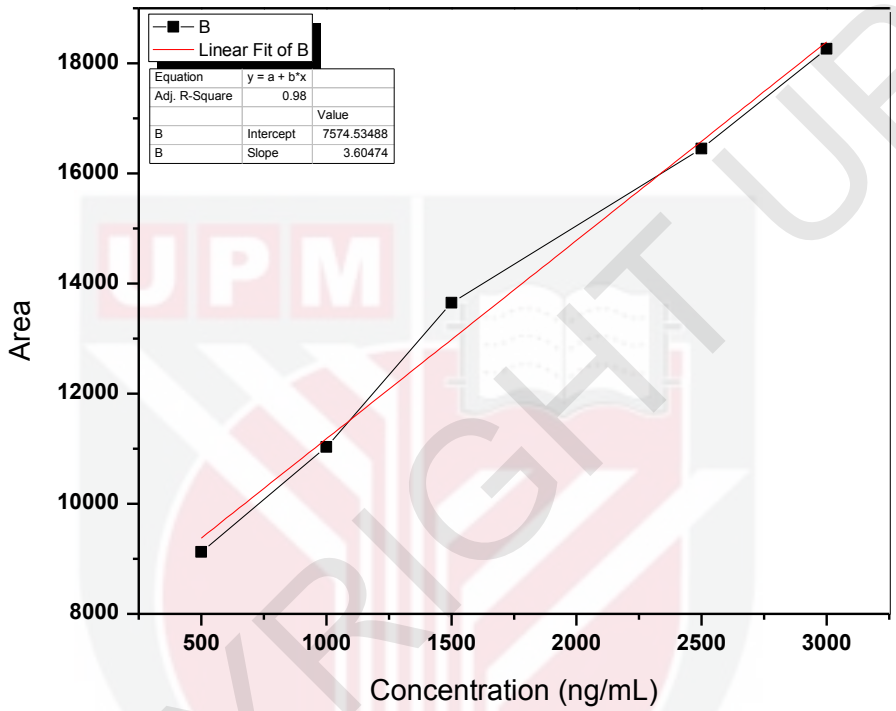
Appendix D: Mid Ventral abdominal incision for OHE



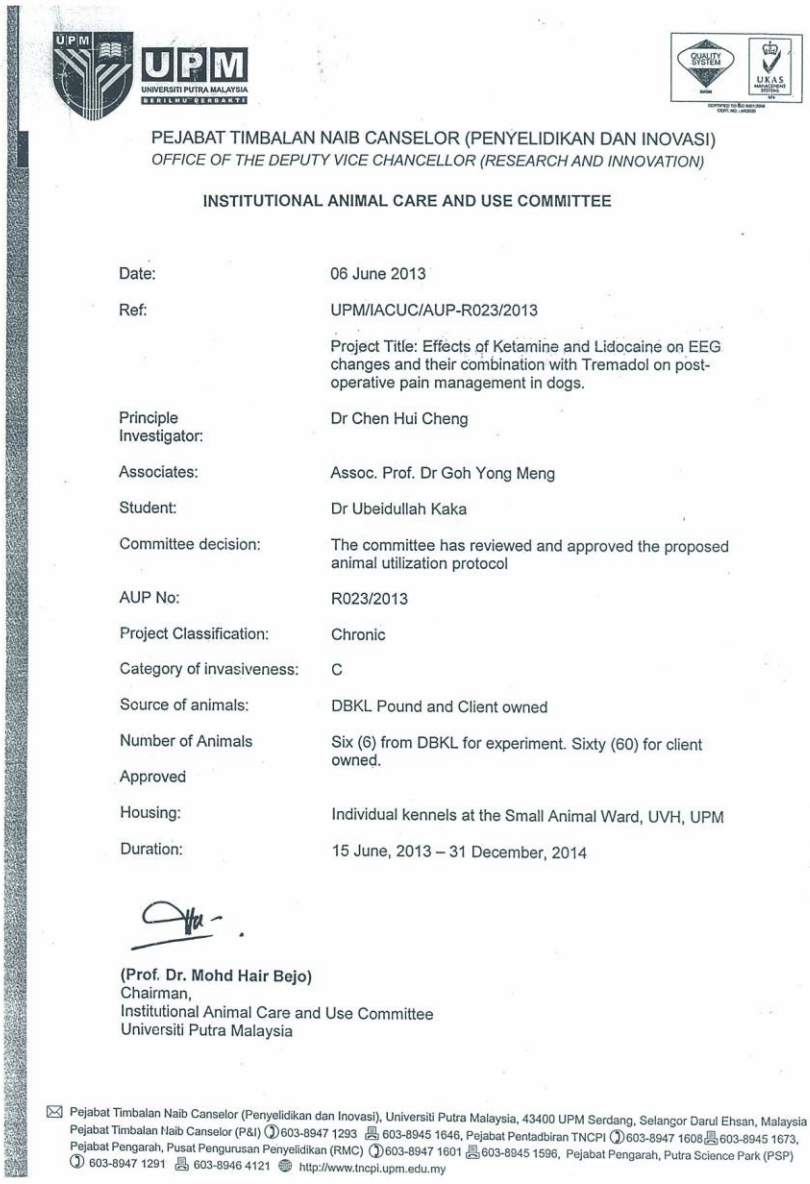
Appendix E: Calibration Curve For Keatmine



Appendix F: Calibration Curve For Lignocaine



Appendix G: Institutional Animal Care and Use Committee Approval



PEJABAT TIMBALAN NAIB CANSELOR (PENYELIDIKAN DAN INOVASI)
OFFICE OF THE DEPUTY VICE CHANCELLOR (RESEARCH AND INNOVATION)

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE

Date:	06 June 2013
Ref:	UPM/IACUC/AUP-R023/2013
	Project Title: Effects of Ketamine and Lidocaine on EEG changes and their combination with Tremadol on post-operative pain management in dogs.
Principle Investigator:	Dr Chen Hui Cheng
Associates:	Assoc. Prof. Dr Goh Yong Meng
Student:	Dr Ubeidullah Kaka
Committee decision:	The committee has reviewed and approved the proposed animal utilization protocol
AUP No:	R023/2013
Project Classification:	Chronic
Category of invasiveness:	C
Source of animals:	DBKL Pound and Client owned
Number of Animals Approved	Six (6) from DBKL for experiment. Sixty (60) for client owned.
Housing:	Individual kennels at the Small Animal Ward, UVH, UPM
Duration:	15 June, 2013 – 31 December, 2014

(Prof. Dr. Mohd Hair Bejo)
Chairman,
Institutional Animal Care and Use Committee
Universiti Putra Malaysia

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LIST OF PUBLICATIONS

Kaka, U., Hui Cheng, C., Meng, G. Y., Fakurazi, S., Kaka, A., Behan, A. A., & Ebrahimi, M. (2015). Electroencephalographic Changes Associated with Antinociceptive Actions of Lignocaine, Ketamine, Meloxicam, and Morphine Administration in Minimally Anaesthetized Dogs. *BioMed Research International, 2015*, 10. doi: 10.1155/2015/305367

Kaka, U., Chen, H. C., Goh, Y. M., Abubakar, A. A., Fakurazi, S., & Ebrahimi, M. (2015). Validation of a Modified Algometer to Measure Mechanical Nociceptive Thresholds in Awake Dogs. *BioMed Research International, 2015*, 7. doi: 10.1155/2015/375421

Kaka, U., Abubakar, A. A., Cheng, H. C., Goh, Y. M., & and Fakurazi, S. (2014). Evaluation of Modified Algometer for the Objective Measurement of Mechanical Pain Thresholds in Awake Dogs. Paper presented at the "The Asian Federation of Laboratory Animal Science Congress", Kuala Lumpur, Malaysia

Kaka, U., Saifullah, B., Abubakar, A. A., Goh, Y. M., Fakurazi, S., Kaka, A., Behan, A. A., Ebrahimi, M., and Chen, H. C. (2016). Serum Concentrations of Ketamine Associated with Mechanical Antinociceptive Effect on Conscious Dogs. Under Review, BMC Veterinary Research.

Kaka, U., Chen, H. C., Goh. Y. M., & Chean, L. W (2016). Electroencephalographic Changes Associated with Non-Invasive Nociceptive Stimulus in Minimally Anaesthetised Dogs. Under Review. Polish Journal of Veterinary Sciences.

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