EVALUATION OF PARACETAMOL, KETOPROFEN AND SELECTED OPIATES IN CANINE PERIOPERATIVE PAIN MANAGEMENT

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APRIL, 2014

DECLARATION

I hereby declare the originality of the work in this dissertation, titled "**Evaluation ofParacetamol, Ketoprofenand Selected Opiatesin Canine Perioperative Pain Management"** was performed and written by me in the Department of Veterinary Surgery and Radiology of the Ahmadu Bello University, Zaria under the supervisions of Prof. A. Z. Hassan, Prof. P.O. Anaja, Dr. Diane Mason and Dr. E.O. Nwasor. All relevant sources of literature are duly acknowledged by means of references and nopart of this dissertation has been previously submitted for an award of degree

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Signature Date

CERTIFICATION

This is to certify that this dissertation, titled "**EVALUATIONOF PARACETAMOL, KETOPROFEN AND SELECTED OPIATES IN CANINE PERIOPERATIVE PAIN MANAGEMENT"** by E. O Abidoye meets the regulation governing the award of Doctor of Philosophy (PhD) of Ahmadu Bello University, Zaria, Nigeria and is approved for its contribution to scientific knowledge and literary presentation.

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DEDICATION

This project work is dedicated to my Lord and Saviour, Jesus Christ, who gave me the wisdom and inspiration to carry out this research work.

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My sincere gratitude goes to the Almighty God, who has seen me through and brought me to the completion of my PhD programme. I know He will forever be with me the rest of my life's journey. Amen.

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ABSTRACT

One of the ways of controlling postoperative pain is the administration of a single analgesic or a combination of different classes of analgesics prior to the onset of noxious stimuli. A constraint to perioperative use of traditional opioids and cyclooxygenase (COX) inhibitors is their undesirable side effects. This study evaluates the suitability of COX inhibitors (Ketoprofen and paracetamol) andselected opiate (tramadol and morphine) were evaluated for their analgesic efficacy in perioperative conditions through single and multi- drug pre-emptive administration.Pain was evaluated through visual analogue pain evaluation, physiologic, neurophysiologic, haematologic, serologic and biochemical parameters.This study is divided into four major (4) protocols, in which a total of 48 dogs were used. In protocol I, samples and baseline data were collected from all the dogs. Protocols II and III were the experimental protocols. Protocol II, consist of two groups (B and C). Group B is the non-steroidal anti-inflammatorydrug group and had eight (8) dogs which were subdivided into two groups (B_1 and B_2) of four dogs each. In B_1 (ACE) paracetamolwas administeredat 0.9 mg/kg while in B_2ketoprofen (KET) was administeredat 2.2 mg/kg. Group C comprises of two subdivisions (C_1 and C_2). C_1 had tramadol (TRA) at 3mg/kg administered and C_2 had morphine (MOR) administered at 0.5mg/kg. Protocol III was the multimodal therapy section. It was subdivided into two groups. Group D_1 (TRAC) had a multimodal combination of tramadol (2mg/kg) and paracetamol(0.5mg/kg) while group D_2 (MOKE) had a combination therapy of morphine (0.5 mg/kg) and ketoprofen (2.0 mg/kg) all administered intramuscularly. Each of thesesubdivisions had four dogs. Protocol IV is the clinical trial of the best drugs based on their performance and had twenty clinical canine surgical cases.The result of the study revealed that visual analogue scale indicated a significant ($P< 0.05$) increase in pain intensity in dogs that were not treated with analgesic

up to the six hourpost induction of pain. Contrary to this, TRA, the multimodal therapy of TRAC and that of MOKE had lower pain intensity even up till the 48th hour. Similar results were obtained when physiologic parameters such as heart rate, rectal temperature and electrocardiographic (ECG) mappings were used to evaluate for pain in the dogs.The electroencephalographic studies revealed that there was electrical burst around the C4 – A2 and C3-A1 region of the brain with amplitudes of 325.8 ±0.8μv^2/Hz in the non-treatment group. Much lower values were obtained in the MOKE with amplitude of 10.0 ± 0.52μv^2/Hz. In conclusion, paracetamol and ketoprofen single administration gave comparative analgesic efficacy. Perioperative administration of paracetamol and ketoprofen did not completely abolish the afferent nociceptivetransmission. Morphine administration gave superior efficacy to tramadol. The combination of tramadol (2mg/kg)/paracetamol (0.5mg/kg) significantly reducedsurgical pain perioperatively, and is available in the open pharmacy.

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ABREVIATIONS, DEFINITIONS, GLOSSARY AND SYMBOLS

°C - degree Celsius
CBC - complete blood count
CNS - central nervous system
CRI -constant rate infusion
CSF - cerebrospinal fluid
CT - computed tomography
ECG - electrocardiograph
EEG - electroencephalogram
e.g. - exempli gratia
et al. -and others
EtCO2 - end-tidal carbon dioxide
Fig. - figure
h - hour
IV - intravenous
IM - intramuscular
kg - kilogram
L - litre
mg - milligram
ml - millilitre
mmol - millimole
μmol - micromole
MRI - magnetic resonance imaging
NMDA - N-methyl-D-aspartate
NSAIDs - non- steroidal anti-inflammatory drugs
COX - cyclooxygenase
% - percent
Tab. - table
U - units
WDR - Wide Dynamic Range
TENS - Transcutaneous Electrical Nerve Stimulation
DCS - Dorsal Column Stimulation
GABA - gamma-amino butyric acid
CCK - cholecystokinin

CHAPTER ONE

INTRODUCTION

1.1. Background of the Study

Pain management in the perioperative period presents a significant challenge not only to the veterinarian but also to pet owners (Nancy, 2002). Despite the various reasons advanced by some Veterinarians on why it may not be important to manage pain, the advantages far outweigh the disadvantages (Mathews, 2000).

Pain management has been of proven benefit in improving the quality oflife and recovery of patients and in lessening the socio-economic burden ofunrelieved acute, chronic and cancer-related pain (Kehlet and Hole, 2001).Proper pain management is a major concern and an area of focus in many parts of the world today (Breivik, 1998). Pain is also one of the primary concerns of the surgeon because of its close ties with clinical outcome and acute postoperative patient well-being. Studies have indicated such negative clinical outcomes to include decreases in vital capacity and alveolar ventilation, pneumonia, tachycardia, hypertension, myocardial ischemia, myocardial infarction, transition to chronic pain states, poor wound healing and insomnia (Carr and Goudas 1999; Breivik and Stubhaug, 2008).

Veterinarianshave ethical obligations to help alleviate animal pain. Whereas mostveterinarians even in Nigeria, accept the fact that animals feelpain and this pain needed alleviation, postoperative pain relief has not been a routinepractice in our veterinary practice today(Flecknell, 1994). Some reasons why analgesics were not administeredin pain

management include,animals lack recognition of pain owing to the apparent lack of anthropomorphically identifiable behavioural changes, patient will harm itself if there's no pain (especially in cases of fracture reduction), treatment costs/ benefits ratio and that anaesthetics masksobservable symptoms(Anon [2], 2009).Thus the physicianshave long struggled with the critique of undermanaging pain in their patients. (Schechter, 1989).

1.2. Statement of Research Problem

The assessment of pain suffered by an animal is difficult(Flecknell, 1994).It is better to predict and prevent perioperative pain than to treat it once established(Anon [2], 2009). A "balanced" approach to the management of painis where the pain pathway is modulated at as many points as possible(Anon [2], 2009).This study may highlight the potential for combining analgesicsand various strategies for opioid administration to optimise the patient comfort (Pearson, 2007).

Increases of serum cortisol have some positive effects among pain patients as it lowers pain sensitivity(Reiche *et al.,* 2004).This factor can also be analysed and quantified in the blood and is used as an index for measuring pain(Feldsein *et al.,* 2010).

1.3. Justification

The advent of multimodal analgesia techniques has greatly facilitated the management of postoperative pain. Total or optimal pain relief cannot be achieved by a single drug or method without major effort or equipment and surveillance or without side effects (Moiniche *et al*., 2002). Multimodal (balanced) analgesia is one of the latest management

strategies where a combination of analgesics like non- steroidal anti-inflammatory drugs (NSAIDS), opioids, local anaesthetics and N-methyl-D-aspartate (NMDA) antagonists are used to provide superior post-operative analgesia with fewer side effects(Olney *et al.,* 1998).

Inadequate postoperative analgesia can negatively influence surgical outcome and duration of rehabilitation.The introduction of the multimodal analgesic therapy is to improve the level of pain control. Careful choice in the use of drug combinations could lead to synergism between the drugs andthis allows lower doses of the individual drugs to be administered, thereby reducing the untoward side effects of each drug.

Poorly managed perioperative pain lead to untoward systemic effects and this may cause the hospital to lose reputation and profit (Nancy*et al*., 2002; David, 2004). Thus, optimally control of perioperative pain, may improvethe overall patient outcome.

Pain also decreases the cooperation of the patient thereby increasing the risk of injury in handling both to the patient and handler (Graveling *et al.,* 2003). The release of cortisol and other substances in the body due to pain also compromises the animal's immune potentials and thus, the likelihood of post- operative infections (Chaudhary*et al*., 2007).Another significant effect of pain is the anxiety associated with it, which obviously negatively affects convalescence(Graveling *et al.,* 2003).

1.4. Aim of Study

i. To evaluate the suitability of paracetamol (acetaminophen), ketoprofen, tramadol morphine single drug administration and multi drug therapyin perioperative analgesia

ii. To develop an effective protocol for perioperative analgesia in dogs.

1.5. Specific Objectives of the Study

i. To adopt a standard pain scoring system for use in dogs in Ahmadu Bello University Veterinary Teaching Hospital, Zaria, Nigeria.

ii. To compare the effects of 2 commonly used cyclooxygenase inhibitors (COX) namely paracetamol and ketoprofen with opioid analgesic (morphine and tramadol) which are used for management of peril-operative pain on patient vital parameters involved in pain related changes.

iii. To evaluate, the efficacy of using COX inhibitors and opioids as multimodal therapy in the management of peri-operative pain using the virtual analogue scale of pain scoring system.

iv. To evaluate neurophysiologically, the efficacy of single drug therapy against the use of multimodal analgesic therapy.

v. To evaluate biochemically and physiologically the safety and efficacy of single drug administration and the multimodal analgesic therapy in dogs undergoing gastrotomy.

CHAPTER TWO

LITERATURE REVIEW

2.1. Introduction

Pain according to the international Association for the study of pain is" an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such…"(Mersey, 1979; Elliott, 2002). Pain can also be defined as an elaborate interaction between sensory, behavioural and emotionalaspects, and past experiences of pain can dictate an individual's future response (Rohitand Siˆan, 2009).

2.2. Background of Pain Management

In the 17th century, Descartes compared pain to a ringing bell and thus postulated that there could be true or false alarm.He used this to distinguish real pain from psychogenic pain (Don, 1996). He further described animals as automata which suggested that animals do not experience pain(Don, 1996). This concept was unfortunately upheld by many Veterinarians till the 20th century (Dohoo and Dohoo, 1998). Many Veterinarians today, however have no problem in admitting that animals do experience pain. Studies evaluating the attitudes of Veterinariansin different countries towards postoperative pain suggest that the use of perioperative analgesics is still inconsistent and tends to be low after many surgical interventions (Hewson,*et al*., 2006; Remi-Adewunmi, 2010). One of the possible explanations for the lack of appropriate analgesic treatment could be the inability of Veterinarians and Veterinary Nurses to recognize pain in a wide variety of species referred for treatment(Flecknell, 1994).

In a questionnaire about analgesia in dogs and cats distributed among French Veterinarians, 14.3% of the respondents considered their knowledge of pain recognition to be inadequate, and more than 50% reported that their methods of pain quantification and monitoring were insufficient (Hugonnard,*et al*., 2004). Aside from their inability to recognize pain, Veterinarians are often relatively reluctant to use perioperative analgesics, mainly because of a lack of familiarity with the available drugs, major concerns about their side effects, and practical objections relatingto the record keeping that is required for controlledsubstances such as opioids (Lascelles *et al.*, 1999;Muir and Woolf, 2001; Wright, 2002).Effective management of perioperative painremains an ethical responsibility for veterinarypractitioners. Over the last decade, there has been arenewed awareness of the need for analgesic treatmentin animals, together with major scientific advancements in understanding the pathophysiologicalprocesses involved in pain transmission (Woolf, 2004).This positive evolution has led to newer theories in thedomain of the optimal use of perioperative analgesia. Terms such as "pre-emptive analgesia", where analgesics are administered before any noxious stimulus occurs (Woolf, 1983; Kehlet and Dahl, 1993; Lascelles *et al.*, 1997; Moiniche *et al.*, 2002), and "multimodal analgesia", where a cocktail of analgesic drugs with different modes of action are combined (Kaneko *et al.*, 1994; Slingsby and Waterman-Pearson, 2001), have emerged and gained interest in routine veterinary practice.

2.3. Pain

2.3.1. Anatomy and physiology of pain

A basic understanding of the physiology of pain is paramount in decision making as it regards the appropriate analgesic to be used in managing pain. Pain that occurs after

most types of noxious stimulation is usually protective and quite distinct from the pain resulting from overtdamage to tissues or nerves. The first type of pain is called the physiologic pain. It plays an integral adaptive role as part of the body's normal defence mechanisms, warning of contact with potentially damaging environmental insults and initiating behavioural and reflex avoidance strategies. It is also often referred to as nociceptive pain because it is only elicited when intense noxious stimuli threaten to injure tissue.It is characterized by a high stimulus threshold, is well localized and transient, and demonstrates a stimulus-response relationship similar to those of the other somatosensations (Woolf and Chong, 1993). According to Willis and Coggeshall, (1991), this mechanism is facilitated by a network of nociceptors and primary sensory neurons that encode the intensity, duration, and quality of noxious stimuli and itsets projections to the spinal cord (Fig. 2.1). Thisnociceptive component consists ofthe processes of transduction, transmission, and modulation of neural signalsgenerated in response to an external noxious stimulus (Woolf, 1995). The following further explains the neurophysiology of pain.

2.3.1.1.Neural pathways

"First pain" responses are conveyed from the periphery to the dorsal horn of the spinal cord in small myelinated fibres (A delta) while "second" pain is conveyed in non-myelinated C fibres. This is important, especially when considering the "gate control theory" detailed below. Also of importance to this theory are afferent stimuli coming in in large myelinated fibres (A beta fibres), from peripheral vibration / pressure / touch receptors (Wall*et al.,* 1974).Neurogenic pain, originating in

damaged or abnormal C fibres, may respond to membrane- stabilizing drugs such as anticonvulsants (e.g. carbamazepine).

2.3.1.2. The response to pain

Responses to visceral pain are very different from those evoked by somatic pain (Millan. 1999). Visceral pain generally results in tonic muscular spasm (teleological, to decrease movement of the affected area) while somatic pain usually causes withdrawal of the affected part of the body "to protect this region from further damage" (Woolf, 1995). Pain, due either to somatic or visceral can have profound autonomic effects (Willis and Coggeshall, 1991). Some of the reasons for this have been alluded to:

i. there is a good degree of cross-over between the somatic and visceral systems, notably at the level of the Wide dynamic ranged cells (WDR) and "complex neurone" in the spinal cord, but also extensively at higher centres, with projections to, for example, the hypothalamus.

ii. It is also worthy to note that there is a close relationship between sensory afferents and sympathetic outflow (Willis and Coggeshall, 1991).

Recent studies suggest that epidural fentanyl alone blocks the neurohormonal response to surgery (Bromm and Lorenz, 1998)

2.3.1.3. Mechanisms of pain

Potential or actual tissue damage leads to pain. Surgery causes tissue damage and in general, the more thetissue damage, the greater the pain produced (Willis and Coggeshall, 1991). To better explain the mechanism of pain, the pathway is divided

intoperipheral receptors, neural pathways, spinal cord mechanisms and long tracts, brainstem, thalamus, cortex and other areas and the descending pathways (Boivie 1996).

2.3.1.4. Peripheral sensitisation

There are two major responses to painful stimuli, a "first pain" and a "second pain". The first pain is localized and often time short lived, the second is more diffused and protracted (Mense*et al.,* 1997).

FIRST PAIN: This is described as sharp, and "pricking". It localises to a well-defined part of the body surface. The mechano-receptors are said to be the receptors for this first pain and they have high threshold (Mense*et al.,* 1997).

SECOND PAIN: This is often described as dulland aching pain which is poorly localised. The receptors for this second pain are termed polymodal nociceptors. This pain last beyond the termination of acute painful stimuli (Merskev. 1986). Sources, pathways, perception of and treatment of the two types of pain are very different. Visceral pain is predominantly of the "second pain" type.

Visceral pain can sometimes be referred to on the bases of the region of the body surface affected. There are evidences that neurotransmitters such as substance P (sP), vasoactive intestinal polypeptide (VIP) and calcitonin gene-related peptide are important mediators, either as neurotransmitters or sensitizers of visceral pain receptors. Prostaglandins, histamine, serotonin, bradykinin, adenosine

triphosphate(ATP), potassium, and Hydrogen ions also appear important in this regard, especially serotonin, which appears to act mainly on 5HT3 receptors (Wall*et al.,* 1974).

In terms of pain perception, thresholds for feeling pain are remarkably constant from individual to individual. That is, peripheral receptor stimulation of sufficient intensity will reproducibly cause pain at the same level in mostpatients. The response of the individual, and his tolerance of the pain, will however differ markedly between individuals of great interest is "Neurogenic Inflammation". This involves, stimulation of C fibreswhich causes a local reaction consisting of vasodilatation and increased capillary permeability (Mogenson*et al.,* 1992). This is due to retrograde transport and local release of sP and calcitonin gene-related peptide. As a consequence, K^+, H^+, acetylcholine, histamine and bradykinin may be released, and these in turn cause prostaglandin and leukotriene production which may end up sensitizing high-threshold mechanoreceptors (Plate I). Neurogenic inflammation may spread to surrounding tissues antidromically (Millan, 1999).

Analgesic drugs that act peripherally include non-steroidal anti-inflammatory agents, corticosteroids, local anaesthetic agents (which may theoretically inhibit neurogenic inflammation if given early enough, an area of great controversy), and even novel drugs such as substance P antagonists such as opioids, serotonin antagonists, baclofen and clonidine(Mogenson*et al.,* 1992).

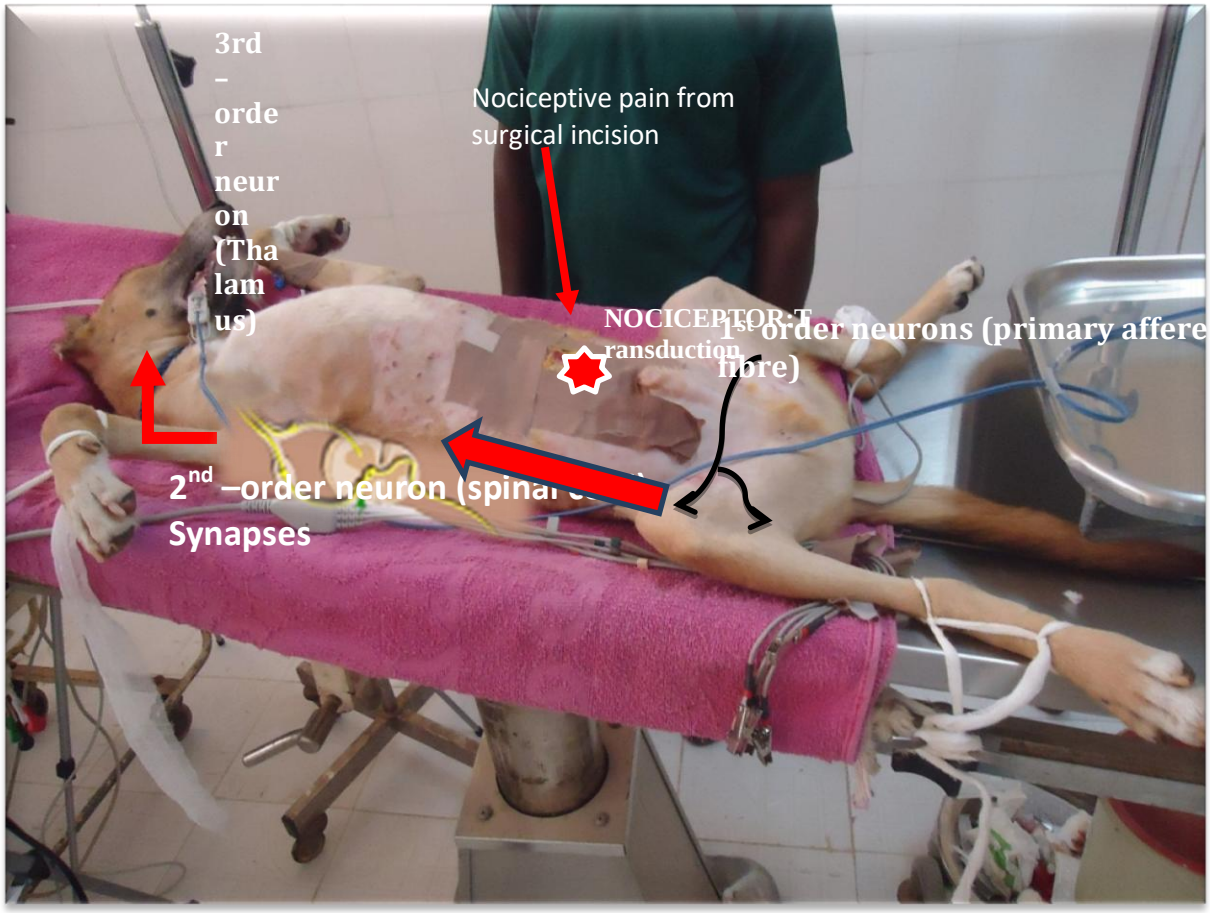
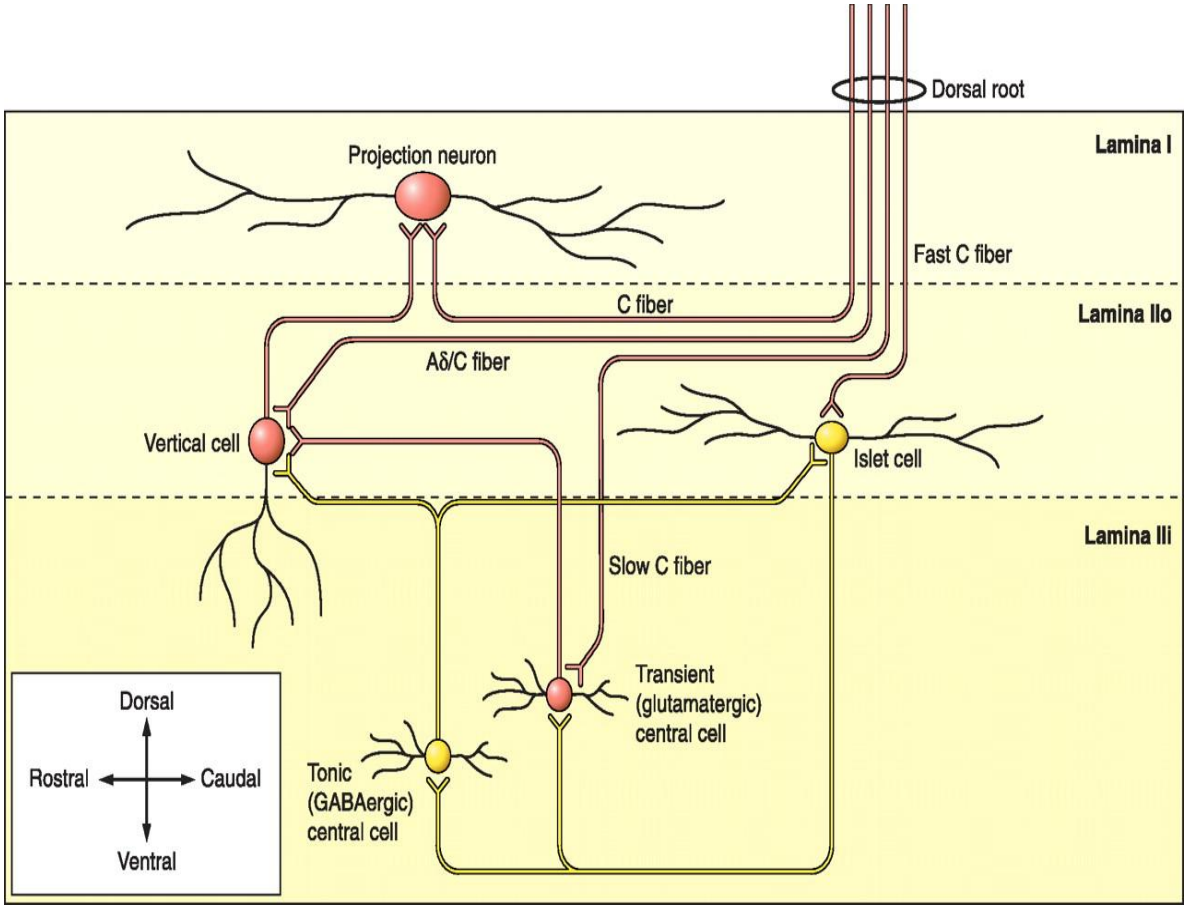


Plate I: A simplified representation of nociceptive processing as a three-neuron chain. A noxious stimulus in the periphery activates a primary afferent fiber that transmits the information to the dorsal horn of the spinal cord. Here, a second order projection neuron that ascends in a spinal tract to the level of the thalamus intervenes. Finally, a tertiary neuron transmits the modified noxious stimulus to higher brain centers, notably the cerebral cortex, for perception



PlateII: Synaptic connections in the superficial dorsal horn (Zeilhofer H U *et al.*, 2012)

2.3.2. Spinal cord pathway.

In this pathway three sub-pathways are involved: Initial connections: laminae in the spinal grey matter close to where the fibres enter the spinal cord, local interconnections, ascending pathways and descending (control) pathways are considered much later (Willis and Coggeshall, 1991).

2.3.2.1.Spinal pathways

A. *Initial connections*

The dorsal root accommodates 70% of the pain fibres while the remaining 30% enters into the motor root. Electrical stimuli produced fromthe nociceptors are conducted to the central nervous system (CNS) through free nerve endings of the primary afferent A delta (Aδ) and C fibres (the primary afferent Aβ fibres that carry non-noxious stimuli). The primary afferent Aδ fibres in the grey matter of the spinal cord transmit information to nociceptive specific neurones in the Rexed laminae (Plate II). Theselaminaeinclude: Lamina I, II, IV, V, VI, VII, VIIIand X (Millan. 1999). The unmyelinated C fibres synapse in laminae I to V, while Aδ fibres synapse in laminae I, V and X(Willis and Coggeshall, 1991).

The two main pathways are: Spino-reticulo-diencephalic tract. Impulses pass from type C fibres to several different "second order" neurons and neospinothalamic tract also known as anterolateral white funiculus (Plate I). This takes most of its fibres from Laminae I and V, and appears to mediate "first" pain (Mogenson *et al.,* 1992).

The important second order neurons are:

Wide dynamic ranged cells (WDR): Which are cells found in the lamina V, VI and VII. These nerve cells are not committed to responding only to pain, they respond also to gentle stimuli and increasing their response as the stimulus becomes more marked (Serpell, 2006).

Nociceptive specific neurones found in lamina I, responding only to noxious stimuli;

Complex neurons: These neuronesreceive numerous inputs and have been poorly studied. They are seen mainly in laminae VII and VIII (Serpell, 2006).

An important property of WDR neurons is "wind up". This occurs with repetitive stimulation at about once per second via C fibres - each added stimulus increases the response of the WDR cell. Wind-up is seen as a good justification for treating pain early and well (Wall *et al.*, 1974). Wind up may be related to stimulation of glutamate receptors especially the N-methyl D Aspartate(NMDA) receptor, a receptor which is very topical at present. Clinically, evidence for wind-up has been hard to come by, although some recent studies attest to the value of pre-emptive analgesia(Mansfield, 1996). Some evidence suggests that mechanisms other than wind-up may be important in the development of visceral pain, although the NMDA receptor appears to still be a major player (Willis and Coggeshall, 1991).

The spino-reticulo-diencephalic system is rich in opiate receptors, while the spinothalamic tract has very few. This explains why opiates (e.g. morphine) have good analgesic properties for visceral pain without affecting (e.g. pinprick) sensation.

B. *Local interconnections*.

There are severalconnections mediated "gating". The basic idea here is that "painful stimuli" coming into the cord on C fibres can be modified by other inputs, which "close the gate on the incoming pain". These inputs come from:delta fibres, beta fibres andothers (Wall *et al.,* 1974).

This arrangement has several practical consequences such as: Transcutaneous Electrical Nerve Stimulation (TENS), Dorsal Column Stimulation (DCS) works, acupuncture works and rubbing the skin locally helps decrease pain(Fitzgerald and Woolf, 1984).

TENS works by high-frequency, low amplitude stimulation of larger peripheral fibres, and this inhibits transmission of pain through the "gates". *DCS* is similar, but works by antidromically stimulating the same A beta fibres (Aβ). Acupuncture works in a different way: it causes low-frequency high amplitude stimulation of small A delta fibres (amongst other fibres), and this also causes inhibition of pain through gating mechanisms. Another difference between acupuncture and TENS is that the effect of acupuncture can be blocked by giving opioid antagonists, which does not inhibit the effect of TENS(Fitzgerald and Woolf, 1984).

Mechanisms of inhibition in the dorsal horn may be very complex - incoming nociceptive fibres express opioid receptors, opioids here blocking sP release, and they probably also act post- synaptically. The presence of these opioid receptors at least partially explains the potent effect of small doses of intra-thecal opiates. In

addition, gamma-amino butyric acid (GABA), somatostatin, neurotensin, cholecystokinin(CCK) and neuropeptide Y may play a role in pain transmission (Wall *et al.,* 1974).

A wide variety of drugs has been used for "antinociception" at the spinal level, these include opioids, alpha-2 agonists and local anaesthetics. Agents such as ketamine and somatostatin may however be neurotoxic, of interest is the potent analgesia induced by spinal octreotide.

C. *Higher ascending pathway*.

*The old spino-reticulo-diencephalicpathway.*This ends in the reticular system of the brainstem, but also sends fibres to the thalamus (the medial nuclei of the thalamus). Probably important are connections between the reticular system and the hypothalamus (and thalamus) system.These may explain autonomic components of the pain response (Helme *et al.,* 1990). Emotional/affective responses to pain may be explained by projections that go from the medial nuclei of the thalamus to most of the cortex, especially the frontal areas, and notably to the anterior cingulate gyrus. The basal ganglia may also be involved in pain discrimination, the affective component of pain, and even in pain (Helme *et al.*, 1990).

The fresh, new "spinothalamic tract.This nips up to the ventrobasal part of the lateral thalamus. Connections go from this tract to the sensory cortex (post central gyrus), which explains the precise localisation of somatic pain (Millan. 1999). It is obvious that this tract is not the main pain pathway, because lesions along this pathway do

not cancel out the sensation of pain, and, in fact, may cause severe pain (Willis and Coggeshall, 1991). This is referred to as *thalamic syndrome.*

d. *Descending pathways.*

Descending modulation of pain sensation originates from three main areas. These are the cortex,thalamus and brainstem, where the *periaqueductal grey matter* (PAG) is particularly important.

Fibres pass from PAG to the reticular formation of the medulla (the nucleus raphe magnus (NRM), and the closely associated nucleus reticularis gigantocellularis pars alpha, and nucleus reticularis paragigantocellularis, all together called the ventromedian medulla (VMM) where connections are serotoninergic, and from there axons descend in the "dorsolateral funiculus" of the spinal cord, to end up on interneurons right next to the substantia gelatinosa (lamina II) in the cord. The synapses here are enkephalinergic. Stimulation of this system causes inhibition of incoming pain impulses. Thus, although serotonin applied peripherally augments pain, its action centrally is important in descending inhibition of incoming painful impulses (Willis and Coggeshall, 1991). New evidence suggests that GABA is also important in inhibition of pain pathways by the VMM.

Apart from the above inhibitory pathway that works mainly on opiates, there is a separate, noradrenaline-based pathway that inhibits pain (Millan. 1999). Noradrenaline-based projections appear to come from the NRM, and also from the locus coeruleus in the pons. This is one explanation why antidepressants which

inhibit noradrenaline uptake may be effective in controlling pain, but it should be noted that antidepressants also inhibit serotonin uptake, so they may also increase activity in the fibres that pass from PAG to medulla (Willis and Coggeshall, 1991).

"On" and "Off" cells

There are probably two main classes of neurones in the PAG and VMM namely the "On" cells which increase pain transmission and the "Off" cells which decreasespain (Millan. 1999).Opioids inhibit "on" neurones and increase transmission in "off" neurones, and noradrenaline also inhibits "on" neurons (Fitzgerald. 2010).

2.3.3. Clinical pain

Pain perception generally is multi-dimensional and each individual perception of pain comprises of sensory-discriminative,affective-motivational and cognitive-evaluative factors (Ladabaum*et al.*,2000). Furthermore, pain can be generated through various means and at the neuraxis.Visceral pain is often limited to base pain treatment on a simple trial-and-error principle depending onthe symptoms reported by the patient. However, the symptoms and subjective pain description doesnot identify the underlying mechanisms of the abnormal pain processing, as well as the perception isnot always confirmed by pathological investigation of the diseased organs (Azpiroz, 2002). Furthermore, patientsdiagnosed with the same disease experience different efficacy of the same compounds, often due tomultiple mechanisms contributing to the pathogenesis of the pain (Galer*et al.*,1993).

2.3.4. Experimental pain

As clinical pain is biased by cognitive and emotional factors and coexisting pain mechanisms,assessment of basic pain manifestations in chronic pain patients is complicated (Main and Spanswick 2001). To overcome this challenge, experimental pain evoked in healthy volunteers establishes a platform to study painprocessing in a standardized manner with reproducible results (Main*et al.,* 1995). In these modelsacute painful stimuli are controlled precisely with respect to localization, intensity, duration andmodality (Main*et al.,* 1997). To mimic clinical pain, long-lasting painful sensations can be applied by infusion ofchemicals to initiate some of the inflammatory processes seen in chronic pain patients. Thepain and analgesic mechanisms may then be assessed by subjective or objective scores.

2.3.5. The ethics of managing pain in animals

Whereas in the past before 1998, there was no consensus reached on what constitute ethical pain management in animals even by Veterinarians, studies have now shown that there has been a rising growth in sensitivity to animal welfare World over both amongst veterinarian and the populace in general (David. 1998). The humane use of experimental animal has now become the order of the day. Recently, there are renewed efforts in research and practice to inculcate the alleviation of pain into practice (Passantino *et al*., 2012). Apart from the moral justification to the use of analgesics many countries today legislate that animals to be used for research, testing or teaching purposes will only be allowed after appropriate bodies approves of it and even then care must be taken to combat pain (Passantino *et al*., 2012).

2.3.6. The taxonomy of pain

Taxonomy is the theory and practice of classification. Classifying pain is helpful to guide its assessment as well as treatment. There are many ways to classify pain and its classifications may overlap. Classification of pain can be based on location, duration, frequency, underlying cause, and intensity(Fitzgerald and Woolf, 1984).

2.3.7. Location of pain

There are two major schemes used to relate pain to body locations. The first relates the specific anatomy to the condition. This scheme identifies sites of pain as viewed from the regional perspective for example, headache, lower back pain, pelvic pain (Fitzgerald. 2010). The second classification focuses on classical body system for example, musculoskeletal, neurologic, vascular pains (Fitzgerald. 2010).These two classification schemes address only one dimension and thus may ultimately fail to adequately define the underlying neurophysiology of the problem.

2.3.7.1. Duration of pain

The duration of pain is the most obvious distinction that could be made in the classification of pain. Under this classification, pain is categorized into acute (these are pain that are less than 30 days in duration), sub-acute (these are pain that persist for up to six months) and chronic pain (Painful sensation that persist for more than six months of duration) (Don, 1996). Recurrent acute pain describes a condition where there are reoccurring isolated episodes of pain (Crue. 1983).

i. *Chronic pain*

Chronic pain is said to be that pain that last longer than six month (Turk and Okifuji. 2001), though some theorists and researchers have placed the transition from acute to chronic pain at 12 months (Main and Spanswick 2001). Vegetative signs very similar to those found in depression, such as anorexia, anhedonia, lethargy, and sleep disturbance are often present. Chronic pain frequently coexists with depression, making it difficult at times to distinguish between the two. Obvious displays of distress, as found in acute pain, are usually absent. Chronic pain is very difficult to recognize (Ru-Rong and Woolf. 2001). Even when recognized there is a tendency not to experience the same intense, visceral empathy that arises so easily in the presence of acute pain. Lack of recognition of chronic pain and difficulty empathizing with it are major barriers to successful treatment (James. 2003).

ii. *Acute pain:*

Acute pain refers to short-term pain that has an easily identifiable cause from the tissue damage that results from surgical or other events. Acute pain often has duration of between 1 second and 6 months and is marked by rapid onset, it is perceived to be sharp in nature and may be followed by a dull, aching pain (Thienhaus and Cole. 2002). Examples of these include pain due to trauma, traumas as a result of surgical procedures or procedure related complications. Other examples of acute pain include pains during labour, parturition, dental work, cuts, burns, fractures. The most severe post-surgical pain occurs within the first 24 to 36 hours after the procedure (Willis and Coggeshall, 1991).

It is difficult to judge by observation alone the degree of chronic pain suffered. This stands in dramatic contrast to our experience with acute pain; the more severe the acute pain the easier it is for us to recognize (Ru-Rong and Woolf. 2001).

2.3.7.2. Treating the underlying causes of pain

Treating the underlying cause of pain can enable the definitive cure of the pain syndrome. At a minimum, however, etiologic clarification will alert the clinician to whether causative or symptomatic treatment is better or, more commonly, whether a combination of both is necessary (Ru-Rong and Woolf. 2001).

2.3.7.3. Intensity of pain

Classifying pain in this manner offers perhaps the least desirable system for classifying pain, because intensity varies for most patients over time and is uniquely subjective (Woolf, 2004). A patient might rate the experience of pain resulting from some pathologic condition as a 10, whereas another patient with the same pathology might describe the intensity of pain only as a 5, both using a 0 to 10 scale (Ranney. 2010).

Pain interfering with appetite, pleasurable activities, or sleep is more a cause of concern than is pain leaving the patient's life otherwise intact, regardless of the reported intensity. Overtime, most patients manage to adapt to their pain; they may exhibit either very little or markedly exaggerated painbehaviour (Remi-Adewunmi 2010).

2.3.7.4. Pain classification based on the cause

Under this category, pain can be classified as somatogenic or psychogenic. Psychogenic pain describes both short- and long-term episodes of pain that occur as the result of some

underlying psychological disorder, rather than in response to some immediate physical injury. Brief episodes, as well as persistent symptoms, are indeed very real and painful for those experiencing psychogenic pain (Lim. 1994). The somatogenic perception involves sensory, emotional and cognitive components. This perception can be categorized into nociceptive, neuropathic, mixed or idiopathic (Dubnerand Basbaum, 1994).

a. *Nociceptive pain*: Pain is termed nociceptive when there is a response to noxious insult from injury to tissues such as skin, muscles, visceral organs, joints, tendons, or bones. Examples include Somatic: musculoskeletal (joint pain, myofascial pain), cutaneous (skin injuries which are often well localized), visceral (hollow organs and smooth muscle) (Dubnerand Basbaum, 1994).
b. *Neuropathic (Deafferentation) pain:* This occurs when pain is initiated or caused by a primary lesion or disease in the somatosensory nervous system. Sensory abnormalities range from deficits perceived as numbness to hypersensitivity (hyperalgesia or allodynia), and to paresthesias such as tingling (Ru-Rong and Woolf. 2001). Examples include, but are not limited to, diabetic neuropathy (mononeuropathy or polyneuropathy), postherpetic neuralgia, spinal cord injury pain, phantom limb (post-amputation) pain, and post-stroke central pain (Ru-Rong and Woolf,2001).
c. *Mixed pain:* Mixed pain is observed in a patient when components of both nociceptive and neuropathic pain coexist. A typical example is in human patients with persistent back and leg pain after lumbar spine surgery (failed low back surgery syndrome) also seen in some patient with complex regional pain syndrome (CRPS), reflex sympathetic dystrophy or causagia) where underlying neuropathic pain coexist with nociceptive pain such as joint ankylosis (Li *et al.*, 2009).

d. *Idiopathic Pain (intractable pain, pain of unknown origin)*: This condition is defined as pain that persists without any identifiable organic lesions or that is disproportionate to the degree of tissue damage (Vetter, 1982). In humans there are three major idiopathic pain syndromes.

    i. The local idiopathic pain syndrome (LIPS), it is also called complex regional pain syndrome (CRPS).

    ii. Type 1 or reflex sympathetic dystrophy (RSD) with symptoms such as osteoporosis caused by disuse and altered vascular supply, dependence on splint or mobility aids.

    iii. Diffused idiopathic pain syndrome (DIPS) also called Juvenile fibromyalgia is seen in about 2-6% of children and adolescents and Non- inflammatory musculoskeletal pain (growing pain), it is a syndrome of leg pain occurring only at night or late in the day with imaging and laboratory findings not diagnostic (Davidson and Kuchta, 2012).

2.3.7.5. Clinical implications of pain classification

Pathological processes never occur in isolation and consequently more than one mechanism may be present and more than one type of pain may be detected in a single patient; for example, it is known that inflammatory mechanisms are involved in neuropathic pain (Mathews, 2001).

There are well-recognized pain disorders that are not easily classifiable. Understanding their underlying mechanisms is still rudimentary though specific therapies for those

disorders are well known.They include cancer pain, migraine and other primary headaches andwide-spread pain of the fibromyalgia type (Sandkuhler, 1996).

2.3.8. Signs of pain in dogs

A dog's behaviour and interactions is unique to the type of pain it is experiencing, and the dog's reaction to pain is dependent upon its personality and the degree of pain it is experiencing(Mathews, 2000). Some of the clinical signs observed can be categorisedinto:

i. posture(hunched back, guarding (protecting) the painful area, "praying" position (front legs and head on floor, hindquarters in the air), sitting or lying abnormally, attempting to rest in an abnormal position, head hanging down.
ii. Movement (stiff, bearing no or partial weight on affected limb, any degree of limp, thrashing, trembling,weak tail wag or low carriage of tail).
iii. Vocalization (for example whining, barking, growling, lack of vocalization etc.)
iv. Behaviour (agitated, poor or no grooming, decreased or absent appetite, dull, inappropriate urination or defecation, and not moving away from it, acts out of character (gentle dogs may bite or become aggressive), licking wound or surgical site(Mathews, 2000).

2.3.9. Causes of pain in dogs

The reaction to pain depends on the different levels of stimuli or injury on the dog. Below are some examples of things that may cause pain. These items are listed according to what level of pain characterizes them. It should be noted that not every dog reacts the same way to pain,it can only be anticipated, based on clinical experience, what the dog is feeling(Taylor and McGehee, 1995; Taylor. 2003).

Irritating or mild pain (dried blood or urine scald,clipper burns or cuts, intravenouscatheterization, minor cuts or scrapes, anal gland evacuation, surgery), mild to moderate pain (endoscopy with biopsy, dental cleaning with or without tooth extraction, arterial catheterization, muscle biopsies, stabilized fractures of tibia/fibula, radius/ulna, castration, spay, cystotomy), moderate to severe pain, areas of burns or ulcerations, corneal ulcers, eye removal, surgery of the mid and lower spine, including disc surgery, declawing procedures, stabilized fractures of femur, humerusor pelvis, mastectomy), severe pain, this includeslarge areas of burns or ulcerations, peritonitis, pancreatitis, surgeries of the neck, including disc surgeries, endoscopy, limbamputations, thoracotomy (Carroll, 1998).

2.3.9.1. The pathophysiology of acute pain

Pain is a complex entity that begins with nociception.Nociception is the process by whichan insult results in the stimulation of specializednerve fibres termed nociceptors. Nociceptorscome in three forms determined by thenoxious stimulus that they detect: mechanosensitive,thermosensitive, and chemosensitive (Cross, 1994). Mechanoreceptors respond to stretching, compression,and crushing. Thermo receptorsrespond to heat and cold. Chemoreceptorsrespond to a large number of compounds,including neurotransmitters (acetylcholine,neurokinin-1, and others), prostaglandins (A2α,thromboxane, and others), bradykinin, histamine,proteolytic enzymes, acids, cytokines(tumour necrosis factor, interleukins, and others),and leukotrienes. Once nociceptors havebeen stimulated beyond their threshold potential,an action potential is propagated from aperipheral nerve to the spinal cord. Peripheralnerves can be of two general types: myelinated Afibres and non-myelinated C fibres. Type A fibresare fast conducting and result in an acute, localized,sharp, and rapid onset of pain. TypeC fibres when stimulated result in a

diffuse,chronic, dull, throbbing pain (Taylor and McGehee, 1995). Both A and C peripheralfibres terminate in the dorsal horn ofthe spinal cord before ascending to the brain forconscious perception. Conscious perception ofnociception is the sensation of pain. Other concurrentsensations or observations (the classicalsigns of inflammation) may be present asa result of cytokine-induced inflammation atthe site of injury: redness, heat,swelling (tumour), pain, and loss of function(Taylor, 2003). Withdrawal reflexes canbe stimulated from nociception at the level ofthe spinal cord before pain is registered. And,in the brain, the reticular activating system (RAS) isstimulated by nociception to cause increasedawareness, cardiopulmonary effects, and stressresponses (Cross, 1994).

2.3.9.2. Pathophysiology of neuropathic pain

Neuropathic pain can be caused by ectopic activity with spontaneous discharge in the peripheral nervous system (PNS) pathways (Jensen et *al.,* 2006). Depending on the location and type of nerve injury, ectopic discharge also may originate in the dorsal-root-ganglion (DRG) cells of the damaged afferent axons. Within the same DRG, cell bodies of uninjured axons may exhibit ectopic activity too (Jensen et *al.,* 2006). Within the central nervous system (CNS), hyper excitability of the pain-signalling neurons may arise, and other mechanisms that facilitate or distort afferent input are likely(Horanyi.1983).

2.3.10. Assessment of pain in small animal practice

While pain could be either detrimental or advantageous to the animal it is important that pain should be assessed in both human and animal patients. The recognition and assessment of pain is an integral part of animal care (Apkarian *et al*., 2001). Pain is intended to assistmedical care providers in all aspects of care for patients with postoperative pain. This

employs the use of evidence-based guidelines to improve the patient's outcome. The overall expected outcome is to improve the postoperative experience, and to reduce the morbidity that is associated with unmanaged pain. The goal of pain assessment is to characterize an individual's pain by location, intensity, and aetiology. A pain assessment should include a detailed history, physical examination, psychological assessment, and diagnostic evaluation (Anon [1]2000).

Typical pain mechanisms in the body cannot be best assessed by questionnaires administered to patients or simple observation of client. Hence, subjective pain symptoms reported by the patient/clients and objective methods assessing the central nervous system response are needed. These methods often monitor diagnostic, physiologic neuro and somatic biomarkers. Recent meta-analysis of human data from positronemission tomography (PET), functional magnetic resonanceimaging (fMRI), electroencephalography (EEG),and magneto encephalography (MEG) studies does provideclarity regarding the commonest regions found activeduring an acute pain experience (Apkarian *et al*., 2001).These areas include: primary and secondary somatosensory,insular, anterior cingulate, and prefrontal cortices aswell as the thalamus (Wagner *et al*., 2007). Furthermore, pain assessment can be based on nociceptive withdrawal reflex responses and autonomic parameters such as heart rate variability (HRV) etc.

2.3.10.1. Pain scoring systems

The main objective of any pain scoring system is to assess pain as well as analgesic efficacy in patients (Mathews, 2000). Pain rating scales used in animals have simply been adopted from scales developed for measurement of pain in humans. The ability to

communicate verbally allows reliable estimation of pain intensity using different scales in adult humans (Flecknell*et al.*, 1999). In the case of children who cannot write or communicate verbally objective demonstration of surgical stress coupled with behavioural reactions like crying, facial expression, posture etc. served as basic criteria for developing infant pain scoring systems (Nancy,*et al.*,2008). Scales designed for acute procedural pain in prelingual children might therefore serve as a fundamental template for acute pain studies in veterinary patients (Hansen 2003).

In veterinary practice, most of the commonly used scales measure the intensity of pain unlike humans in which other dimensions like affect, quality and location of pain (multidimensional) are assessed (Holton,*et al*., 2001). Pain intensity is a quantitative estimate of the severity or magnitude of perceived pain (Jensen,*et al*., 1986).

Different scales have been used to measure acute pain intensity in small animals including simple descriptive scale, numerical rating scale and visual analogue scale (VAS) (Lascelles,*et al*., 1994; Holton*et al*., 1998; Slingsby and Waterman-Pearson, 2001).

a. Simple descriptive scale

This scale usually consists of four or five expressions to describe different levels of pain intensity. Each of these expressions is assigned a number, which represents the pain score for that animal. For example, Holton *et al*. (1998) looking at dogs after surgery used the following scoring system;

The observer has chosen the most suitable descriptive term, which was then converted into a numerical score like, no pain = 0; mild pain = 1; moderate pain = 2; and severe pain = 3.

The advantages includes that it is simple to use and that its results will not be affected by visual acuity. The disadvantages of simple descriptive scale are that it lacks sensitivity due to limited number of pain descriptors that lead to over/under assessment of pain and analgesic efficacy and there is inter observer variability.

b. Numerical rating scale

This scale consists of multiple categories with different descriptive definitions of pain behaviours in each category and numbers are assigned to each descriptive level. The number chosen by an observer represents the pain score (Holton *et al*., 1998).

The advantages of the numerical rating scale are that there is thorough evaluation of the patient due to several categories and that it has an easy method of tabulating the score. However, the disadvantages includes lack of accuracy as categories are scored by whole numbers, this implies that there is equal differences between categories which may not be true, also there is lack of specificity with descriptive pain behaviours. Again it encourages inappropriate statistical analysis since the results are not normally distributed.

c. Visual analogue scale:

This technique is widely used in human medicine (Collins*et* al., 1997; Remi-Adewunmi,*et al.,* 2012) and has been used in various veterinary analgesic studies. Typically, visual analogue scale (VAS) is a 100 mm straight horizontal or vertical line anchored with descriptors of pain intensity, such that 0 represents no pain and 100 represents the worst possible pain, on either end of the line. The observer draws an intersecting line along the scale that best represents his/her estimated level of animal pain.

Measuring the length of line from 0 to the mark made in mm i.e. from extreme left to right gives the pain score for the animal. In addition, the VAS can be used to assess the level of dogs' sedation in the peri-operative period. In this system, the level of sedation will be assessed by observing dogs' posture, mental alertness, and its ability to stand and walk. At each assessment, a mark will be made on a 100 mm scale, on which 0 corresponds to 'no sedation' and 100 corresponds to fast asleep (Lascelles *et al*. 1998).

The advantages of VAS include the fact that there is more sensitive in detecting subtle variations as the scale is not limited to some labelled categories of pain. Also it gives a broad sense of whether pain is improving or getting worse in the course of evaluation, andavoids the use of indefinite descriptive terms and provides many points to select. However the disadvantages are Inter-observer variability when more than one observer evaluates the same animal, variation due to visual acuity among observers, and VAS scores are not linear, and i.e. the difference in pain between each successive increment is not equal.

2.3.10.2. Diagnostic biomarker in the evaluation of pain

The search for biomarkers in pain is,like in many other fields, now increasingly concernedwith 'omics' research (Marchi *et al.,* 2009). In this case, a vast arrayof molecules usually sampled from all kinds ofbody fluids is analysed simultaneously to possiblyallow geno- and pheno-typing of specificpain entities. The idea that biomarkers may also be used to identify and quantify pain has been investigated in preclinical and clinical studies

(Marchi*et al.*,2009). Several biomarkers have been employed in the evaluation and measurement of pain in both human and animal subjects.

a. Cortisol

Cortisol as one of the most important hormones present in the cerebral cortex of the brain regulates physiological responses in the body. This hormone is a glucocoticoid which is produced by the cortex of the adrenal gland in response to adrenocorticotropic hormones which is secreted by the pituitary gland upon activation by the neurons in the paraventricular nucleus of the hypothalamus. When there is physiological or psychological stress cortisol is released and its level is modulated by feedback inhibition mechanism (Reiche *et al.,* 2004).

Earlier reports indicated that during abdominal surgery, serum cortisol response isreleased largely through autonomic afferentpathways from the intraperitoneal organs (Kehlet *et al.,* 1980) and not the somatic sensory pathways that is the major release mechanism of cortisol. Increased cortisol production issecondary to preceding increase in Adrenocorticotropic hormone (ACTH) secretion (Kao *et al*.,1975; Oyama and Takiguchi 1970).

b. Electroencephalogram (EEG)

The discovery of electroencephalographic studies by Hans Berger in 1929 has led to a great breakthrough in the field of neuro-diagnosis and ever since then there has been advances in research and technology in this field of study (Tudor *et al*., 2005; Line *et al.,* 2008a).

Electroencephalography (EEG) generally speaking, allows the use of non-invasive access to the brain processes at an integrative level of the CNS with a high degree of spartio-temporal resolution through the use of high density recordings and interpolations. This devise employs the use of montages placed on the head strategically and sometimes at other areas of the body depending on what is to be measured. EEG reflects the cerebral function with co-activation of the different regions of the brain. These signals can be analysed using parametric and non- parametric methods.

The non-parametric method employs such methods as the EEG mappings to study frequency analysis while the parametric methods include the power spectra graphs and sensory evoked potentials (Line,*et al*., 2008b).

i. Using EEG frequency analysis to evaluate pain

EEG is used to image the electrical activity in the brain generated by neuronal firing between various brain centres. The firing is usually randomly distributed in time when a person is in resting state, but the neural networks can be synchronized and activated sequentially and in parallel as a response to an external stimulus (Olesen,*et al.,* 2011). The resting state EEG has been used to reflect the pathophysiology of pain in chronic pain patients and alterations in the CNS during pharmacological intervention (Knott, 2000). In contrary, the evoked brain potentials (EPs) following an external painful stimulus has been used to study the nociceptive response to acute pain in patients or after modulation of the CNS by drugs or chemicals (Staahl,*et al*., 2011). EEG has the advantage of high temporal resolution, relatively low-cost and feasibility in clinical settings, which were the main reasons to choose this method for all four studies in the present study. On the contrary, the

most important limitation of EEG is the relatively poor spatial resolution in respect to identification of activated brain centres (Frokjaer,*et al.*, 2010).

Electroencephalography (EEG) frequency bands and Fourier analysis are often used to obtain information from the frequency components of the EEG signals (Frokjaer, *et al.*, 2010). The EEG frequency bands are typically comprised of 7 bands; delta (0.5-3.5Hz), theta (4.0-7.0 Hz), alpha1 (7.5-9.5 Hz), alpha2 (10-12 Hz), beta1 (13-23 Hz), beta2 (24-34 Hz), and gamma (35-45 Hz). 3D topographic plots on a head model display the power distribution of the brain activity(Staahl *et al.*, 2011).

In response to tonic pain relatively consistent changes in EEG frequency bands have been found; (a) increase in low frequency delta power; (b) rare change in theta power; (c) decrease in alpha power; and (d) increase in beta power (Bromm and Lorenz, 1998).

ii. Digital Electroencephalography (dEEG)

Electroencephalography has been used for examination of epileptic dogs and cats for almost 50 years (Croft, 1962). A universally used EEG recording protocol has not been established so far, although many researchers focused on finding the best recording method. Many veterinary EEG laboratories use their own recording and anaesthetic protocol with different numbers of EEG electrodes and different anaesthetic regimes (Berendt,*et al.*, 1999; Bergamasco,*et al.*, 2003; Croft, 1962; Jeserevics,*et al.*, 2007; Wrzosek *et al.*, 2009). The latest publications also analysed qEEG data in order to optimize the diagnostic output of their EEGs (Bergamasco *et al.*, 2003; Jeserevics *et al.*, 2007; Wrzosek,*et al.*, 2009). Digital

electroencephalography (dEEG) is also fast growing in popularity in veterinary practice and its use in diagnosis cannot be overemphasized (Cwynar and Zawadzki, 2010).

c. *EEG power spectrum*

Fast Fourier transformation (FFT), a mathematical procedure, converts the raw EEG signal into its component sine waves of different frequency, characterised by corresponding amplitude. The power spectrum thus generated is simply distribution and derivation of spectral EEG variables from the corresponding frequencies and amplitudes. Quantitation of EEG depends on analysis of the power spectrum. Commonly used quantitative variables of the EEG power spectrum in response to nociception in different species of animals are median frequency (F50), total EEG power (Ptot) and spectral edge frequency 95% (SEF) (Miller, 1995; Murrell,*et al*., 2003). F50 is the 50% quantile in the EEG frequency distribution spectrum, Ptot is the total area under the EEG frequency spectrum and SEF is the 95% quantile i.e. the frequency below which 95% of total power is located in the EEG power spectrum.

2.3.11. Management of pain in dogs

Treatments can vary from simple physical therapy to complicated drug regimens. There are two major categories of pain that can occur: acute and chronic. Acute pain occurs with trauma and surgery while chronic pain is associated with conditions like arthritis and cancer. The types of therapy tobe used will often depend on whether the dog is experiencing acute or chronic pain.

There are generally five classes of pain reducing alternatives that can be used for pain managementin dogs.These alternatives include:

2.3.11.1. Non drugs

i. *Nutraceuticals* are non-drug nutrients that play a major role in strengthening normal body tissues. They aid in repairing damaged tissues and assist in improving efficient body metabolism. Adding nutraceuticals to the daily diet has noticeably improved the life quality of many dogs (Matthew, 2011). Most commonly used nutraceuticals include in their ingredients EFAs (essential fatty acids such as omega-3 and omega-6 fatty acid). Other ingredients such as glucosamine, chondroitin sulphate, methylsulfonylmethane, and flax seed oil have proven to be helpful in decreasing pain and discomfort from arthritis and degenerative processes. Examples of nutraceuticals incudes heat or cold packs, limited low-impact exercise when appropriate, comfortable bedding with plenty of support, general nursing care including cleaning, grooming, and petting, weight management for obese animals with arthritis (El Sohaimy, 2012).

ii. *Joint Protective (chondro-protective) agents:* These nutritional supplements are given safely to dogs and cats by Veterinarians. They supply the body with the building blocks of joint cartilage. They are helpful in relieving some joint pain such as arthritis and osteochondritis desicans (OCD). They are said to be non-toxic (El Sohaimy, 2012). These drugs include polysulfated glycosoaminoglycans, glucosamine and chondroitin sulphate (El Sohaimy, 2012).

2.3.11.2. Drugs

i. *The non-steroidal anti-inflammatory agents (NSAIDs).* Pain sensation and inflammation rely on messenger chemicals called prostaglandins. There are two types of

prostaglandins, COX 1 and COX 2. Cyclooxygenase (COX) is necessary for both prostaglandin formations. Older NSAIDs prevent the formation of both prostaglandins, COX 1 protect the lining of the stomach and small intestine and also assist clotting and kidney blood flow(Donnelly and Hawkey, 1997). COX 2 cause inflammation, swelling and pain while the newer NSAIDs blocks COX 2. The older NSAIDs cause more problems (Lascelles, 2000). All these products must be used with caution because there is potential for stomach and intestinal problems and prolonged blood clotting time. Examples of the older NSAIDs includes aspirin, ibuprofen, phenylbutazone, Piroxicam, Naproxen, Flunixin, meglumine(Peretz, 1998).All NSAIDs are well absorbed when given orally. However, in acute pain it can be administered parenterally. They are eliminated from the body by the liver and kidneys (Donnelly and Hawkey, 1997).

*The Special Problem of Cats and NSAIDs:*Cat's liver does not have enough bilirubin-glucuronide enzymes. Because of this, NSAIDs tend to linger in the feline's blood stream. However, feline can tolerate meloxicam and ketoprofen (Donnelly and Hawkey, 1997). Other possible side effects of NSAIDs is that animals with liver disease cannot metabolise and eliminate these drugs normally and because the liver plays an important role in eliminating and metabolising NSAIDs from the body (Donnelly and Hawkey, 1997). Therefore, it is contraindicated to use NSAIDs in the face of known liver disease. Non-steroidal anti-inflammatory drugs (NSAIDs) sometimes also cause kidney damage in cats and dogs. Other common side effect observed is stomach and intestinal bleeding(Peretz, 1998).

The Newer and Safer NSAIDs:Examples of these drugs includes; Caprofen, Ketoprofen, Etodolac, Meloxicam, Tepoxalin Valdecoxib. They are safer than the "old" NSAIDs. Because the newer ones are COX-2 selective, they are less likely to cause stomach or intestinal bleeding(Peretz, 1998).

a. *Non Related NSAIDs Relievers*:Acetaminophen: It is a para-aminophenol derivative with anti-fever and pain control activity, but very little anti-inflammatory effect. Paracetamol does not produce stomach ulcers or retard blood clotting.Paracetamol is a medication commonly used to alleviate fever and pain (McConkey, *et al.*, 2009). Dogs are less sensitive to paracetamol than cats. For example, a 25 kg dog would need to ingest over seven 500 mg tablets in order to suffer toxic effects. In the cat, one 250 mg paracetamol tablet could be fatal (McConkey, *et al.*,2009). Paracetamol is eliminated from the body primarily by formation of glucuronide and sulphate conjugates in a dose-dependent manner. The biologic half-life of paracetamol in normal adults is approximately 2 to 3 hours in the usual dosage range. It is somewhat shorter in children and somewhat longer in neonates and in patients with cirrhosis. The elimination half-life is approximately 3 hours for the extended-release product. The elimination half-life of paracetamol in the cerebrospinal fluid according to pooled data is 3.2 hours. In addition, to severe liver failure, paracetamol causes damage to red blood cellsParacetamol is more effective in inhibiting COX enzymes in the brain rather than in the body (Bertolini *et al.*,2002).

d. Methocarbamol: Methocarbamol is a muscle relaxant that exerts its effect by acting on the central nervous system rather than on the muscles themselves. It is a rather save drug. Although it does not directly lessen pain, it may relieve muscle tension associated

with arthritis in pets. It has weak sedative properties and may make the urine appear darker (Bertolini, *et al., 2002)*.

Dissociative anaesthetic agents.

ii. N-methyl-D-aspartate *(NMDA) Receptor Antagonists or Blockers***:**

N-methyl-D-aspartate receptor antagonists block pain by binding to the N-methyl-D-aspartate (NMDA) receptor (Zeevalk and Nicklas, 1992). N-methyl-D-aspartate blocking medications include ketamine, dextromethorphan, Gabapentin and amantadine. The opioids methadone, dextropropoxyphene, and ketobemidone are also antagonists at the NMDA receptor (Olney, *et al.,* 1998).

a) **Ketamine**: Ketamine, developed in 1962, was initially promoted as a fast acting general anaesthetic (Jensen, 2000). A few years later, in 1970, the Federal Government of Nigeria approved ketamine for human use, and as a result it soon became popular as a battlefield anaesthetic. The first evidence of illicit abuse of the drug was on the West Coast (Dotson, *et al.*, 1995). Later, during the late 1970s and early 1980s abuse began to increase across the country (Dotson, *et al.*, 1995).

   This medication is commonly used as a general anaesthetic in cats. However, studies have found that it reduces pain when it is applied to the skin as a gel or paste. There have been some studies that found that ketamine, given by mouth, also alleviates pain (Lau and Zed, 2001).

   Ketamine is a preparation that can be used systemically as intramuscular, subcutaneously and intravenously, also it is used intra-nasally and orally to achieve

anaesthesia (Jensen, 2000; Craven, 2007). And though it can be injected, the rapid onset of effects from oral or nasal use makes it more convenient and marketable than the injectable forms (Haskins*et al.,* 1986). It is primarily manufactured as an injectable liquid, however, the illicit producers evaporate the liquid to form a powder that can be snorted or compressed into pills (Anis*et al.*,1983).

b) **Dextromethorphan**:This is a common cough suppressant used in humans and pets. It is also an NMDA inhibitor. This is a rather safe medication when given at recommended dosage (Drachtman*et al.*, 2002).

c) **Amantadine**:Amantadine is the most commonly used oral drug in this class. It was originally developed as an antiviral compound, and has also been used to treat drug reactions that affect coordination and Parkinson's disease in humans (Hayden*et al.*, 1985). It appears to effectively block pain in dogs. The dose of amantadine must be reduced in pets with poorly functioning kidneys. It has been given on a daily basis, but in most cases, it is given for one to two weeks and then discontinued until pain worsens. Side effects are uncommon, but may include agitation or diarrhoea(Peter*et al.*, 2009).

d) **Gabapentin**:Gabapentin has been used for many years to treat chronic pain in humans (Mathiesen*et al.*, 2007). It may offer some potential for use in dogs to lessen chronic pain (Werner*et al.*,2001).

e) **Tricyclic antidepressants**:From studies in humans, the tricyclic antidepressant, is sometimes effective in reducing chronic pain

iii. Alpha-2 agonists

These drugs usually are anaesthetic agents that act by blocking as alpha-2 agonist.However when given at sub-anaesthetic doses, they tend to relieve pain examples are Xylazine.Medetomidine hydrochloride is approved as an anaesthetic and pain reliever for use in dogs recovering from surgery (Olney*et al.,* 1998). It also belongs to a class of drugs called alpha-2 adrenoreceptor agonists. At anaesthetic doses this medication slows heart rate (Melissa, 2003).

It is metabolized by the liver and excreted through the kidneys so it should not be given to dogs that have liver or kidney disease (Melissa, 2003). It should also not be given to dogs at times that they are agitated and fearful at the animal hospital or dogs that might go into shock due to coexisting diseases (Melissa, 2003).

iv. Corticosteroids

All of the corticosteroids mimic the effects of the body's own cortisone which is produced in two adrenal glands. They are all the most effective blockers of inflammation and resulting pain. However, they all have major side effects when given over extended periods of time (Watson*et al.,* 1996). These changes include, weight gain, fluid gain, increased thirst and urination, thinning of the skin, liver changes, decreased resistance to infectious disease, mood swings, and increased blood sugar (Watson*et al.,* 1996). When they must be used, they should be given in the minimal amount that will control inflammation and should not be given more than two or three times a week (Mogenson*et al.,* 1992). A few corticosteroids had been used in humans for nasal allergies while in dogs, beclomethasone which is used topically daily, and however their use is very limited in this species.

Prednisolone. Prednisone and prednisolone can be classified as glucocorticoids.Their effects mimic that of natural cortisol, which is produced by the adrenal gland (Watson*et al.*, 1996). They usually break down stored resources such as fats, sugars and proteins so that they may be used as fuels in times of stress (Joubert *et al.,* 2006). Glucocorticoids are the second most effective anti-inflammatory, analgesic medication other than the opiate but are often not used because of their effectson glucose and protein metabolism (Dohoo and Dohoo, 1996).However, they have severe non-painful side effects and must only be given occasionally in measured doses or reserved for dog and cats in the twilight of their lives.

*Dexamethason*e. Dexamethasone is another member of the cortisone class of hormones. They are steroids but unlike the anabolic steroids which build muscle mass and strength, dexamethasone causes break-down of stored resources (fats, sugars and proteins). Dexamethasone is also a powerful anti-inflammation and anti-pain medication. However, the same side effects that limit prednisone/prednisolone apply to this medication (Joubert *et al.,* 2006). Dexamethsone has a longer action than prednisone/prednisolone.

v. Opiate narcotics

*The Government Regulated***:** Opiates or Opioids are the most powerful pain-relieving compounds available for pets and humans (Mark, 2001). They all mimic natural brain chemicals that limit our perception of pain. However, they are highly addictive and should be reserved for pain that will not respond to other medications or when pets are in terminal condition. Another limitation is that with time, doses have to be increased to obtain comparable pain relief. Side effects include euphoria, depression of breathing, physical dependence, slowed heart rate, constipation and itching. They may also cause contraction of the pupils of the eyes, and sedation. In humans, they are generally given to alleviate the

pain of terminal cancer or painful nerve conditions (Dertwinkel*et al.,* 1998). In pets, they are given to stop the pain of arthritis or cancer, when all other medications fail. In dogs in late hip dysplasia, corticosteroids are more likely to be given. Injectable and oral forms of opiates are rarely dispensed for pets in the Nigeria. In Nigeria, the National Drug Law Enforcement Agency (NDLEA) monitors the use and frowns on any long-term use of opioids, fearing they might be abused illegal by human (Obinna, 2008). All opiates are called class -2 narcotics by the NDLEA. Veterinarians and physicians fear prosecution by the NDLEA and use them only cautiously.

Fentanyl

Fentanyl patches are the most commonly used form of opiate narcotic in pets (Hofmeister and Egger, 2004). Fentanyl was first synthesized in the laboratory in the late 1950s to control pain in humans; particularly those suffering from cancer (Egger*et al.,* 2007). It is about 90 times as potent as morphine (Hofmeister and Egger, 2004). Unlike oral or injectable opioid narcotics, fentanyl patches slowly and continuously releases the drug giving smooth, continuous pain relief. Fentanyl passes through the pet's skin and provides very steady pain relief. Veterinarians most often used fentanyl short-term, after surgery, in advanced cancer or subsequent to body injury (Egger*et al.,* 2007). Fentanyl is sold as a transdermal adhesive patch which is placed on a hairless portion of the pet's skin. In medium and larger dogs, complete patches can be given (Gellasch*et al.,* 2002). In large cats, a whole patch can also be used. In smaller cats, only a portion of the plastic liner is folded back. Patches should never be cut. In dogs, one patch lasts for 72 hours but it takes 12-36 hours for enough of the drug to be absorbed. In cats, the effect of the patch can last up to 120 hours. Cats absorb enough of the drug to be effective within 5-8 hours. In dogs

and cats, side effects include excitement or lethargy, poor appetite, and low body temperature. Fentanyl patches are sold in sizes that deliver 25, 50, 75 and 100 micrograms of the drug per hour. The 25 mcg/hr patches work well on 3.6-5.4kilogram cats when only half the protective liner is removed (Gellasch*et al.*, 2002). Ingestion or excessive heat on the patches is lethal to the pet and the other household members. Should this occur, naloxone or buprenorphine are the antidote if administered early enough.

Morphine

Morphine sulphate is available in injectable mostly in Nigeria although tablet, liquid and capsule preparations can be seen. The oral preparation is often disliked by dogs and cats because of its bitter taste. Morphine is a relatively specific mu opioid receptor agonist and has been used to provide analgesia during the perioperative period (Kamata*et al* 2012). Morphine can be synthetically produced, but is more easily derived from opium, which comes from the unripen seedpods of the poppy plant (Durant and Yaksh, 1986). Morphine is a phenanthrene alkaloid with a pH of 7.4, with the tertiary amine nitrogen being highly ionized, making the molecule water soluble. Morphine acts as an agonist at stereospecific opioid receptors at pre- and postsynaptic sites in the brainstem, spinal cord and in peripheral tissue. These opioid receptors are normally activated by three endogenous peptide opioid receptors: enkephalins, endorphins, and dynorphins. Morphine mimics the actions of these endogenous ligands by binding to opioid receptors and results in activation of antinociceptive systems (Stoelting and Hillier 2006).

Pethidine

This is an injectable narcotic drug that is one fifth as powerful as morphine. It is an excellent drug for controlling pain for short periods in dogs (Lister, 1960). It is not suitable for long term use because, with time, pets become resistant to its action. The dose of this drug in dogs is 2 mg/pound given intramuscularly or orally every 4 hours (Holden, 2007).

Oxymorphone

This medication is a semi-synthetic opioid ten times as strong as morphine. It is given by injection and its effects last 4-6 hours (Batema*net al.,* 2008). It is said to be a good drug for postoperative pain in dogs and cats (Holden, 2007).

Tramadol

Tramadol is a synthetic opioid drug that has a dual mechanism of analgesic action as a serotonin and norepinephrine reuptake inhibitor and a mu-opioid receptor agonist (Xie*et al*., 2008).Formation of metabolite M1 is important for the analgesic effect of tramadol (Ide*et al.,* 2006).

Because tramadol is not technically an opiate, it is not controlled by the National Drug Law Enforcement Agency. It is one of the most promising drugs available to Veterinarians for treating chronic postoperative pain (Giorgi*et al*., 2009). It has two modes of action: mu agonist and monoamine reuptake inhibition similar to the newer, human antidepressants. It appears to be comparable to pethidine or codeine in its pain-relieving affect. Administering tramadol with NSAIDs, or mu agonists increases the analgesic effects (Giorgi *et al*., 2009). It tends not to cause vomiting as the opioids often do. The drug is inexpensive and available in generic form. Tramadol can be used as an analgesic in both dogs and cats. Since most NSAIDs are dangerous in cats, tramadol provides a better option for cats with chronic pain

issues (Giorgi*et al*., 2009). Side effects are uncommon but they include sleepiness and colic. In dogs, tramadol is usually given twice a day – but it can be given more frequently if required.

Buspirone

Buspirone is a highly effective medication when used for treatment of anxiety and premenstrual syndrome (PMS) symptoms in humans (Pavlakovi*ćet al.,* 2009). It is very safe when given at correct dosages to dogs and cats. More recently, it has been evaluated for its pain-relieving effect. In experimental rats, it was effective in blocking the pain of burns, wounds and inflammation. Buspirone should not be used along with the MO class of antidepressants because dangerous increases in blood pressure can result (Kishore-Kumar, *et al.,* 1989).

Butorphanol

This mixed pain-receptor blocker is a less controlled form of narcotic (C-IV). Butorphanol is used as a pain reliever and cough suppressant in multiple species including dogs, cats, ferrets, rabbits, birds, and horses (Goldstein*et al.,* 1998). It may also be used to prevent vomiting in animals undergoing chemotherapy (Abboud*et al.,* 1991).This opioid agonist-antagonist is administered by injection or intranasal spray. It has been given to dogs and cats by subcutaneous injection three times a day. After twenty minutes, its pain-controlling properties take effect and last for eight hours (Vachharajani*et al.,* 2002). It can also be given orally. It causes fewer side effects than the traditional opioids narcotics. However, butorphanol will cause eye dilation, confusion and pain at the site of injection - especially

when given to cats. It is not considered to be useful in the management of chronic pain. The injectable liquid butorphanol can also be given by dropper to cats. Since it has no taste, cats will not fuss about a bitter taste. It is not absorbed well when given in this manner to dogs. Some possible side effects are loss of appetite, vomiting, incoordination, and restlessness (Olsen*et al.,* 2008).

Buprenorphine

This drug is a partial mu agonists that binds to the mu receptors in the brain thus prevents their activation in the sensation of pain. Buprenorphine is approximately 30 times stronger than morphine (Morgaz*et al.,* 2013). However, it is a medication with very few serious side effects. It works best when pain is no more than moderate. It can also be prepared by compounding pharmacies as a transdermal patch and administered through the skin, similar to fentanyl. Although these patches take up to six hours, it maintains its pain-controlling effect for up to twelve hours. With subsequent patches, pain control becomes more uniform (Morgaz*et al.,* 2013).

vi. Herbal and Holistic Remedies for older dogs

Herbal or holistic therapies for pain control are becoming more popular. These products tend to have mostly inconsequential side effects and can be used indefinitely. Glucosamine sulphates, chondroiten sulphates, grapenol, and shark cartilage are just a few products available in veterinary formulas. A reputable quality source of the components is important to increase chance of successful pain control (Wirth *et al.,* 2005).

Acupuncture

Acupuncture has been used as a therapeutic modality for more than 3000years, but it is only since the 1970s that a greater understanding of the underlying mechanisms of acupuncture analgesia (AA) has developed (Oldendick *et al.,* 2000). This growth in understanding of AA has paralleled the scientific advances made in uncovering the physiology of pain perception. The mechanism by which acupuncture controls pain is still theoretical but the recipients of successful treatments can attest to the effectiveness (Audette and Ryan, 2004). There are no negative side effects and improvements can be rapid and long lasting in some cases. There are so many options and choices to control any discomfort the pets may be suffering from (Price, 2000).

2.3.11.3. Multimodal pain management techniques

Before now single drug therapy had been found to be very popular. This however had not been devoid of the attendant side effects of the drugs used (Skinner, 2004). The use of Opioid's for example is accompanied with respiratory depression, post-operative nausea and vomiting (PONV), over sedation, and pruritus (Skinner and Shintani 2004). On the other hand, the NSAIDs particularly at higher doses are associated with their familiar side effects such as gastrointestinal disturbances, gastric ulcerations, increased bleeding time and renal impairments. Local anaesthetics are limited by its short duration of action and cardiovascular collapse (Sandler *et al.*, 1991).

As pain involves multiple mechanisms that rely on different receptor systems, it is beneficial to utilize a multimodal approach to achieve pain relief in the postoperative setting (Pyati and Gan. 2007). The concept of multimodal analgesic therapy was introduced to provide effective postoperative pain relief, reduce opioid-related adverse effects, reduce surgical stress response and improve clinical outcomes by combining various analgesic

techniques and different classes of drugs with varying mechanisms of action to achieve additive or synergistic effects (Elia*et al.,* 2005).

An ideal postoperative analgesic regimen is expected to provide effective pain relief, reduce opioid-related adverse effects and the surgical stress response, and improve clinical outcome, e.g. morbidity, mortality and duration of hospital stay. The concept of multimodal analgesia was introduced to achieve these goals by combining various analgesic techniques and different classes of drugs to improve postoperative outcome ((Kehlet, 2004). However, available data are conflicting and do not necessarily show that multimodal analgesia has resulted in improved outcome and concomitant reduction in the adverse effects of opioids(Kehlet*et* al., 1999; Kehletand Hole, 2001). The failure to improve clinical outcome may be due to inappropriate combination and dosages of analgesics (Parvataneni, *et al.,* 2007). In addition to adequate analgesia, postoperative morbidity and duration of hospital stay depend on other factors such as initiation of early nutrition, mobilisation and comprehensive rehabilitation programmes (Chia*et al.,* 1998).

CHAPTER THREE

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1. Experimental animals

Thirty two (32) dogs of both sexes were acquired from dog breeders that have relatively fair pedigree records and kept in the kennel of the Small Animal Unit of the Ahmadu Bello University Veterinary Teaching Hospital Zaria, Nigeria for 2 weeks prior to surgery for acclimatization. The mean body weights of the dogs were 21 ± 4 kg. During the period of acclimatization, blood samples were collected from all the dogs for heamo-parasitic screening and presurgical evaluation of the dogs, these samples were sent to parasitology and clinical pathology for complete blood count (CBC). Infected dogs were treated accordingly.

3.1.2. Equipment and instruments

Multi-parameter veterinary patient monitor (General Meditech Inc.), Electroencephalograpy (EEG) machine (Contec medical systems co. LTD),Audicom® AC9800 Automatic Electrolyte Analyser (Jiangsu Audicom Medical Technology Co., Ltd.), Micro-haematocrit reader (BD Adams™), Micro haematocritbottles, Surgical packs, drapes, Surgical tables, working tables stands, surgical lamps, Waste trolleys and pans, Anaesthetic gas and machines breathing monitor (Kruuse™ Inc.), Pulse oximeter (General

Meditech® Inc.),Electronic stethoscope (Contec® medical systems co. LTD), Cortisol ELISA kit, Electric cordless trimmer (Oster™) were all acquired for the study (Plate III).

3.1.3 Medications/ drugs

Dewormers (pyrentel parmoate and praziquantel), Propofol injection, chlorpromazine, atropine, halothane, morphine powder, pentazocine, pethidine, piroxicam,(Feldene®), diclofenac (Roche®), Paracetamol, ketoprofen, suxamethonium, epinerine, ringer solution and physiologic saline solution.

3.1.4 Consumables:

Electrodes for the ECG and EEG machine, surgical blades, dressing gauze, adhesive plaster, ceftriaxone (Rocephine®), chlorhexidine, porvidone iodine, izal, syringes and needles, cotton wool, dogfoods: Rice, beans, roasted soybeans, Cray fish, bone and meat, pesticide (Amitrax®), drip, whole blood delivery sets, sample bottles and Normal saline.

3.2 **METHODOLOGY**

3.2.1. Surgical technique

3.2.2. Presurgical preparation of dogs

All experiments conducted in this study were in accordance with the guidelines of Research Ethics and Animal Use of theAhmadu Bello University. Food and water were withheld from all dogs participating in this study for 12 and 2 hours, respectively prior to surgery. All dogs to be included in this study had no concurrent medications used for fifteen days before each procedure.

Presurgical evaluations were performed on the subjects. These include blood samples taken for complete blood count, serum samples for cortisol and electrolyte evaluations.

A liberal shaving of the ventral mid-thorax region towards the pelvic brim was done with about 15cm on either side of the ventral midline and then given antiseptic bath.

3.2.3. Restraint/ anaesthesia

The dog was pre-medicated with chlorpromazine at the dose of 4mg/kg and induction was with propofol at 5.5mg/kg, the subject was intubated using size 8 endotracheal tubes, after which it was striped to the surgical table on dorsal recumbency (Plate V). Isoflurane gas anaesthetic was used for maintainace of anaesthesia.

The EEG montages were then connected as shown schematically in Plate IV and held in place by the cap (Plate III) and perioperative recording were made. Similarly, multiparameter patient monitor were connected to monitor the ECG, temperature, heart rate,partial saturation of oxygen(SPO2), and (NIBP) Non- invasive blood pressure (PlateIX).

3.2.4. Surgical procedure

A rectangular draping was achieved with four drapes and held in place by towel clamps (Plates VII and VIII). A 5-6cm cranial midline incision was made behind the xiphoid cartilage towards the umbilicus, through the linea alba to the peritoneum (Plate VII). The fat filled fulciform ligament was excised after ligating the cranial deep epigastric vessels. The stomach was exteriorised and saline soaked sterile gauze was applied around it. The stomach was held in place by two stay nylon sutures about 4 cm apart. A 1.5cm incision was made on the stomach. The stomach was then explored.

Gastric incision was closed by a double row of Cushing sutures using a size 2-0 polygalactin 910 (vicryl®). The stay sutures were removed and the stomach replaced in the abdomen after the wet gauze were removed. Abdominal incisions were closed routinely via a 2 layer closure using a size 2-0 vicryl.

3.2.5. Protocols

The study was divided into four protocols as shown in Table 3.1.

Protocol I: (Pre-operative baseline data): All dogs used in this experiment were subjected to baseline physiologic, biochemical, clinical and haematological baseline evaluation. This was done 48, 6 and 3 hours pre-operatively.

Protocol II (Single drug therapy protocol): 20 dogs were randomly assignedinto threemajor groups (Groups A to C). Groups B and C were subdivided into two subgroups of four (4) dogs each.

i. Group A (4 dogs) comprised of the control group (NAN): In this group surgery were performed without the use of any analgesic agent.

ii. Group B (NSAID group): This group were subdivided into two (B_1-B_2) with each group consisting of four dogs each

   a. Group B_1(ACE):acetaminophen (Paracetamol) was administered at a dose of 0.9mg/kg IM 12 hours pre-operative and repeated 12, 24, 48 and 72 hours post-operatively.

   b. Group B_2(KET):ketoprofenwas administered at a dose of 2.2 mg/kg IM, 12 hour pre-operative and repeated 12, 48 and 72 hours post-operatively.

iii. Group C (Opioids and Opioid derivatives). This were subdivided in two groups namely C_1–C_2 with each group composed of four per group dogs as follows;

a. Group C_1(MOR): morphine was administered at a dose rate of 0.5mg/kg IM, at 0 hour pre-operative and was repeated 6, 12, 24, 48 hours post-operatively.

b. Group C_2(TRA): tramadol will be administered at a dose of 3.0mg/kg IM, 12 hour pre-operative and was repeated at 12, 24, 48 and 72 hours post-operatively.

Protocol III (Multimodal/combination therapy): This was subdivided into two sub-groups namely D_1–$D_2$with each group composed of four per group dogs as follows;

a. Group D_1(MOKE): A combination of morphine and ketoprofen was administered at a dose of 0.5mg/kg of morphine as pre-emptive analgesic 10 minutes before the surgery and ketoprofen administered 2.0mg/kg IM 1hr after given as a combination drug.

b. Group D_2(TRAC): A combination of tramadoland paracetamol were administered where tramadol was at 2.0 mg/kg IM was used as pre-emptive analgesic and paracetamol at 0.9mg/kg IM also given 1hr after.

Protocol IV Clinical trial

The result from the best and most affordable in group B-D was evaluated and used in the veterinary Teaching Hospital, Zaria on twenty surgical cases. This was done with the consent of the client, who duly completed and signedthe consent form (Appendix I).

3.2.6. Experimental design

Table 3. 1: The experimental design for the study evaluation of analgesic in canine perioperative pain management.

PROTOCOL 1	***BASELINE DATA COLLECTION FROM ALL THE DOGS THAT WAS USED***						
	CBC	ECG	Physical exam	Cortisol	EEG		**QEEG**
GROUPS	**PROTOCOL 2** EXPERIMENTAL TREATMENT GROUPINGS						**PROTOCOL 3**
	GROUP A	**GROUP B**		**GROUP C**			**GROUP D**
4 DOGS PER GRP	NO N ANALGESIC GROUP	PARACETAMOL	KETOPROFEN	MORPHINE	TRAMADOL	MORPHINE + KETOPROFEN	TRAMADOL + ACETAMENOPHEN
CODE 1, 2, 3, 4.	NAN	ACE.	KET.	MOR.	TRA	MOKE	TRAC
PROTOCOL 4	**CLINICAL TRIALS**						
	DEVELOPMENT AND ADMINISTRATION OF CLIENT CONSENT FORMS USE OF THE DRUG COMBINATIONS WITH BEST RESULTS FROM THE EXPTAL GROUPS						

Key: CBC – Complete blood count
ECG – Electrocardiography
EEG – Electroencephalography
QEEG- Quantitative Electroencephalography



Plate III: EEg montages placed on the head of an anesthesied dogsat FP1,FP2,T3,T4,C3,C4,O1,O2 positions and connected to the monitors where readings were recorded wit the aid of an adjustable EEG skull cap (arrow).

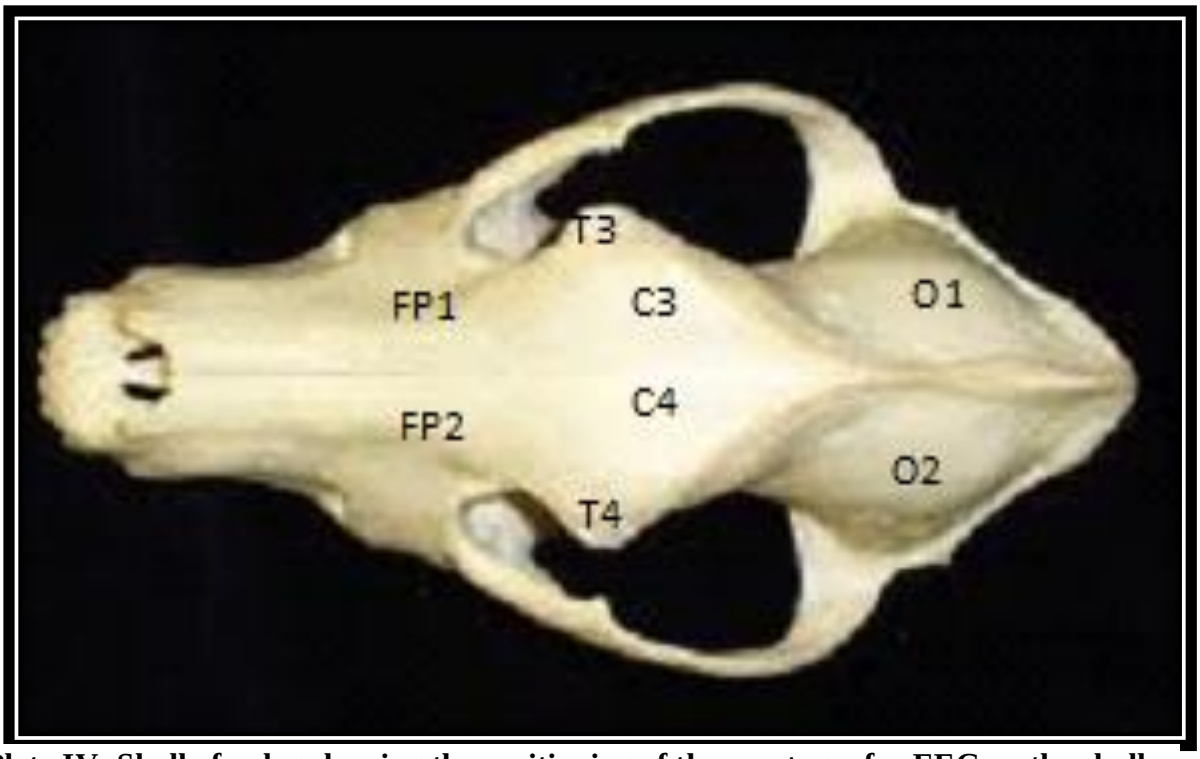


Plate IV: Skull of a dog showing the positioning of the montages for EEG on the skull of the dog



Plate V: Experimental dog on dorsal recoumbency on the surgical table. Note the positions of the five electrodes for the monitoring of the ECG (arrows). Note also the rectal temperature probe (arrow head) and the Blood presure cuff (A)



Plate VI: Gastrostomy with the dog in position. Note A= sterile gauze bandage, B= EEG connection head, C= the suction machine, D= Anaesthetic gas machine, E= sterile draped flow to the trolley with surgical instruments arranged on the surgical tray, F= kidney dish with antiseptic.

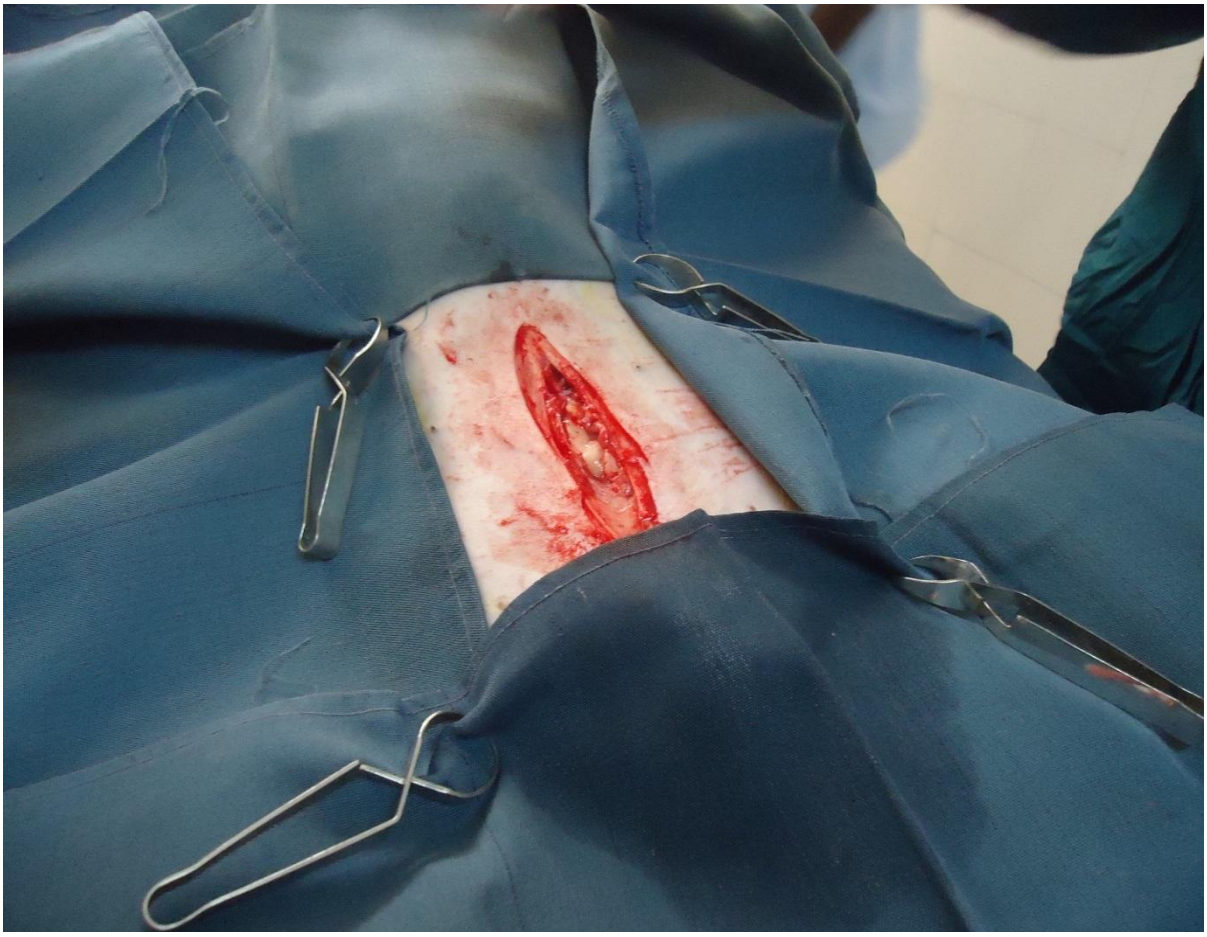


Plate VII: A 6 cm cranial midline abdominal incision made to access the abdominal cavity in one of the experimental dogs

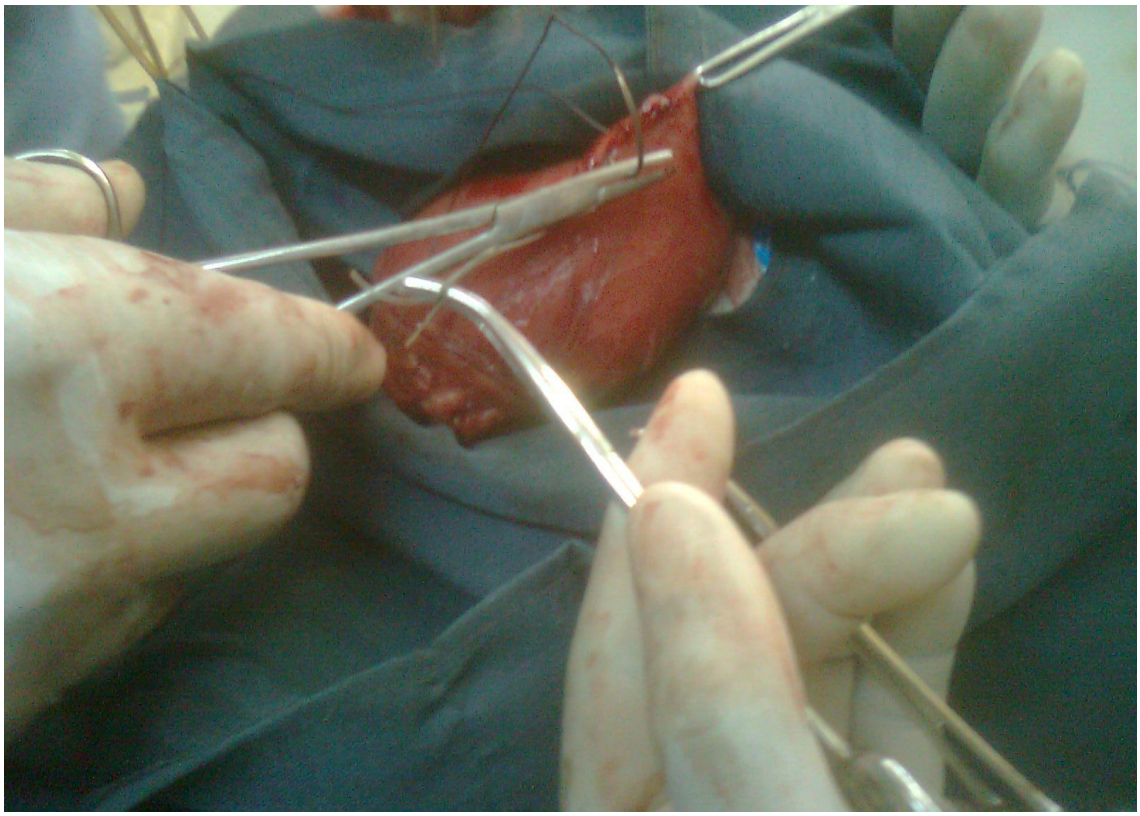


Plate VIII:Suturing the stomach at the greater curvature using Connell surture parthern and a size 2-0 polygagactin 910 suture material.

3.2.7. Post-operative evaluation of patient

Post operatively, all patients were evaluated on a daily basis for 3 days and assessment of analgesia was done based on the pain scoring chart in appendix I.

3.2.8. Pain assessment

Peri-operative assessment of pain was achieved using both objective and subjective pain assessment.

3.2.8.1. Subjective pain assessment

i. *Behavioural pain assessment*: Pre-surgical physical examination and post-surgical assessment of the dogs movements (restless, restricted movement, trembling), vocalization (groaning, whining, whimpering, barking, growling, screaming, crying, lack of vocalization), response to palpation (protecting, biting, vocalizing, withdrawing, orienting, escape), urinary and bowel habits (increased urination, failure of house training, urinary retention), body posture (hunched, laterally recumbent, prayer position), self-awareness (guarding, self-mutilating), attitude (increased aggressiveness or timidity (fearfulness), weak tail wag or low carriage of tail) and the like were used for behavioural pain assessment (Patricia *et al.*, 2001). The patients were scored using both behavioural and physiological criteria enumerated by Firth and Haldane (1999) in development of their postoperative pain scale system.

Pain scoring using the virtual analogue scale (VAS): Each of the study animals was pain scored using the pain scoring charts in appendix 1. After the administration of study medication, pre-medicated with chlorpromazine at the dose of 4mg/kg and induction was with propofol at 5.5mg/kg, the subject was intubated using size 8 endotracheal tubes, after which it was striped to the surgical table on dorsal recumbency (Plate V). Isoflurane gas anaesthetic was used for maintainace of anaesthesia. Efficacy assessments were recordedone (1) hour before surgery and continue for the next forty eight (48) hour period after completion of surgery. Experimental dogs were required to stay in the kennel within the study centre during this period. Each of the dogs completed the visual analogue scale (VAS) assessments beginning one (1) hour before the surgery and continue at 30 minutes (min) after closure of surgery. Assessment continues post operatively,2, 6, 12, 24 and 48 hours. The visual analogue scale (VAS) was measured as 0–100 millimeter(mm),where 0 mm is no pain and 100 mm is the worstimaginable pain that could be observed (Desjardins *et al.,* 2001). Parameters that were used in scoring include vocalization, posture, rest, movement, irritability, appetite, aggressiveness and other attitudinal changes such as trying to hide (Appendix 1). Each of the parameters that were measured was scored as low (1 point), Mild (2 points) and severe (3 points). The results that were obtained were subjected to statistical analysis.

ii. *Physiologic parameters assessment***:**Heart rate, pulse rate, respiratory rate, ECG,Non-invasive blood pressure, rectal temperature and the oro-nasal temperatures, partial saturation of oxygen (SPO2) wereused to assess the

physiological responses of the experimental animals to painful stimulus, particularly during anaesthesia using a veterinary multiparameter monitor (Plate IX).

Electrocardiograph (ECG): Electrocardiographic tracing were obtained by the placement of five electrodes, (one each per limb and the fifth electrode was place on the right aspect of the thoracic cavity at about the same level as the heart) of the experimental dog. The electrodes were placed on shaved, cleansed and dried areas as described and connected through a clipped ECG cable to the multiparameter monitor (Plate IX The tracing obtained were noted for any changes to the P-QRS-T. and they were adequately interpreted (plate IX).

Non-invasive blood pressure: The Non-invasive blood pressure (NIBP) were monitored for the experimental dogs on the left fore limb around the radius and ulna bones. The hair around the area was clipped and A pressure cuff (Tycos pre-calibrated infant cuff: Parks Electronics Laboratory, Beaverton, Oregon) of adequate width, approximately 40% the circumference of the leg, was placed just below the elbow. Non-invasive blood pressure was measured at intervals 10 minutes. The systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP) and the Mean arterial blood pressure (MAP) were obtained from the Veterinary multiparameter monitor (Rysnik, *et al.*, 2013). Data collected were then transferred into an Excel-spread sheet for analysis.

Partial saturation of oxygen (SPO2): The SPO2 probe (General Meditech® Inc.) from the multiparameter monitor was attached to the tongue of the anaesthetized

dogs to monitor the partial saturation of oxygen (plate IX).The SPO2 was monitored every 10 minute interval as described by Nancy, (1992).

3.2.9. Objective assessment

i. *Electroencephalography (EEG):*Perioperative surgical pain causes a significant change in EEG variables recorded under experimental conditions and this can be used to objectively assess pain. To achieve a more accurate quantitative assessment of the physiologic parameter, an 8 channels (plate IV) EEG was employed. The montages were attached to the head of the dogs as shown in Plate III. The electrodes used were 12 × 4mm. The electrodes were placed over a skull cap placed on the head of the dog. They are placed at positions left and right frontal parietal (FP1 and FP2) thalamus (T3 and T4), centre positions (C3 and C4), and the medulla oblongata (O1 and O2) positions of the skull (plates III and IV).An awake, baseline continuous EEG recording was performed for approximately ten minutes. The same recording technique was repeated after administration ofthe entire different test drug done on the subjects. The data was collected and stored on a computer program. Each tracing was evaluated, the focal were observed for spikes and spindles per tracing average also power spectrum graphs, beam waves, beam spectrum graphs and compressed spectrum graph were collected.The data collated were subjected to quantitative electroencephalography.

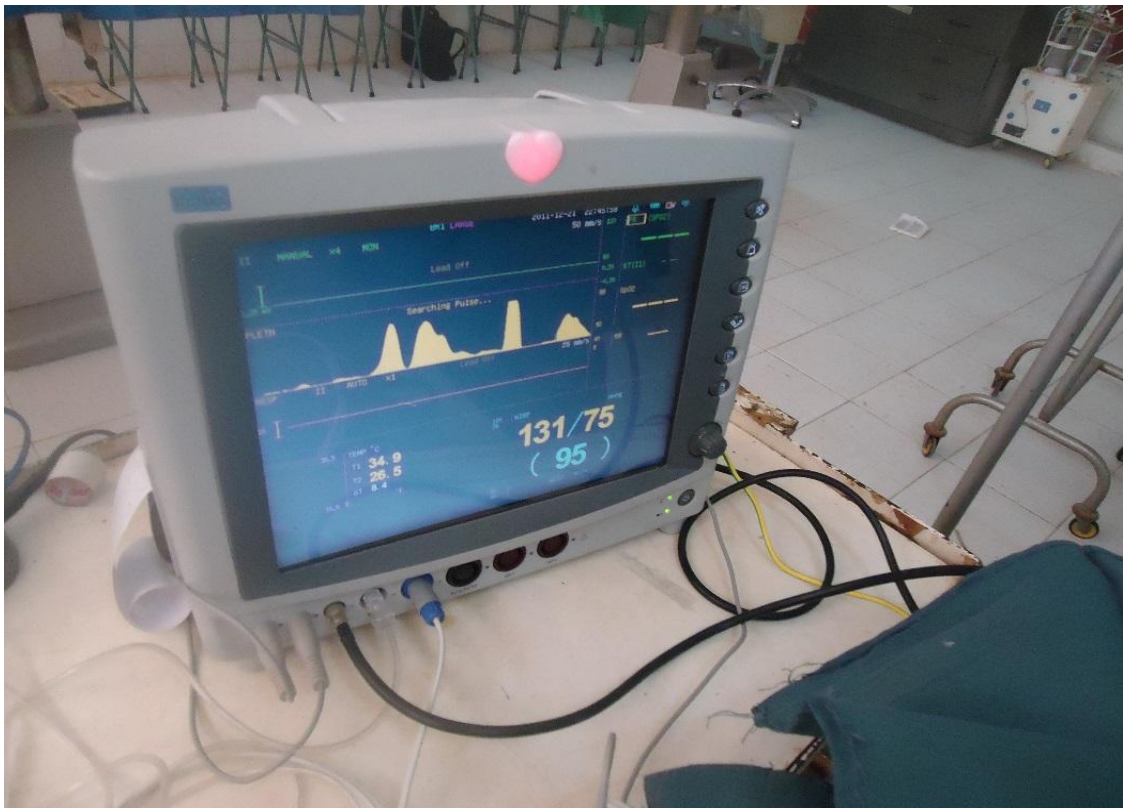


Plate IX: Veterinary multi-parameter monitor (General Meditech Inc.) for monitoring the physiologic parameters

ii. *Biochemical analysis*: This comprised of the serum cortisol analysis. This was used to measure objective pain pre, and post-surgically. Collection of blood was via venepuncture (through the attachment of indwelling venous catheter) for 5ml which was then centrifuged and the serum separated and stored at -20^{o}C (Plate X). Cortisol was measured via the use of cortisol ELISA rapid test kit (Plate X). Cortisol concentration was estimated 24 hours before surgery, and then 6 hours after the surgery for each of the animals (Feldsein*et al*., 2010).

The serum samplesthat were collected were stored at -20^{o}C and they were not allowed to stay beyond thirty (30) days. The samples were tested for cortisol (Plate X). The micro plate wells for each of the serum samples, control, standard and experimental samples were assayed in duplicates. 0.025ml of the appropriate serum reference, control or specimenwas assigned into the micro wells. Then 0.05mls of the working cortisol enzyme reagent were added into the wells this was later followed by swirling of the microplates and then 0.05ml of cortisol biotin was added to the wells, swirled for about 20-30 seconds and then covered and incubated at room temperature for 60 minutes. The content of the microplates was discarded at the end of the incubation period. 350µl of wash buffer was added and later decanted (this was done for 2-3 times) after which 0.1ml of the working substrate solution

was added to the respective wells and incubated for another 15 minutes. Stop solution was finally added, gently mix for 15 -20 seconds (Plate X) and the microwells absorbance was read in a microplate reader (Plate XII).

iii. *Serum Urea and Electrolyte Analysis:*Serumelectrolytes, urea and blood gasses were monitored pre, and post-surgically in all the animals that were tested. The measurement of urea, sodium (Na), potassium (K), chloride (Cl^-), ionised calcium (Ca^{2+}), serum pH and serum anion gap (AG) were done using the indirect ion selective electrode with the Medical clinical auto analyser (AC 9900) Audicom® series electrolyte analyser (Plate XI). Serum collected is stored at 0°C until use. The serum samples are then transferred into the Audicom® sample bottle and placed in its rotator where the electrodes test the samples (D'Orazio, *et al* 2000). The analyser has programs that control its use in testing and calibrations and also the analyser is equipped with intelligent monitoring sensors, which can accurately detect the sample, air bubble and waste reagents. All electrodes used for AC9000 series electrolyte analyser are mounted in aluminium alloy electrode shield case. The result was automatically generated and printed from the Audicom®. The results generated for sodium, potassium, calcium, pH, anion gap was analysed and were subjected to ANOVA. The result from urea was subjected to paired sample student T test. (appendix VII, VIII, IX,X, XI, XII and XIII)

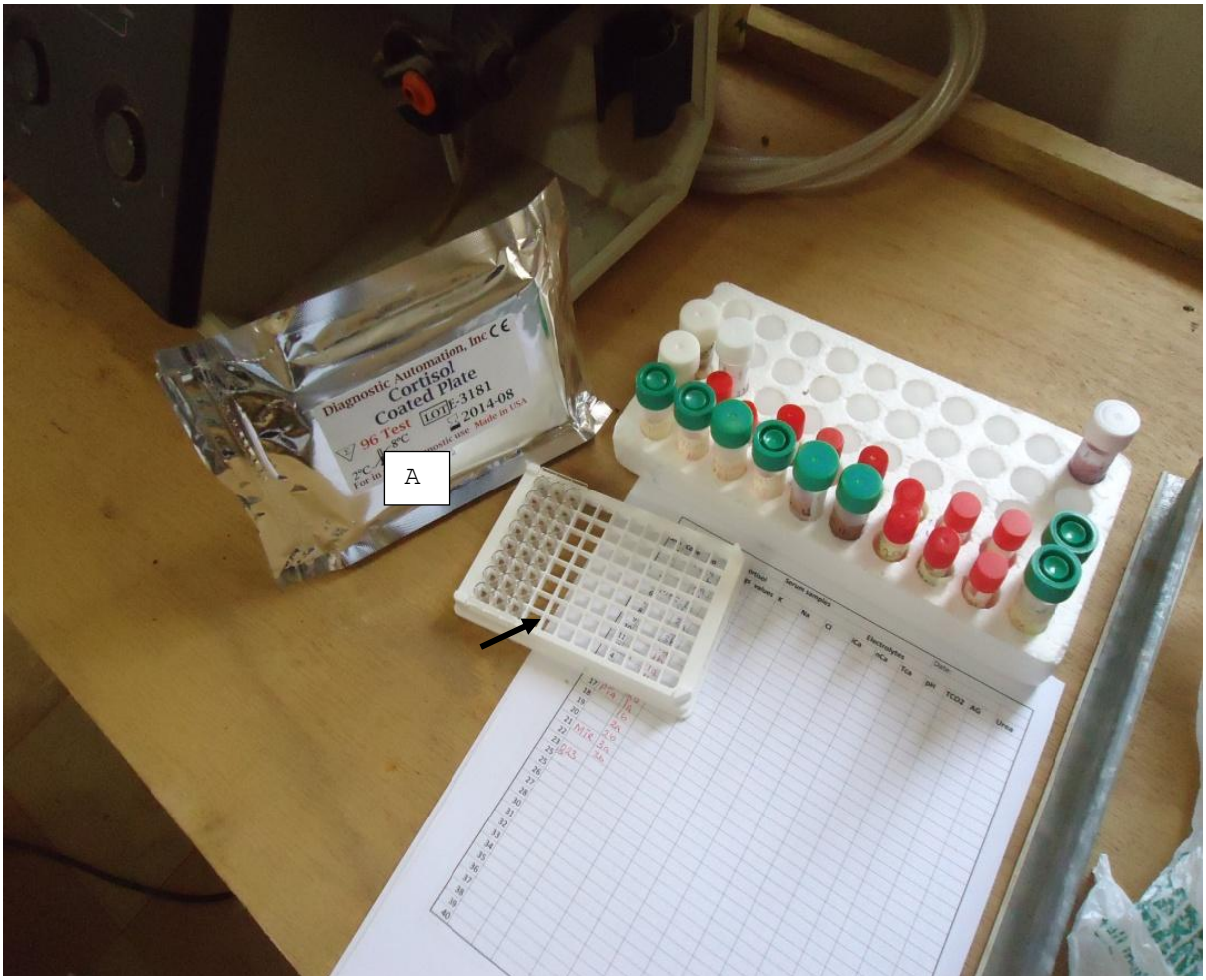


Plate X: Cortisol kit and some serum samples about to be analysed in the chemical pathology laboratory of ABUTH Shika, Zaria Nigeria. Note Microhematocrit rack (arrow). Serums with red caps are those collected pre surgically

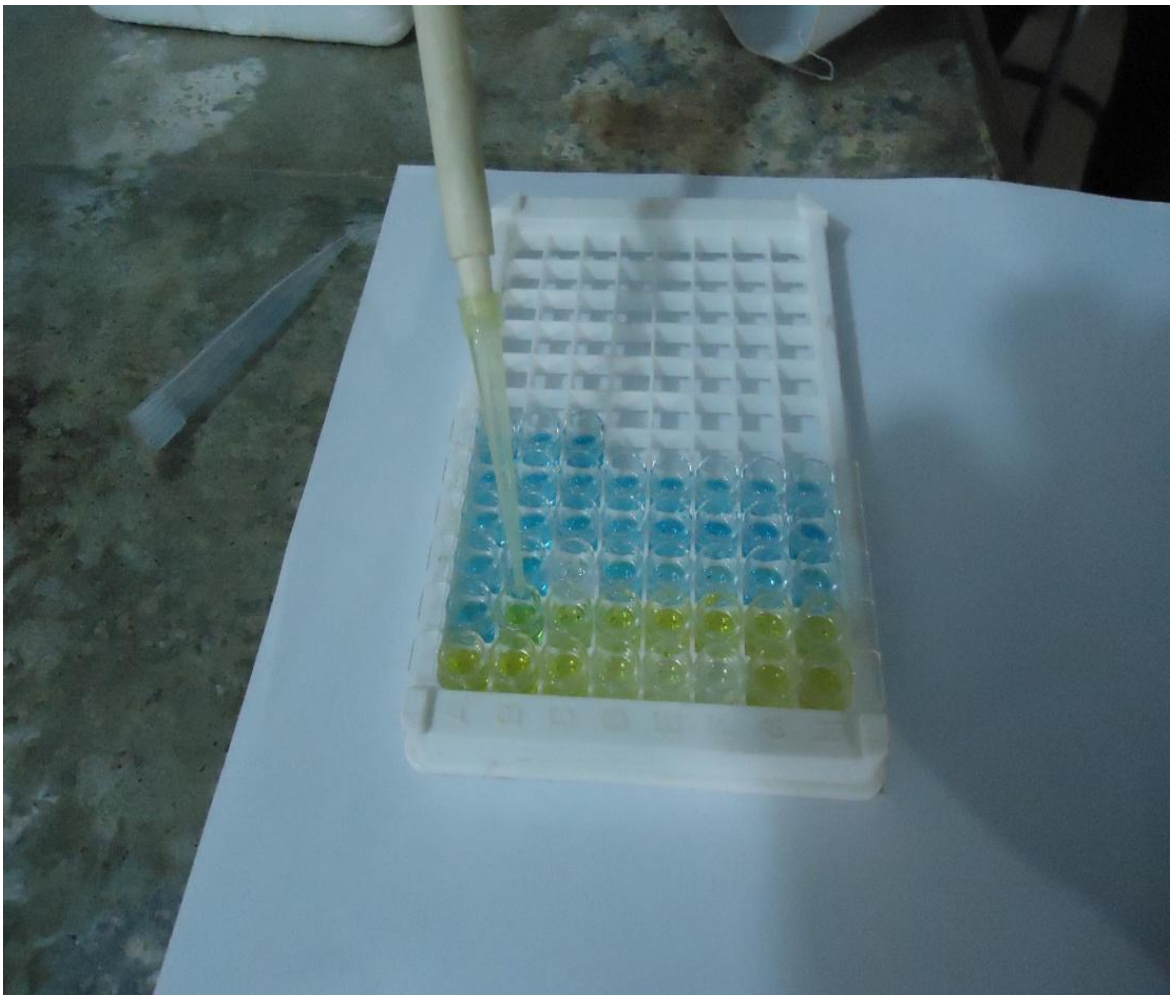


Plate XI:Serum analysis where stop solution was added to cause a change in colour from blue to yellow.



Plate XII: Reading of the microplate on the microplate absorbance reader. A= microwells, B=Printer, C= the microhematocrit well, D= recording sheet

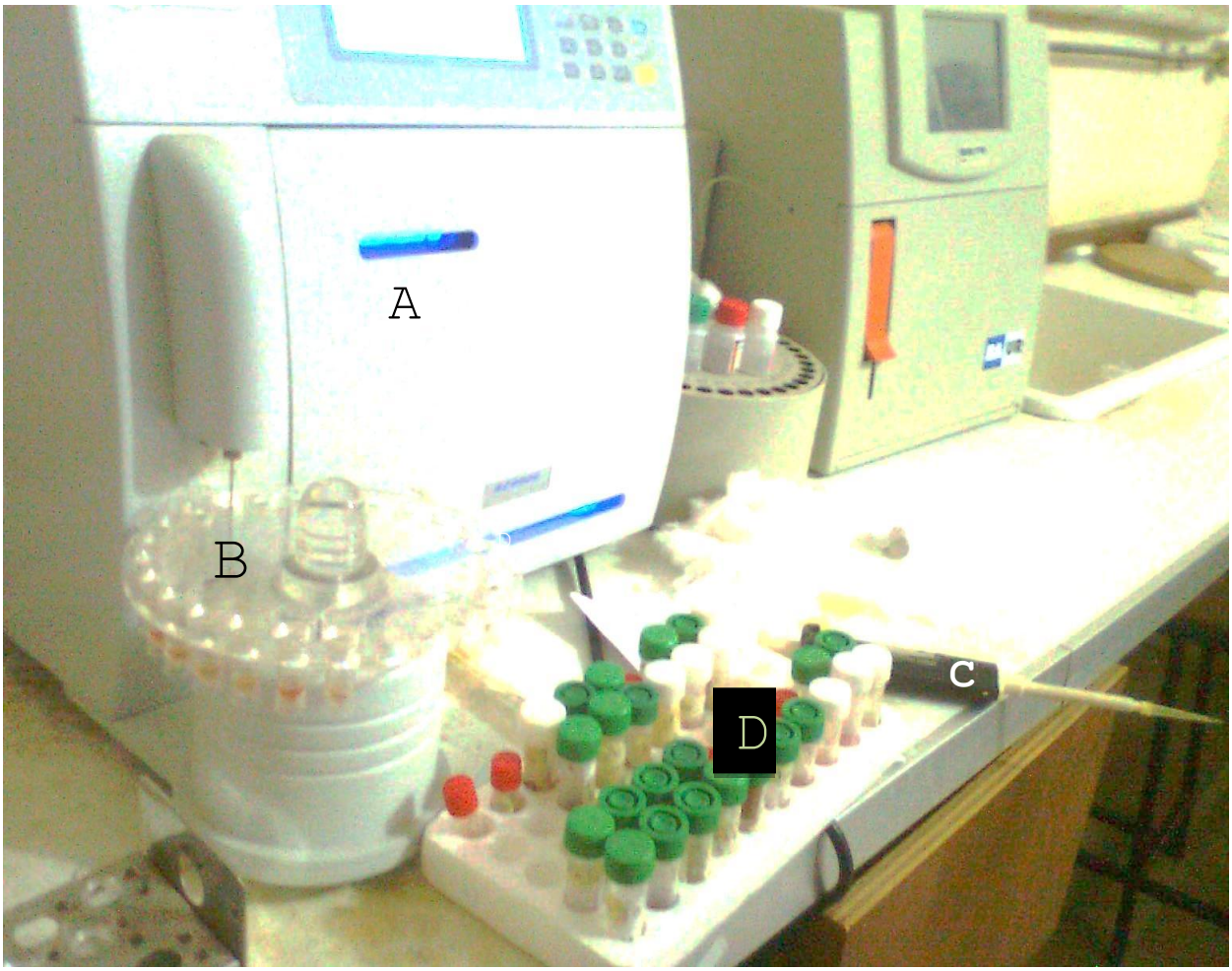


Plate XIII: Audicom® autoanalyser (A) used to analyse serum urea and electrolytes. where B= automatic serum feeder for the autoanalyser, C= micropipette with nozzle, D= serum samples

CHAPTER FOUR

RESULTS

4.1. Efficacy Evaluation

The treatment groups were statistically comparable with respect to baseline demographics. The presurgical evaluation of the complete blood count indicated normal blood picture range without any significant changes (P> 0.5) in the blood picture (Table 4.1), with the RBC count been 5.8±1.23 x106/µl which is within the normal range. The total leucocyte count (WBC) also collected was also within normal values as observed 16.2±3.15 x109/L. The variation within the neutrophil, lymphocytes, basophils and the eosinophil observed did not have any significant variation in values.

The mean age, body weight, duration of surgery, selected surgical variables and subjective pain score are shown (Table 4.2). The mean age for the experimental dogs used was 2.7 ± 2.14-years while the mean body weight for all the dogs used for the experiment was 13.64 ±7.4 kg. The mean surgery time throughout the experimental period was 30.71 minutes. Whereas the mean end tidal isoflurane observed in the experiment was 1.49%, the value for NAN was significantly higher than that which was consumed in the groups treated with analgesics. However, the values obtained were within the normal rage.

The operative procedures were performed on dogs at the Small Animal Surgery Theatre without any surgical complications such as peritonitis, haemorrhagic complications or even

death in all the cases and the animals handled carefully. Throughout the experiment none of the dogs showed any significant side effects as a result of the administration of the analgesic (eg vomiting, nausea).

4.2. Pain Scoring Using the Virtual Analogue Pain Scoring

There was a statistical significant increase between the values of the pain score that was observed with the subject that was not treated with analgesic (NAN).The increase in the pain intensity was noticed 30 minutes after the surgery as soon as the effect of anaesthesia was weaning from the experimental dogs (6.31± 1.23).This effect continued all throughout the period while the subjects were under observation (Fig 4.1, Table 4.3). The pain intensity score also showed a gradual increase and then at its peak at 6 hours for ACE (4.25 ± 0.91), TRA (3.50 ± 0.91), and MOR (2.97 ±1.91), while for KET it reached its peak at around the 12^{th} hour (3.19 ± 0.91).

There was also a significant difference in the pain intensity between the single drug administration and the multi- drug administrations (Table 4.3). TRA and ACE peaked at the 6^{th} hour there was no significant increase in the pain intensity for TRAC (2.22 ± 0.55) rather, the intensity was declining.This could be attributed to the synergistic effect of the two drugs on the patient. A similar result was also observed where the peak pain intensity for KET (3.19 ± 0.91)was 12 hour and 6 hours for MOR (2.97 ± 1.91) and the combination of these two drugs showed a non-significant increase in the pant threshold throughout the period of study.

Table 4.1: The complete blood count (CBC) obtained pre-surgical evaluation for the experimental dogs

Parameters (values)	Values obtained	Normal Values
Packed Cell Volume (%)	42±3.23	40-59
Hemoglobin (g/dl)	14±2.5	14-20
Red Blood Cell Count (x10^6/µl)	5.8±1.23	5.6-8.7
White Blood Cell Count (/µl)	16,200±3.15	6,000-17,000
Neutrophils (/µl)	10,780±2.22	3,000-12,000
Lymphocytes (/µl)	3,220±1.56	530-4,800
Monocytes (/µl)	1700±0.50	100-1800
Eosinophils(/µl)	400±0.50	0-1,900
Basophils (/µl)	100±0.50	Rare
Platelets (/µl)	100±0.50	145-440

Complete blood count (CBC) were analysed as Mean ± SEM; Confidence interval (CI) = 95%; df =1; $P \leq 0.05$

Table 4.2: Mean (± SD) values of general characteristics and selected surgical variables in the experimental and clinical trial dogs

	NAN n=4	ACE n=4	KET n=4	TRA n=4	MOR n=4	TRAC n= 14	MOKE n=14	Mean
Age (year)	1.93±1.44	2.9± 2.5	3.45± 2.2	2.3±1.44	2.9± 2.5	2.45± 2.2	3.00± 2.7	2.70
Body weight (kg)	14.22± 7.95	15.35± 9.00	12.40± 6.50	13.20± 7.65	14.40± 5.25	12.50± 8.20	13.42± 7.00	13.64
Surgery time (min)	41±7.93	40±9.39	19±9.93	25±6.70	32±7.93	30±7.93	28±7.93	30.71
Time from drug administration to surgery	20	20	20	20	20	20	20	20.00
Mean rectal temperature (° C)	38.3± 1.03	37.77 ± 1.00	38.03± 0.70	37.27± 0.69	37.68± 0.53	38.14 ± 0.29	38.35 ± 0.16	37.93
Mean heart rate (per min)	155± 19.78	114 ± 21.16	101 ± 12.99	112 ± 17.71	119 ± 26.44	102 ± 7.70	87 ± 9.21	112.86
Mean respiratory rate (per min)	56 ± 6.14	28 ± 2.69	25 ± 2.40	36 ± 4.64	27 ± 7.92	20 ± 1.96	30 ± 2.37	31.71
End tidal isoflurane (%)	1.57± 0.11	1.48± 0.12	1.48± 0.20	1.49± 0.11	1.48± 0.10	1.47± 0.12	1.47± 0.10	1.49
Oxyheamoglobin saturation (%)	96.06	92.1	95.04	94.71	93.3	93.84	92.88	93.99

Table 4.3: MeanPain intensity scores over time of the dogs treatment groups(Visual Analogue Scale) following gastrotomy.

Dogs Treatment Groups	TIME (HOURS)						
	-1.0	**0.5**	**2**	**6**	**12**	**24**	**48**
NO ANALGESIC (NAN)	3.00± 0.98	6.31± 1.23 [a]	6.89 ±0.91 [a]	7.27 ±0.91 [a]	7.02 ±1.25	7.05± 1.29	7.05± 0.81
PARACETAMOL (ACE)	2.72 ±0.65	2.41± 0.49	3.38± 0.37[a]	4.25 ±0.91	4.00 ±0.91	2.28 ± 0.32	2.25 ± 0.33
KETOPROFEN (KET)	2.22 ± 0.73	2.19± 0.50	2.35± 0.37	2.69 ±0.91	3.19 ±0.91	2.66 ± 0.29	2.25 ± 0.33
TRAMADOL (TRA)	2.66 ± 0.72	2.41 ±0.50	2.55 ± 0.37	3.50 ±0.91	2.80 ±0.91	2.22 ± 0.29	2.25± 0.33[b]
PETHIDINE	2.63 ± 0.66	2.19 ±0.48	2.37 ± 0.23	2.47 ±0.91	2.35 ±0.91	2.16 ±0.30[b]	2.06 ± 0.21
MORPHINE	2.41 ± 0.78	2.63 ±0.48	2.44 ± 0.37	2.97 ±1.91	2.49 ±1.95	2.22 ± 0.29	2.19 ± 0.27
MORPHINE + KETOPROFEN (MOKE)	2.63 ± 0.78	2.50 ±0.52	2.29 ± 0.36	2.29 ±0.56	2.10 ±0.85	1.91 ± 0.48	1.88 ± 0.35
TRAMADOL + PARACETAMOL (TRAC)	2.84 ± 0.78	2.50 ±0.52	2.22 ± 0.36	2.22 ±0.55	2.00 ±0.50	1.91± 0.48	1.94± 0.35

Objective behavioural scores are reported as Mean ± SD. Numerical pain scores are reported as mean SD.See appendix I for criteria for assignment of objective behavioural scores. Numerical scores were assigned by a single observer. [a]Significantly (P < 0.05) different from value obtained immediately after surgery. [b]Significantly (P < 0.05) different from valueobtained after administration of salinesolution.

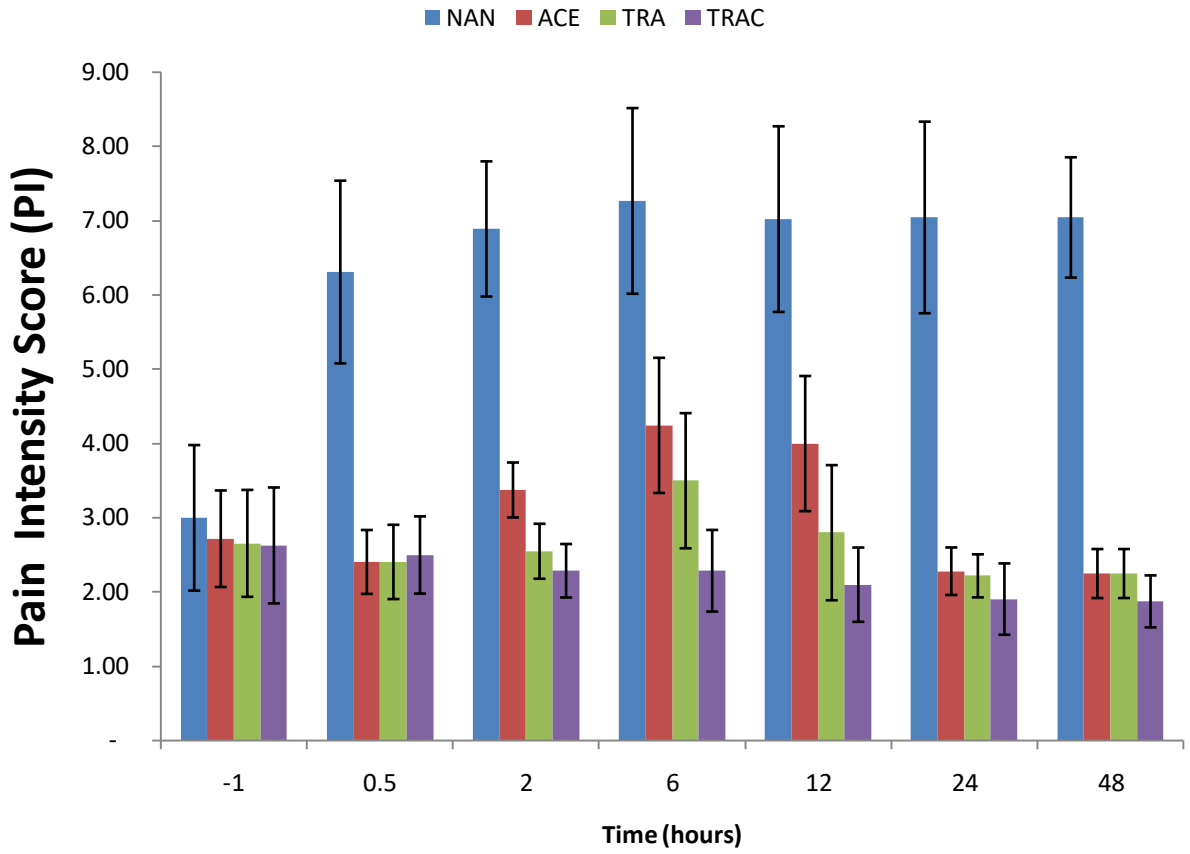


Fig. 4.1: Visual pain scores between the control (NAN), paracetamol (ACE), tramadol (TRA) and a multimodal therapy of tramadol and paracetamol (TRAC) groups.

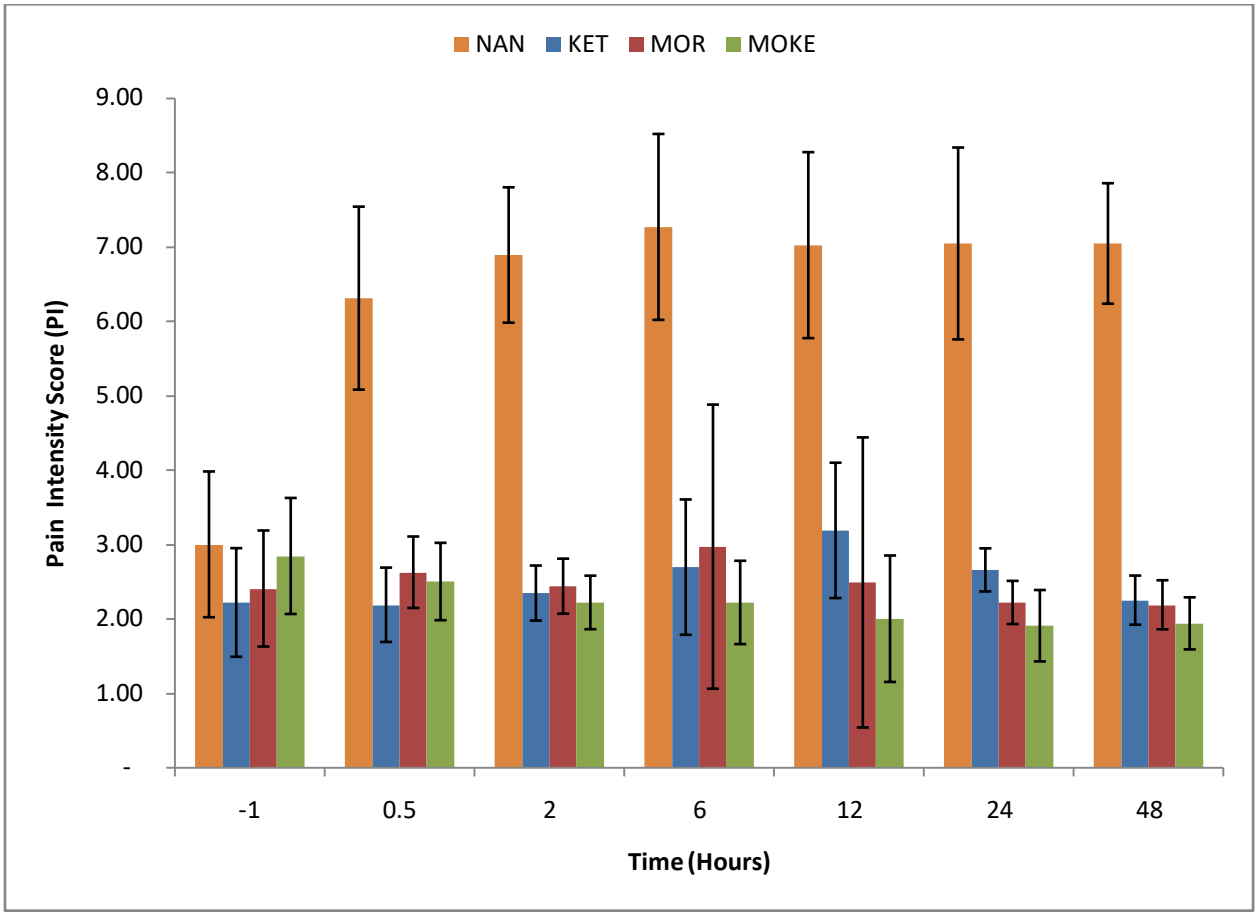


Fig. 4.2: Visual pain score betweenNon treatment (NAN), single treatment with morphine (MOR), ketoprofen (KET), and a combination therapy of morphine and ketoprofen (MOKE)



Plate XIV: Dog in the NAN group exhibiting signs of back aching 24 hours post gastrotomy

4.3. Physiologic Parameters

There was no significant adverse drug reactions(such as dizziness, nausea, depression and vomiting) due to the drug administered noticed in all the groups tested.

4.3.1. Rectal temperature

The single drug therapy of paracetamol, tramadol and morphine lowered considerably the rectal temperature (RT) of the anesthetized dogs (Fig 4.3 and Fig 4.4), with ACE at lowest value at 1 hour into the surgery (36.9 ± 0.40), TRA at 36.13 ± 0.56 after 2 hours, KET at 37.6 ± 1.11 in one hour and MOR 37.47 ± 0.78 at the 40 minute into the surgery (Fig 4.3 and Fig 4.4).The lowered rectal temperature was not observed in the multimodal therapy of TRAC rather, it was observed that the combination produced a more stable rectal temperature values. Similarly, MOKE multimodal therapy (Fig 4.4) produced a stable rectal temperature. There is significant difference in the rectal temperature value observed in the single drug therapies and the multimodal therapy groups. However KET produced a more stable RT than the ACE so is TRA more stable than MOR.

4.3.2. Heart rate

The mean heart rate (HR) observed (NAN 155.18 ±19.78,ACE 113.88 ± 21.16, TRA 111.94 ± 17.71, MOR 113.67 ± 26.03, TRAC 88.55 ± 7.70 and MOKE 102.45 ± 9.21) showed that dogs treated with analgesic either singly or in combination had heart rate within the normal range, while there was significant difference between the non-treated group (NAN) and the treated groups.Dogs treated with MOR showed increase in heart rate spikes at 30minutes into the surgery (171.00 ± 11.02), one hour (170.67 ± 4.2) and at four hours (112.33 ± 23.35) post surgically. Dogs treated also with TRA had a sharp

increase in the HR at 40mins into the surgery (161 ± 4.47) and then a gentle drop to within the normal range. A similar result was also seen in ACE however, MOKE had a stable HR throughout the experimental period (Fig 4.5).

4.3.3. Respiratory rate

The mean respiratory rates (RR)± SD were NAN (55.86 ± 6.14), ACE (28.22 ± 2.69), KET (24.71 ± 2.40), TRA (36.41 ± 4.64), MOR (28.65 ± 7.92), TRAC (25.78 ± 1.96), MOKE (19.84 ± 2.37). in this result, there was a statistically significant increase in the respiratory rate of NAN when compared to the other test groups (Appendix VI). However, MOKE and TRAC had a more stable respiratory rate when compared to the single treatment groups of MOR, TRA, ACE and KET (Fig 4.7 and 4.8). Although there was no statistically significant deference in the respiratory rate between KET, TRA and MOKE, there was clinically significant difference in RR in which apart from MOKE the next drug that gave a slightly stable though higher RR was KET (Fig 4.8).

4.3.4. Saturated peripheral oxygen (SPO2)

The values of the saturatedperipheral oxygen (SPO2) in the anesthetized animals were between 86-100 % for all the tested groups throughout the period of this study. The variations in the values of these groups were no significant (Fig 4.9).

4.3.5. Blood pressure

The treatment group that was administered MOR(29.67 ± 2.31) intramuscularly exhibited a significant drop in the mean arterial blood pressure (MAP) 30 minutes into the surgery (Fig 4.11).Similar drop in MAP values was also observed in TRA (50.00 ± 8.66) 20 minutes into the surgery (Fig 4.10). The drop in MAP seen in ketoprofen was

transient. It is noteworthy however to observe that there was a statistical significant drop in MAP of p< 0001 in the negative control, tramadol and morphine groups. The change that was observed in the non-treatment group (Fig 4.10) was an increase in MAP that only began to stabilize 60 minutes after the animal was anaesthetized. The TRACmultimodal treatment exhibited a very impressively stable MAP throughout the experimental period. MOKE showed that the ketoprofen addition neutralized the effect of morphine whereby there was just a slight drop in MAP.

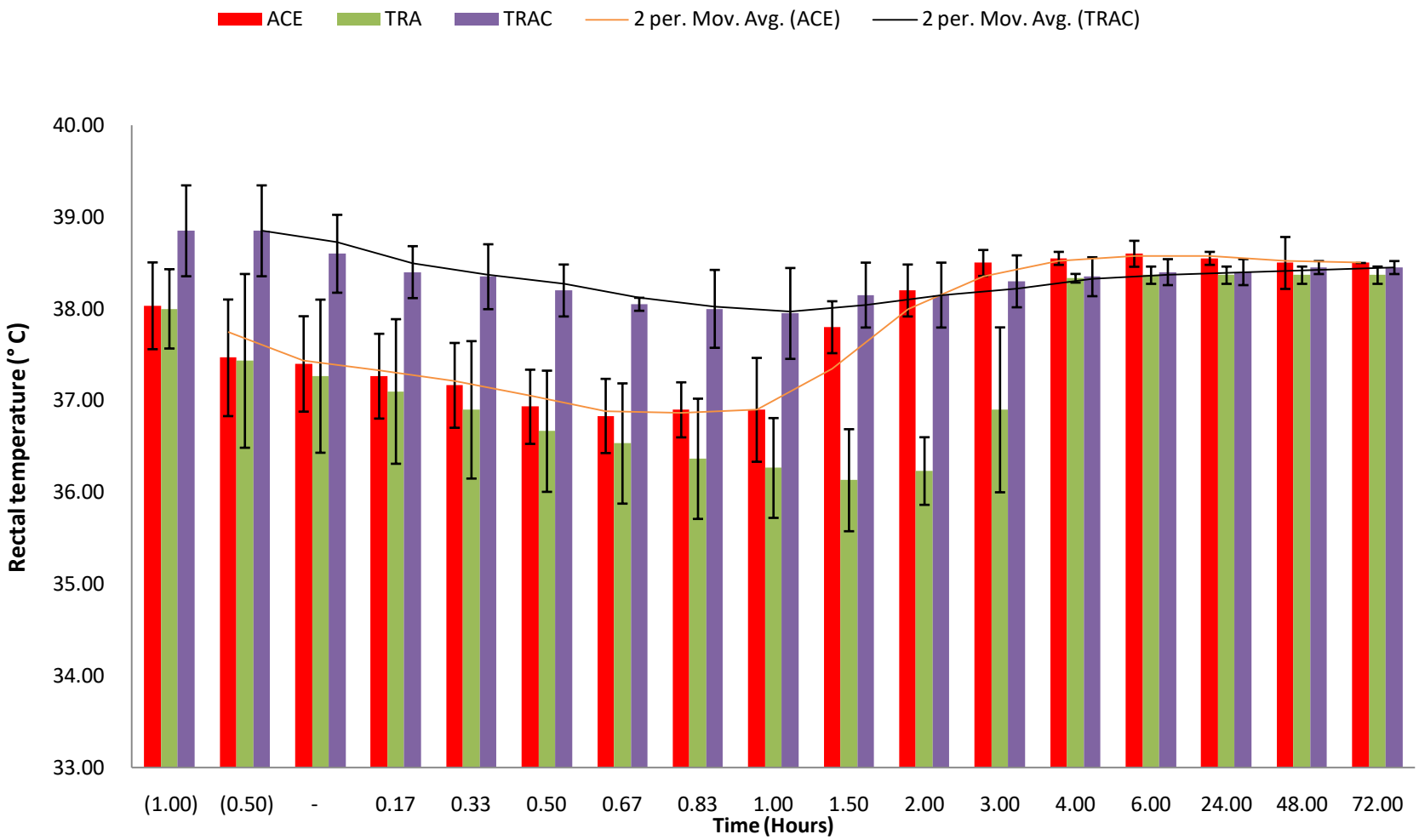


Fig. 4.3: Perioperative rectal temperature (RT) between single treatment groups paracetamol (ACE), tramadol (TRA) and multimodal therapy using tramadoland paracetamol (TRAC) in pain management

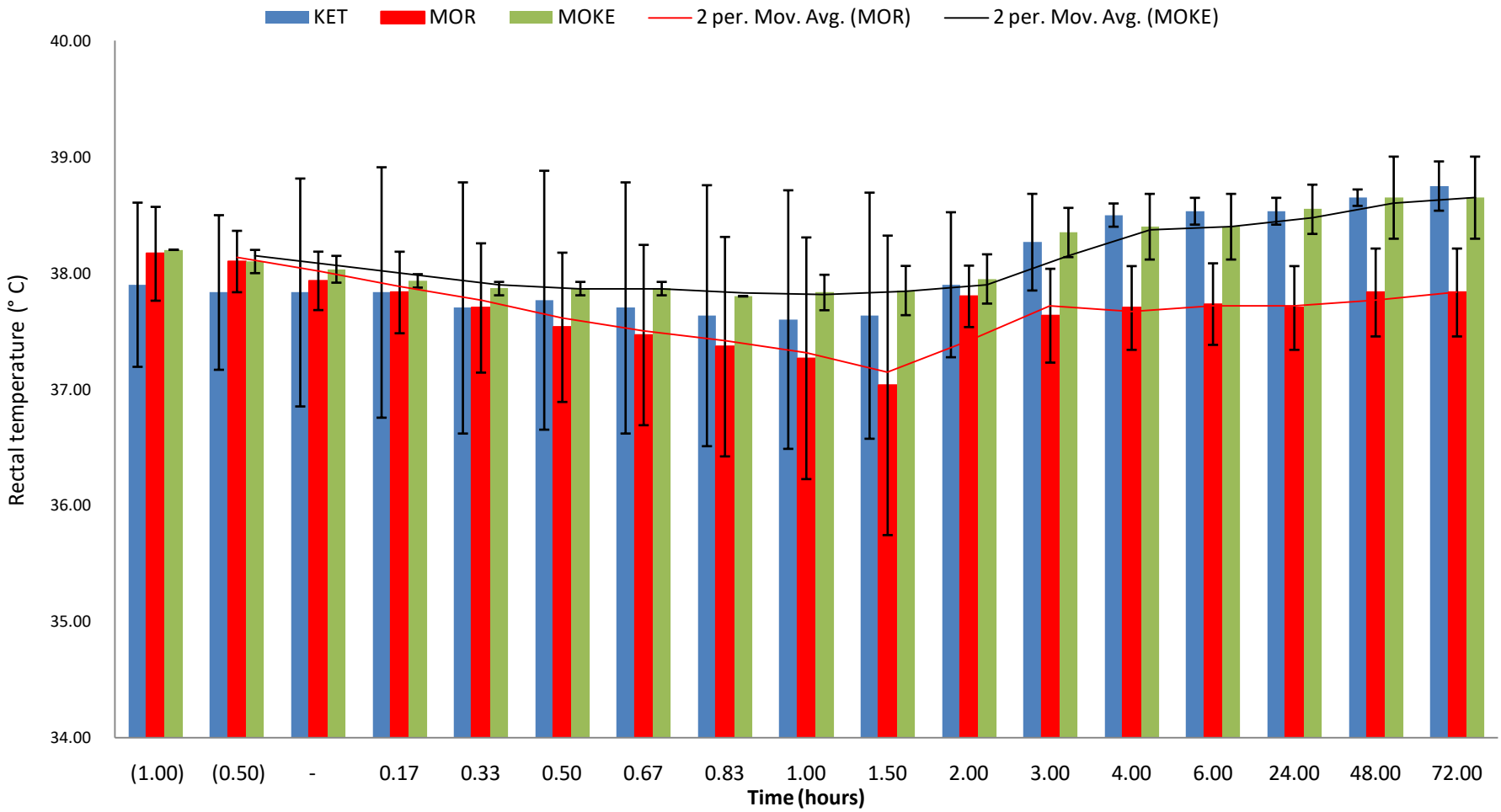


Fig. 4.4:Perioperative rectal temperature between single treatment groups using ketoprofen (KET) morphine (MOR) and the multimodal therapy of morphine and ketoprofen (MOKE) treatment in pain management in dogs.

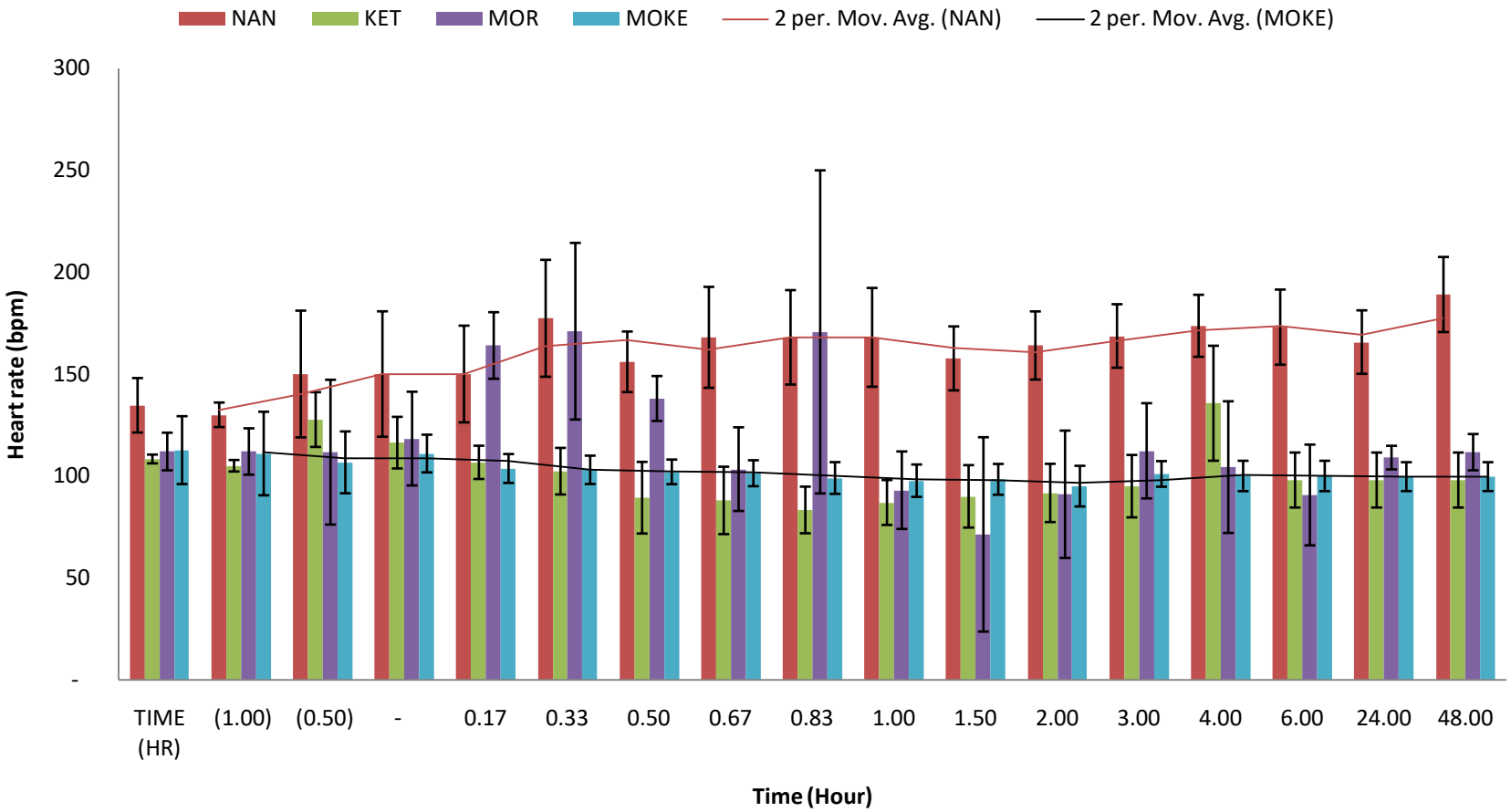


Fig. 4.5: Perioperative heart rate of thesingle drug treatment with ketoprofen (KET), morphine (MOR) and a combination of morphine and ketoprofen (MOKE) in managing perioperative pain.

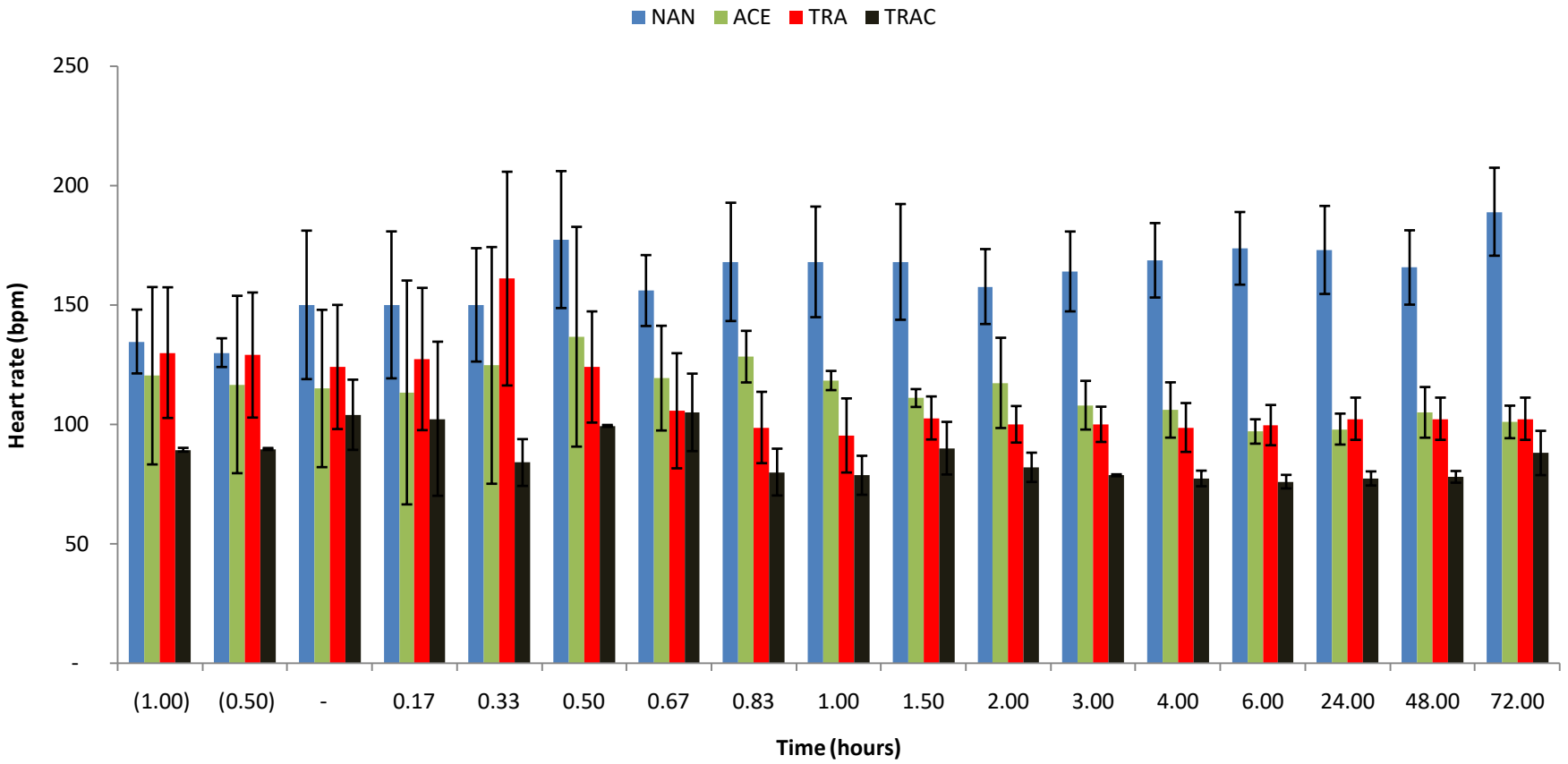


Fig 4.6. Perioperative heart rate between single drug treatment with paracetamol (ACE), tramadol (TRA) and multimodal therapy of tramadol and paracetamol (TRAC) on perioperative pain management in dogs

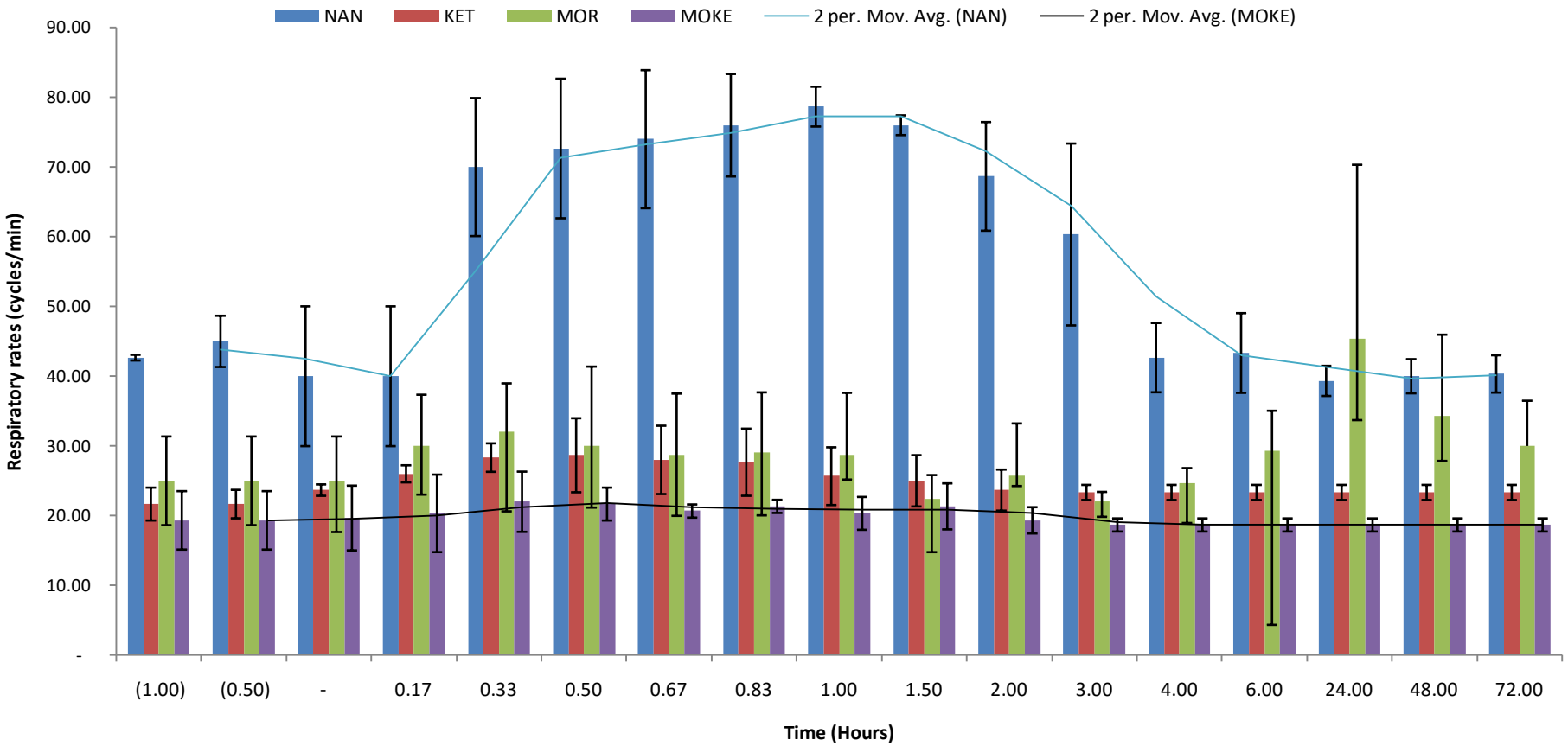


Fig. 4.7: Perioperative respiratory rate following single drug treatment with ketoprofen (KET) morphine (MOR) and a multimodal therapy of morphine and ketoprofen (MOKE) on pain management in dogs.

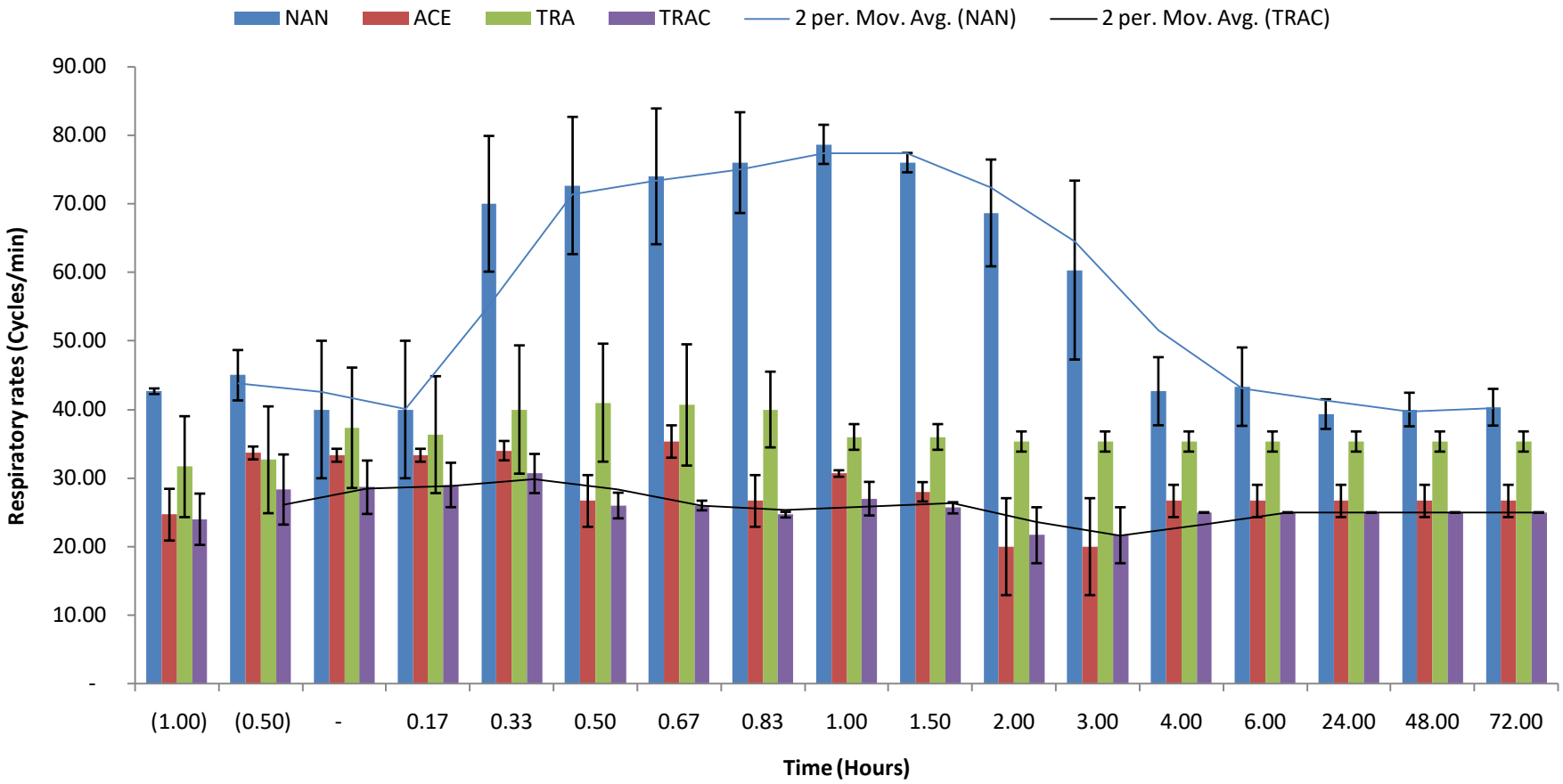


Fig. 4.8: Perioperativerespistory rate following a single drug treatment with paracetamol (ACE), tramadol (TRA) and a multimodal therapy of tramadol and paracetamol (TRAC) on pain management in dogs.

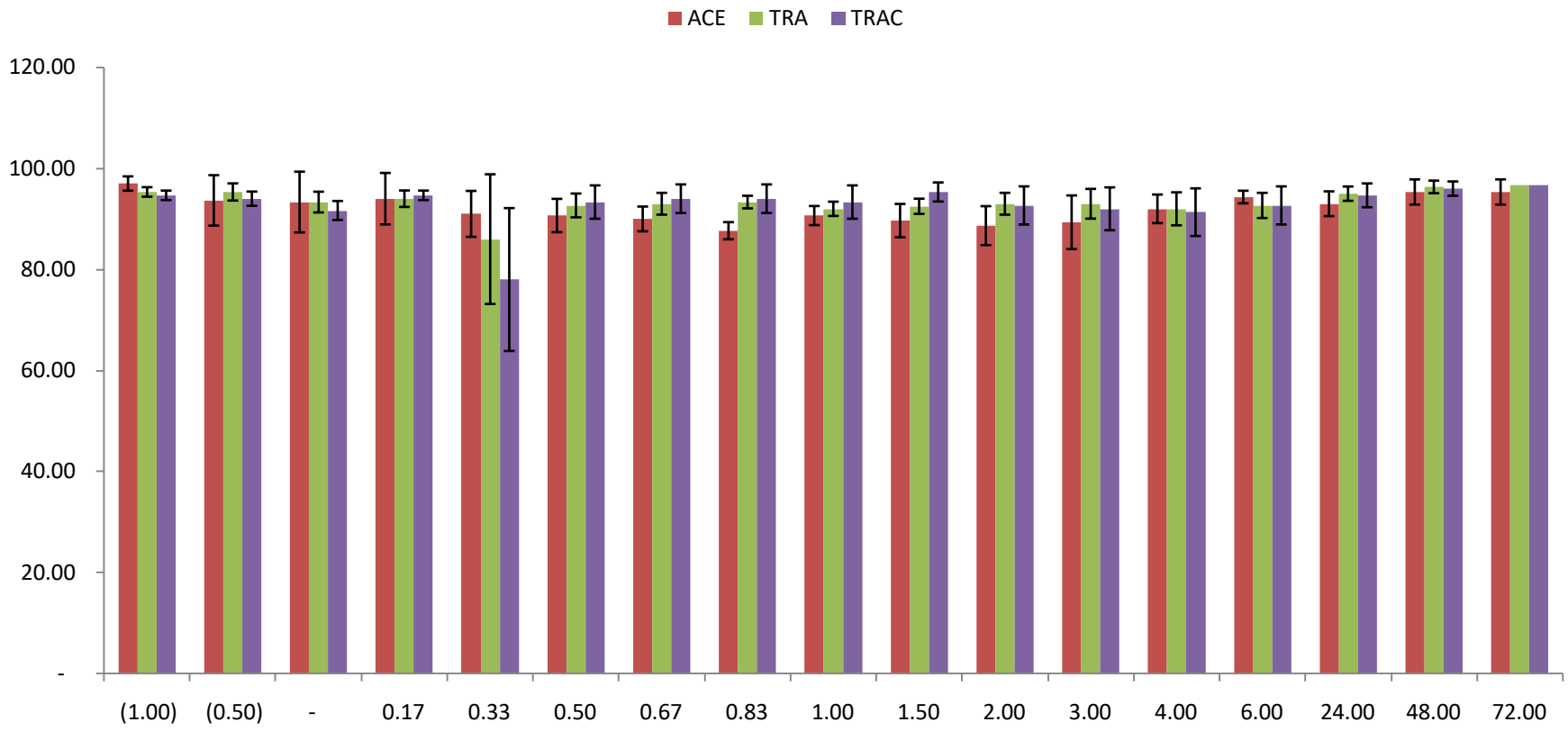


Fig.4. 9: Perioperativeperipheral saturation of oxygen (SPO2) following a single drug treatment with paracetamol (ACE), tramadol (TRA) and a multimodal therapy of tramadol and paracetamol (TRAC) on pain management in dogs.

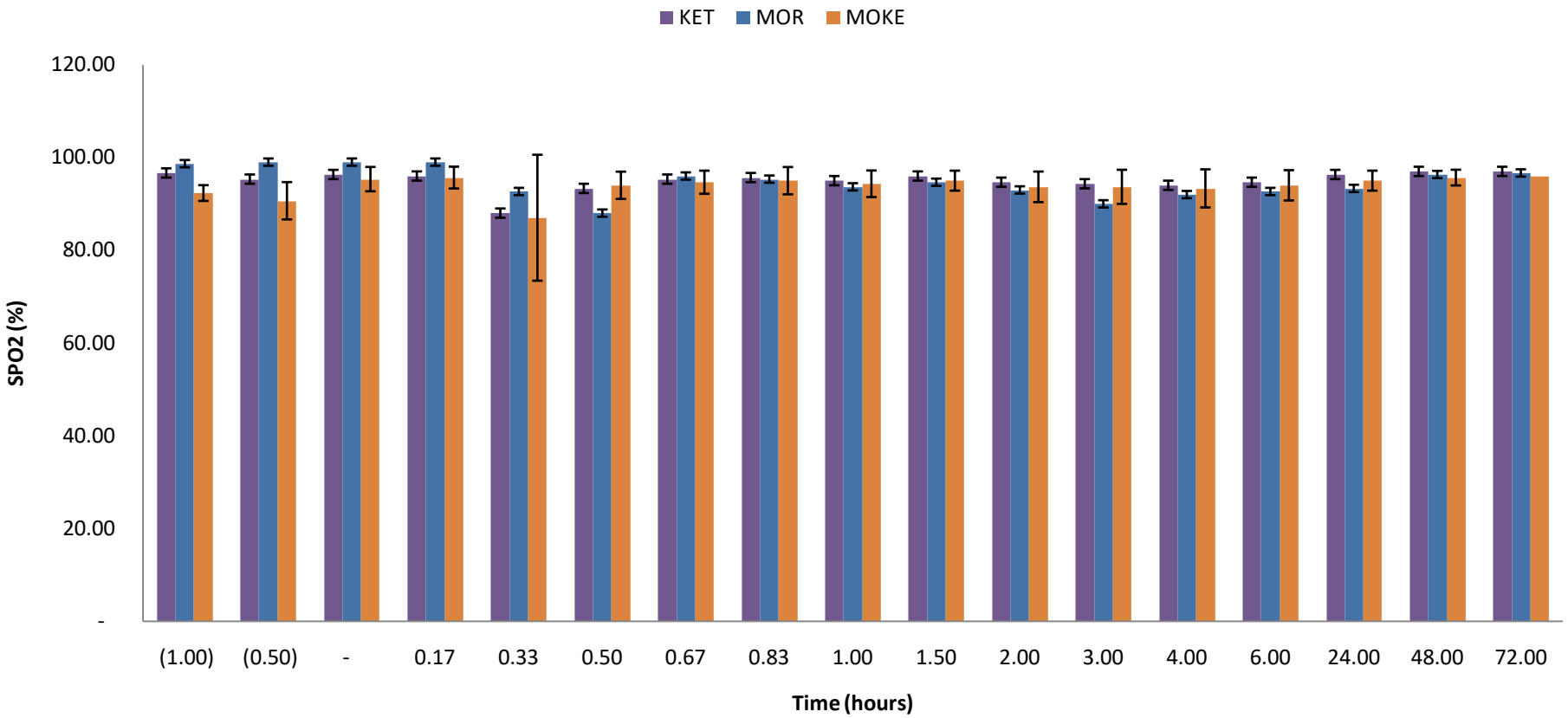


Fig.4. 10: Perioperative peripheral saturation of oxygen (SPO2) following single drug treatment with ketoprofen (KET) morphine (MOR) and a multimodal therapy of morphine and ketoprofen (MOKE) on pain management in dogs.

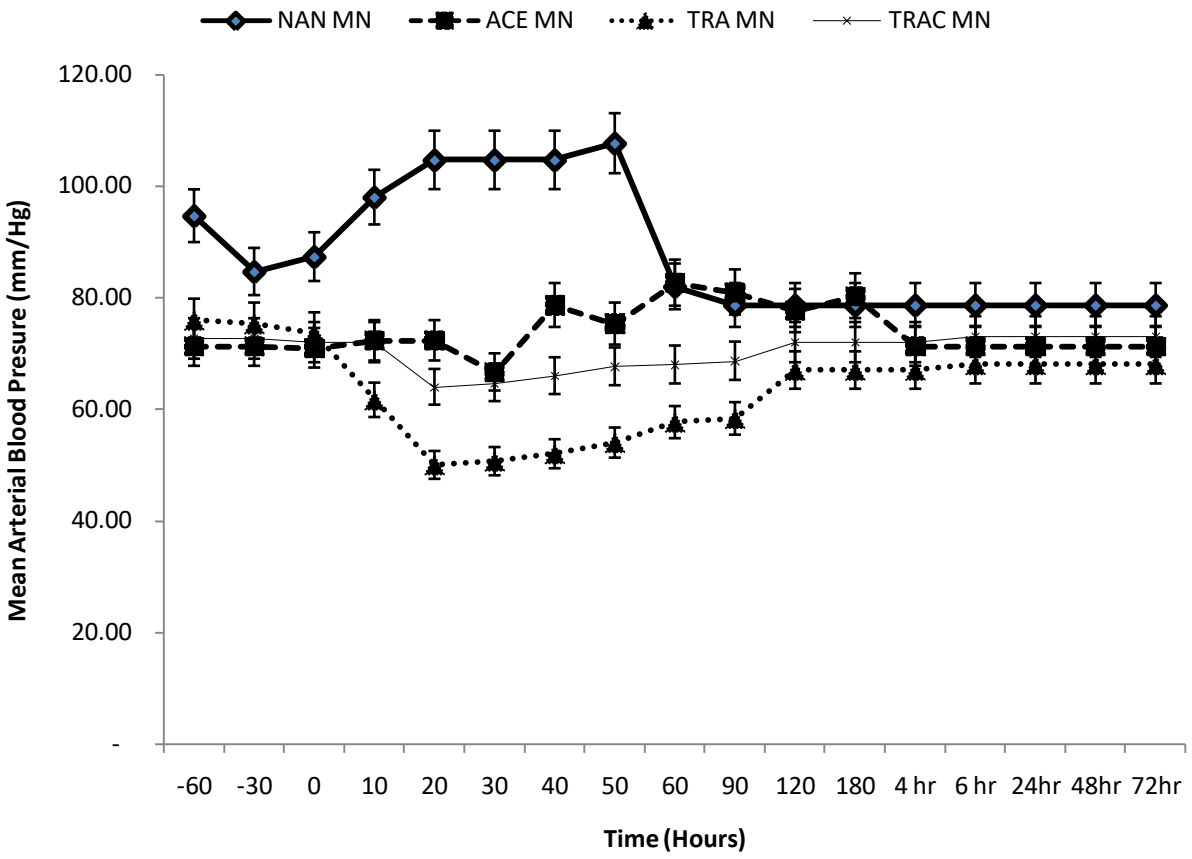


Fig. 4.11: Variation in perioperative mean arterial blood pressure (MAP) following single treatment with paracetamol(ACE), tramadol (TRA) combination therapyof tramadol/paracetamol (TRAC) and control (NAN) on pain management in experimental dogs.

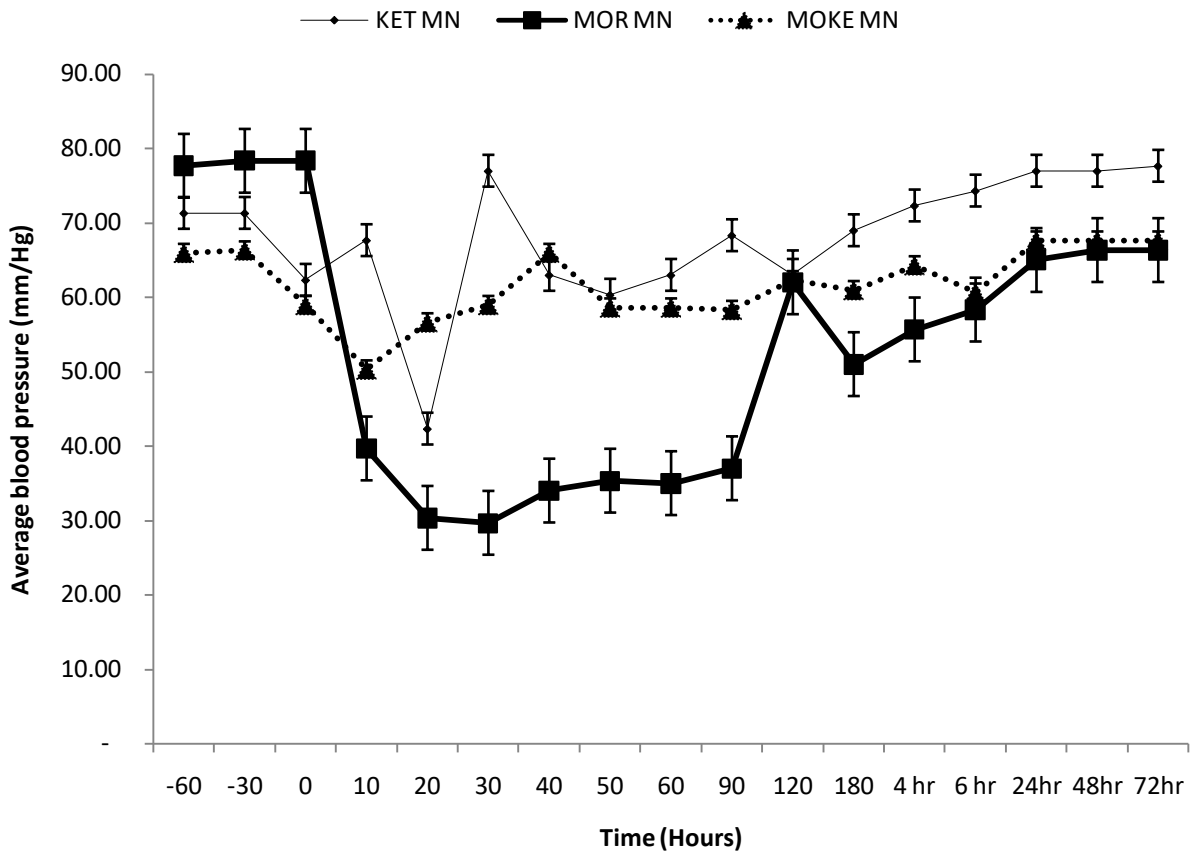


Fig. 4.12: Variation in perioperative mean arterial blood pressure (MAP) following single treatment with ketoprofen (KET) morphine (MOR) and a combination of morphine and ketoprofen (MOKE) on pain management in experimental dogs.

4.4. Electrocardiographic Evaluation

The ECG recordings were conducted at 25mm/sec speed in all the experimental dogs. Recordings for the various analgesics are presented in Fig. 4.13 - Fig. 4.23. It was observed that various components were quite discernible in unipolar and bi-polar limb leads. Therefore, comparisons were based on lead II electrocardiogram.The baseline ECG mapping obtained for the dogs indicates the normal P-QRS-T wave mapping (Fig 4.13). The rhythms were also regular and the rate were found to be normal.

The intrasurgical ECG mapping observed for the group that had no analgesic (NAN) had mechanoelectrical alternans due to irregular R wave amplitude and ST wave (Fig 4.14), however, post-surgical ECG mapping revealed irregular T wave alternans where the amplitude of the T wave were not to be the same (Fig 4. 15).

The lead II ECG mapping obtained for paracetamol (ACE) when administered (5mg/kg) intramusculary. Paracetamol at the therapeutic dose, exhibited in most instance similar to that obtained as the base line ECG which was the normal ECG mapping with very few instances where there were signs of muscular fibrilation sighted (Fig 4.16). Similarly, paracetamol/tramadolcombination (TRAC) were also showed a normal ECG tracing thruogh out the period under investigation

For most part of the experiment ketoprofen (KET) had a normal ECG mapping, However, during the time of surgical incision there was ECG maping sugestive of electrical alternans in which there was alteration in the QRS amplitude which occurs leading to pericordial imbalance (Fig 4.17) as a result of movement of heart in the pericardial fluid.

Tramadol (TRA) ECG mapping was normal in some of the instances during this investigation. 30 minutes post administration of this drug there was intermitent mechanical alternans due to muscular tremors in some of the experimental dogs (Fig 4.18). At the point of surgical incision, one of the dogs exhibited alternating current artifact (Fig 4.19), this was not seen in the other dogs in this group. Besides that, for the the most part of the experiment and post surgically the ECG mapping obsrved were that of a normal ECG with regular R – R interval (Fig 4.20).

At 10 minutes post intramuscular administration of (0.5mg/kg) morphine (MOR), there was an intial excitement in the heart rate which was evidenced by a tall peakedP-wave amplitude with an irregular QRS complex wave, as a result of transient compensatory right arterial hyperthrophy and multifocal arterial tachycardia (Fig 4.21). However, about 20 minutes later at the time of intra surgical incition, the ECG mapping had normalised with very few episodes of muscular fribrilations once in a while (Fig 4.22).
The multimodal therapy of morphine and ketoprofen (MOKE) gave a normal ECG tracing throughout the surgery except at the initial stage of about 10 minutes post administartion in two of the cases where electrical alternans due to the alternating amplitude of the R wave was noticed (Fig 4.23).



Fig. 4.13: Baseline ECG mapping from the group that was administerd with ACE. Notes the P-QRS-T wave mapping, the regular R-R wave interval and the normal sinus rhythm at a rate of 140/min (25mm/sec and 10 mm/mV).

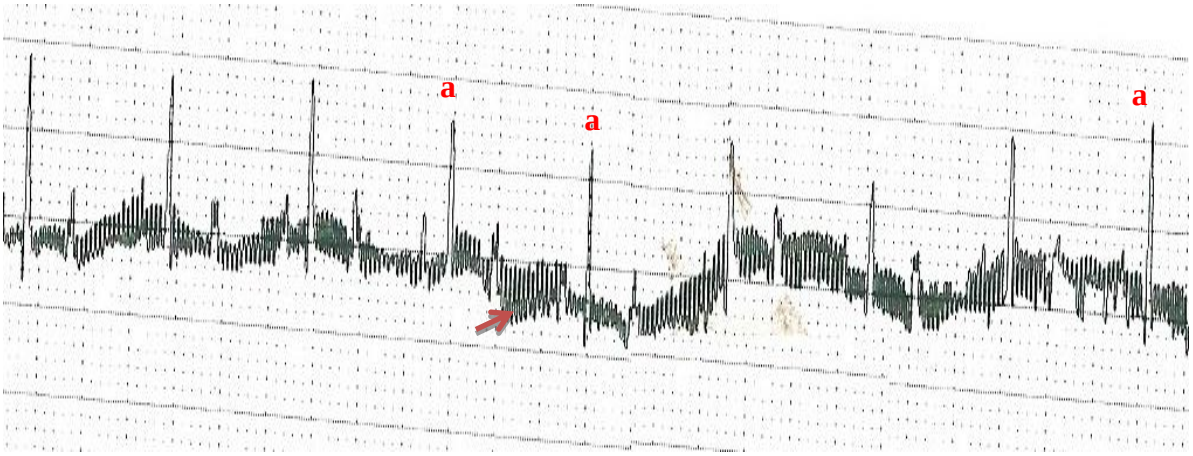


Fig. 4.14: ECG during incision of a dog that went through gastrotomy without analgesia (NAN). Note the irregular R wave (a) and the irregular ST wave due to electrical alternans. Also notemechanical alternans (arrow) at a rate of 140/min (25mm/sec and 10mm/mV).

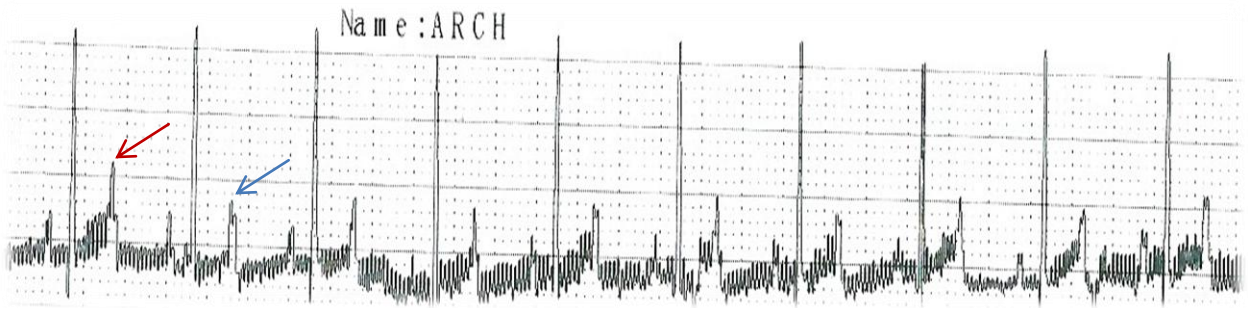


Fig. 4.15:Post-surgical ECG mapping of an anaesthetized dog from the non-treatment group (NAN). Note the irregular T waves (Blue and red arrows) indicating T wave alternans. at a rate of 140/min (25mm/sec and 10mm/mV).

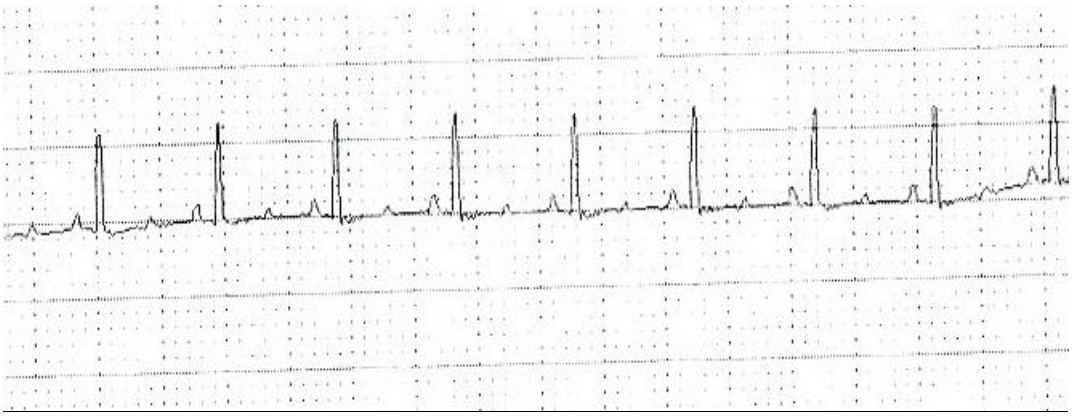


Fig. 4.16: Intra-surgical ECG mapping of an anaesthetized dog that was administered with ACE. Note the regular P-QRS-T wave and the constant R – R interval and the normal sinus rhythm at a rate of 140/min (25mm/sec and 10mm/mV).

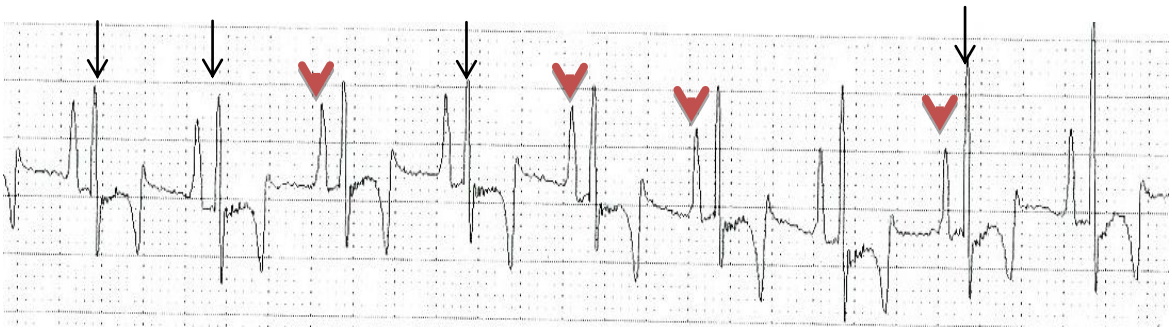


Fig. 4.17: ECG tracing seen in one of anesthetized dogs that was treated with ketoprofen (KET) showing electrical alternans. Note the tall peaked and alternating P waves (arrow heads), Q waves, R waves (arrows) and S waves. (25 mm/sec and 10 mm/mV).

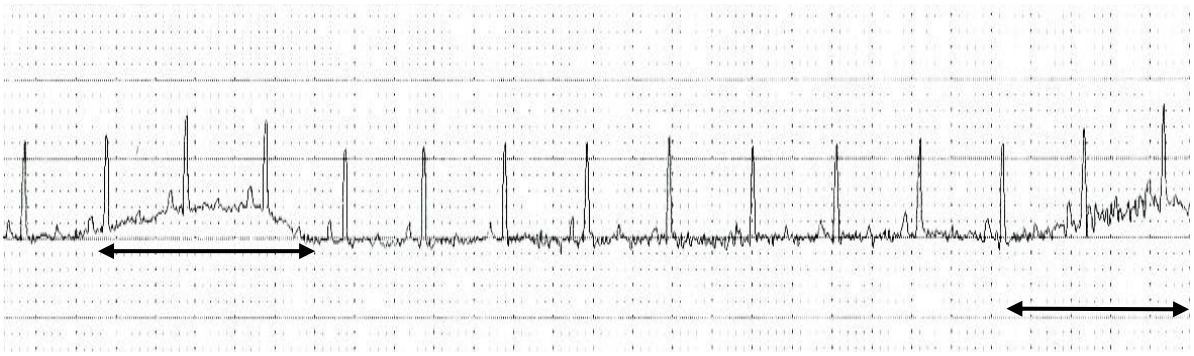


Fig. 4.18: Electrocardiographic (ECG) mapping 30 minutes post administration of TRA. Note normal P-QRS-T rhythms with intermittent mechanical alternans due to muscular tremors (double ended arrows).

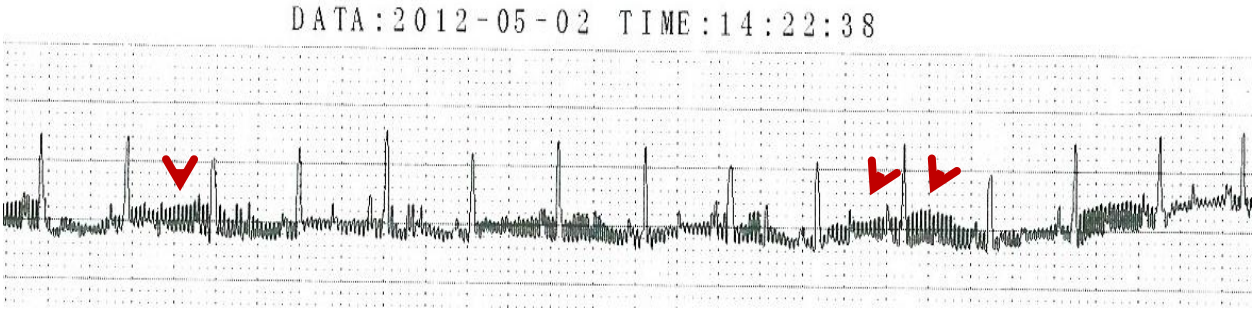


Fig. 4.19: ECG at the point of surgical incision in the tramadol group (TRA). Note the alternating current artefact (red arrow heads)

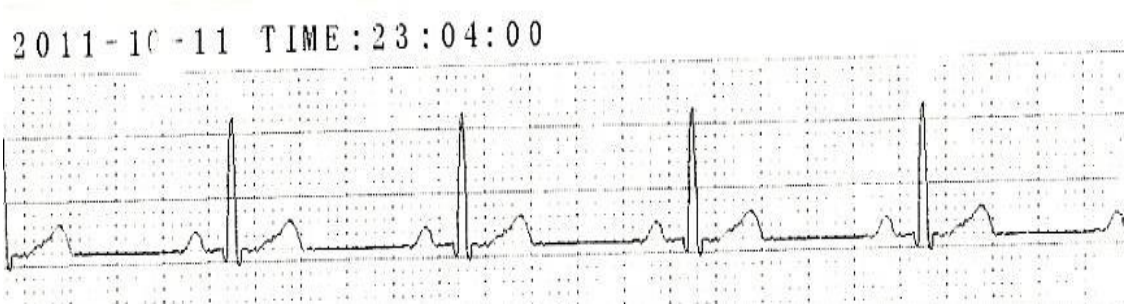


Fig. 4.20: Electrocardiogram (ECG mapping) of Lead II dog treated with 2mg/kg Tramadol intramuscularly post-surgical evaluation using veterinary multi-parameter patient monitor. Sensitivity 500µv and chart speed 25mm/ second.

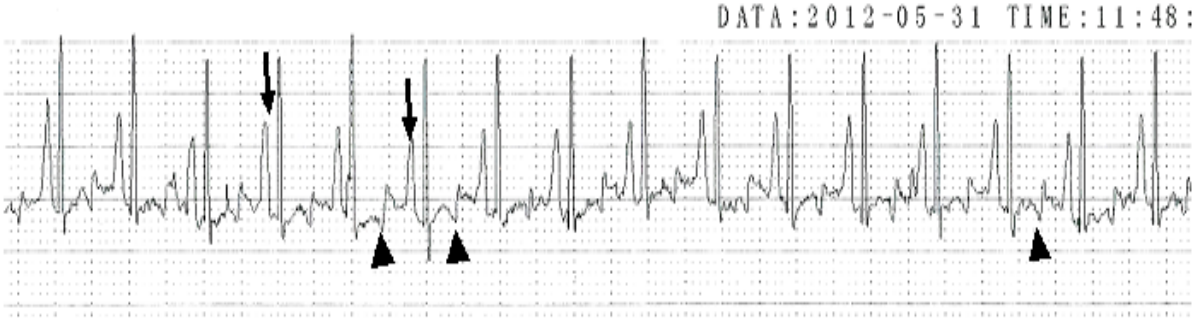


Fig. 4.21:ECG recording of dog injected with Morphine 0.5mg/kg intramuscularly 10 minutes post administration. Note pointed P-wave of amplitude of 1.5mm (arrow) and T wave abnormalities including Peaked hyper acute T waves, with T-wave inversions in the right precordial leads. (arrow heads).

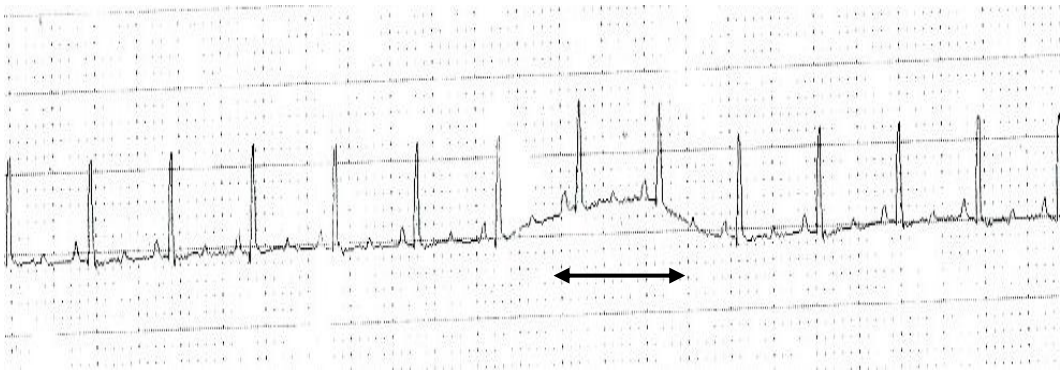


Fig. 4.22: ECG mapping of dog injected with morphine 0.5mg/kg intramuscularly at surgical incision. Note that the sinus rhythm has normalised except for slight fibrillation (arrow).

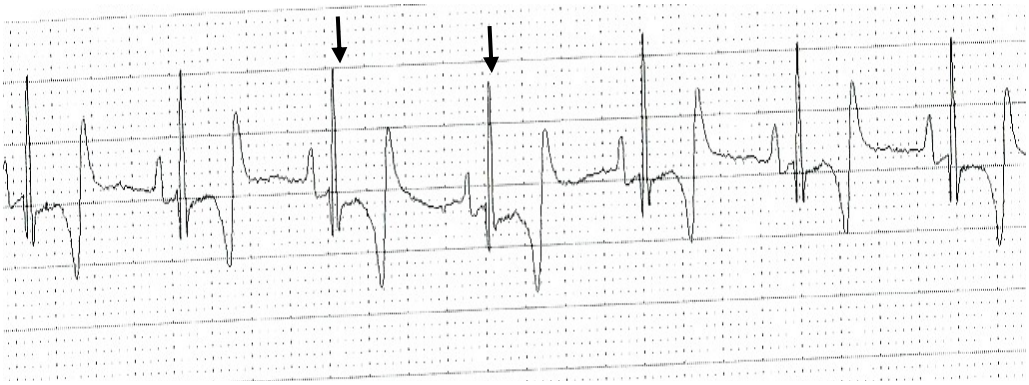


Fig. 4.23: ECG tracing seen in one of anesthetized dogs that was treated with a combination of morphine and ketoprofen (MOKE) showing electrical alternans, inverted S wave and presence of prominent U waves (arrow head). Note the alternating R waves (arrows)

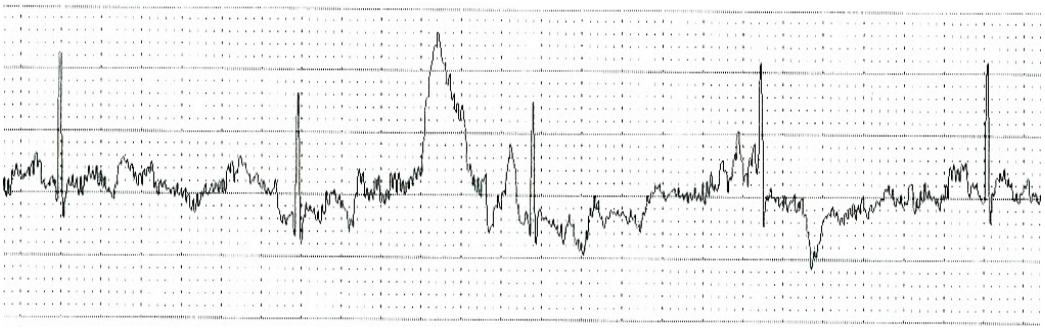


Fig. 4.24: ECG sinus rhythm tracing from one of the experimental dogs treated with a combination of morphine and ketoprofen at the point of surgical incision. Note low resolution pixelated ECG tracing that makes it difficult to ascertain the type of fibrillations observed.

4.5 Cortisol and Serum Electrolyte Evaluation

The mean serum profile of the different treatment groups were presented graphically Fig 4.25 – Fig 4.26 and appendix X. There was an increase in the serum cortisol level in the non-treatment group (NAN) from 2.50 ±0.0 to 3.60 ±0.27 (appendix X)especially when pain was inflicted on the subject through incision and surgical manipulation. Some of the other treatment groups displayed a reduction in the serum cortisol level (Fig. 4.25 and Fig. 4.26).

There was a significant decrease ($P< 0.05$) in the serum cortisol level for ACE in which the serum cortisol level decresed from 2.67 ± 0.12 just before the administration of the drug to 1.33 ± 0.12 nmol/L (50.2% decrease) 30 mins post administration when surgical incision was made. Similarly, KET decreased from 3.23 ± 0.53 to 2.43 ± 0.41 nmol/L30 minutes post administration which amounted to 24.8% decrease from the initial value (Fig. 4.26).

Tramadol (TRA) at time 0 minutes had an average serum cortisol level of 5.20 ± 0.0 and this decreased to 2.67 ± 0.20 nmol/L (48.9% decrease) 30 minutes after the administration of tramadol and surgical incision was instituted (Fig 4.26). Ironically, when morphine (MOR)was administed, the average serum cortisol level which was 5.17 ± 1.18 at time 0 just before the administration of morphine, increased 30 minutes after administration of the drug to 7.33 ± 0.24 nmol/Lwhich amounted to a 48.4% increase (Fig 4.25).

The effect of TRAC and MOKE drug combination was similar to that seen with TRA and ACE in which there were decrease in the serum cortisol level 30 mins post

administration of the drug. In TRAC there was a 28.9% increase (Fig 4.26) while that of MOKE was 45.3% increase (Fig. 4.25).

The blood urea nitrogen (BUN) level for all the treament groups including the non-treatment group (NAN) had a normal urea level of within 2.5 – 9.6 mmol/L. There was no significant change in the BUN pre and post surgically (Appendix XII). However, there was increament in the BUN values for paracetamol from 8.03 ± 0.29 presurgically to 8.55 ± 1.17 mmol\L. This increament was also seen in the multimodal therapy group of MOKE with an increament of 7.75 ± 0.19 to 8.05 ± 0.28 mmol\L. The other treament group of KET, TRA, MOR and the multimodal therapy of TRAC all exhibited a decline in the BUN values post surgically (Table 4.4).

The values obtained for the serum potasium for the treatment groups were within the normal range of 3.6-5.5 mmol\L in most of the groups except in the post surgical MOR treatment groups. These values were however of significance for MOKE multimodal therapy and MOR single drug therapy group in which there were significant increase. ACE, KET, TRA single drug therapy group and TRAC multimodal therapy group had increase in the serum potasium from the pre surgical values to the post surgical values but these increase were not statistically significant (Appendix XIII). MOR increased from the Pre-surgical value of 3.92 ± 0.35 to a post surgical value of 6.08 ± 0.65 mmol\L which showed a significant rise of 35.52%. Also, MOKE multimodal therapy which had a presurgical value of 4.63 ± 0.58 decrease to 4.00 ± 0.03 mmol\L which was a 13.60% decrease from the initial value (Table 4.5).

There was a significant difference between the presurgical and post surgical values of ketoprofen, in which there was significant increase from 144.10 ± 1.36 to 148.30 ± 1.18 post operatively (Fig. 4.6). In all the other values obtained for the other treatment groups there were no statistical significant change observed (appendix XIV). The values from the treatment groups were also within the normal range of between 139 – 154 mmol\L.

Serum chloride was within the normal range throughout the experiment in all the treatment groups. There were also no significant change in the serum chloride level in the dogs. Although clinically there was a decrease in serum chloride from the presurgical values in ACE (118.15 ± 1.70 to 117.05 ± 0.49), MOR (115.20 ± 5.72 to 111.20 ± 1.35) and the multimodal therapy of MOKE (99.00 ± 1.15 to 95.00 ± 0.58). KET, TRA and TRAC on the other hand exhibited an increase in the serum chloride level. However when comparing the values of the serum chloride within the diferent drug treatment group, MOKE had a significantly low sodium level.

The normal value of Ionised (free) blood calcium is between 1.1-1.4 mmol/L. In this study, the values that were obtained pre and post surgery were within the normal values for most of the treatment groups except in the KET group in which the presurgical free calcium was 1.09 ± 0.09 and later became 0.90± 0.31 mmol\L post surgically (Table 4.8). the change in values were not significantly diferent in all the cases.(appendix XVI and XVII).

There was no significant change in the values obtained in the blood pH for all the treatment groups. However, there were some clinical differences in the values of ACE, KET, and MOR where they increased from the presurgical values obtained. TRA on its

own had a decreased from there presurgical values (Table 4.9).Similarly, there were no significant changes in the pre and post-surgical values of serum anion gap (AG) from all the treatment groups.

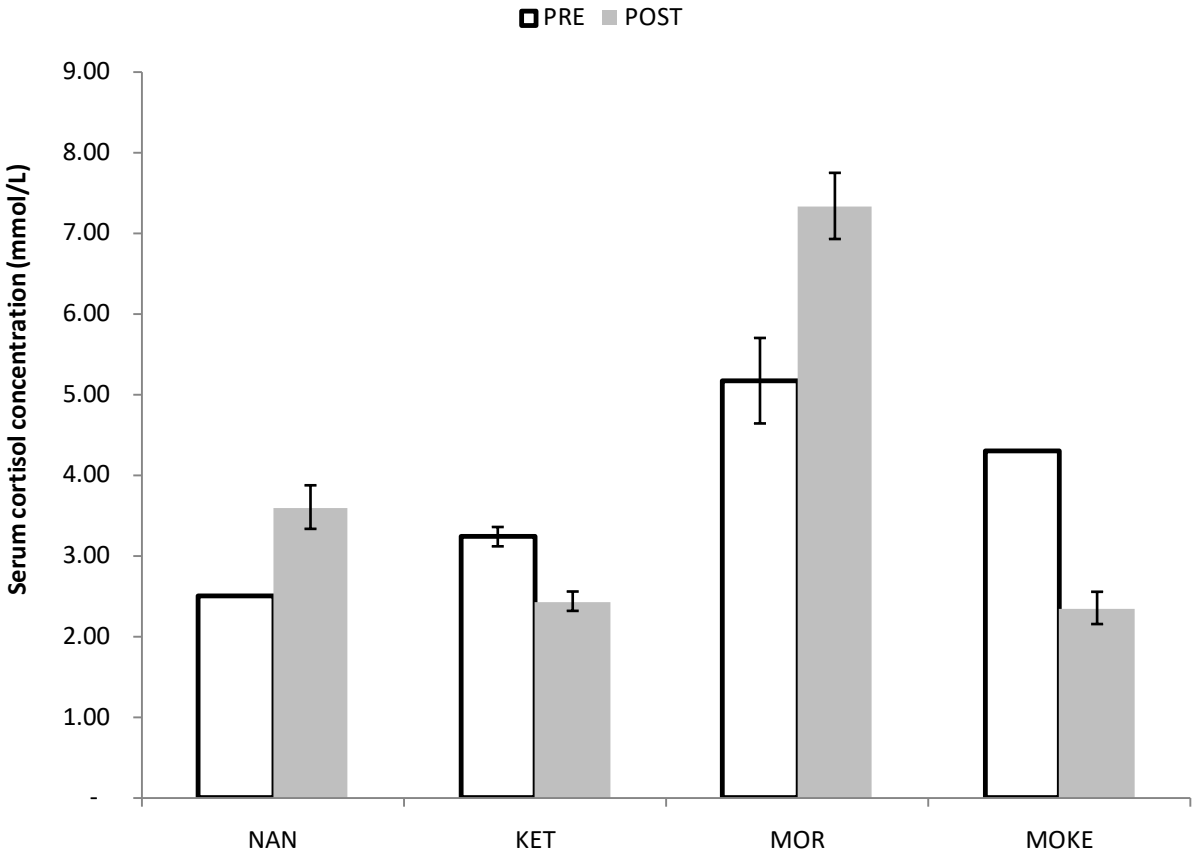


Fig. 4.25: Perioperative serum cortisol level at pre and post-surgery period and between single treatment drugs ketoprofen (KET), morphine (MOR) and a multimodal treatment of morphine and ketoprofen (MOKE) respectively.

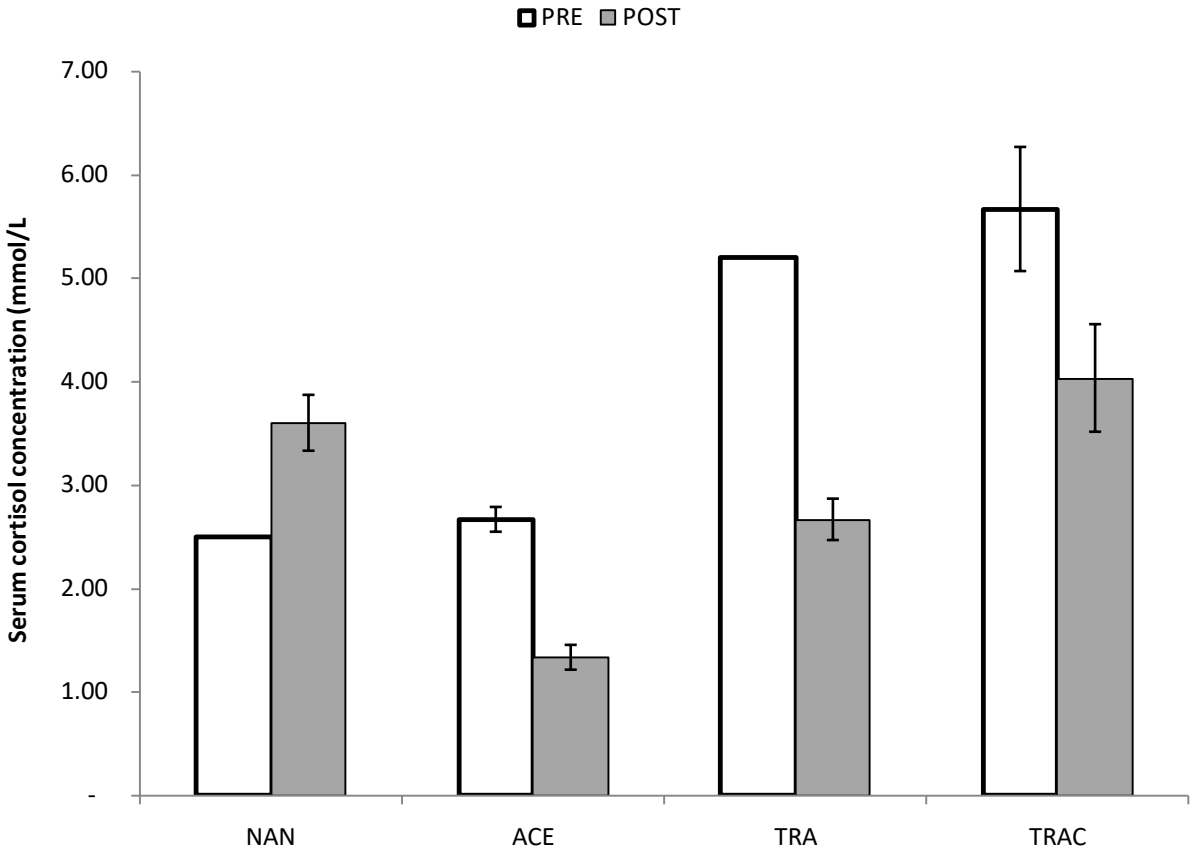


Fig. 4.26: Shows the result of perioperative serum cortisol level at pre and post-surgery period and between single treatment drugs paracetamol (ACE), tramadol (TRA) and a multimodal treatment of tramadol and paracetamol (TRAC) respectively.

Table 4.4: Bloodurea nitrogen (BUN) level pre and post-surgery for the different drugtreatment groupsmeasured in mmol\L

DRUG	PRE	POST
Paracetamol	8.03 ± 0.29	8.55 ± 1.71
Ketoprofen	8.70 ± 0.53	8.65 ± 0.45
Tramadol	9.10 ± 0.25	8.85 ± 0.09
Morphine	9.05 ± 0.27	8.70 ± 0.43
Tramadol + Acetaminphen	8.25 ± 0.17	7.85 ± 0.10
Morphine + Ketoprofen	7.75 ± 0.19	8.05 ± 0.28

Key: Mean ±SEM; CI= 95% and DF= 1; * P ≤ 0.05

Table 4.5: Serum Potassium (K^+) level (mmol\L) pre and post-surgery for the different drug groups

DRUG	PRE	POST
Paracetamol	5.20 ± 0.26	5.14 ± 0.04
Ketoprofen	5.51 ± 0.26	4.95 ± 0.35
Tramadol	5.78 ± 0.05	5.76 ± 0.17
Morphine	3.92 (0.60)	6.08 (0.92)*
Tramadol + Acetaminphen	5.23 (0.73)	4.57 (0.03)
Morphine + Ketoprofen	4.65 (0.10)	4.00 (0.05)*

Key: Mean ±SEM; CI= 95% and df= 1; * P ≤ 0.001

Table 4.6: Serum Sodium (Na^+) level (mmol\L) pre and post-surgery for the different drug treatment groups

DRUG	PRE	POST
Paracetamol	145.85 ± 2.74	149.60 ± 2.37
Ketoprofen	144.10 ± 1.36	148.3 ± 1.18*
Tramadol	149.57 ± 3.58	154.80 ± 3.35
Morphine	150.85 ± 11.29	148.57 ± 2.78
Tramadol + Paracetamol	145.55 ± 0.61	145.50 ± 2.71
Morphine + Ketoprofen	136.50 ± 2.02	139.00 ± 1.15

Key: Mean ±SEM; CI= 95% and df= 1; * P ≤ 0.05

Table 4.7: Serum Chloride (Cl^-) level (mmol\L) pre and post-surgery for the different drug treatment groups

DRUG	PRE SURG	POST SURG
ACE	118.15 ± 1.70	117.05 ± 0.49
KET	109.20 ± 0.49	115.87 ± 4.97
TRA	109.95 ± 1.41	111.95 ± 1.65
MOR	115.20 ± 5.72	111.20 ± 1.65
TRAC	112.85 ± 0.38	112.05 ± 1.65
MOKE	99.00 ± 1.15	95.00 ± 0.58

Key: Mean ±SEM; CI= 95% and df= 1; * P ≤ 0.05

Table 4.8: Ionised (free) serum calcium level (mmol\L) pre and post-surgery for the different drug groups

DRUG	PRE	POST
Paracetamol	0.93 ± 0.07	1.12 ± 0.16
Ketoprofen	1.09 ± 0.09	0.90 ± 0.31
Tramadol	1.22± 0.03	1.17 ± 0.03
Morphine	1.23± 0.11	0.98 ± 0.20
Tramadol + Acetaminphen	1.06 ± 0.11	1.06 ± 0.22
Morphine + Ketoprofen	1.19 ± 0.07	1.09 ± 0.12

Key: Mean ±SEM; CI= 95% and df= 1; * P ≤ 0.05

Table 4.9: Serum pH level pre and post-surgery for the different drug groups

DRUG	PRE	POST
PARACETAMOL	9.04 ± 0.16	9.09 ± 0
KETOPROFEN	8.73 ± 0.20	9.18 ± 0.50
TRAMADOL	8.86 ± 0.38	8.76 ± 0.08
MORPHINE	8.52 ± 0.15	8.95 ± 0.14
TRAMADOL + ACETAMINPHEN	8.31 ± 0.20	8.32 ± 0.05
MORPHINE + KETOPROFEN	8.58 ± 0.10	8.43 ± 0.07

Key: Mean ± SEM; CI= 95% and df= 1; * P ≤ 0.05

Table 4.10: Serum AG level pre and post-surgery for the different drug groups

DRUG	PRE	POST
Paracetamol	8.85 ± 0.35	10.30 ± 2.30
Ketoprofen	17.07 ± 1.44	19.85 ± 1.45
Tramadol	27.30 ± 2.50	28.35 ± 4.95
Morphine	18.25 ± 8.50	28.50 ± 3.27
Tramadol + Acetaminphen	14.25 ± 0.05	18.80 ± 3.90
Morphine + Ketoprofen	21.15 ± 0.65	20.45 ± 2.15

Key: Mean ± SEM; CI= 95% and df= 1; * P ≤ 0.05

4.6 Neurophysiological Evaluations

The raw EEG signal was visually inspected prior to analysis. No intraoperativeawareness was reported by any of the dogs in the treatment groups in this study.Artefact- free 30-minute EEG signals at 30 (from immediately after drug injection to 30 minute), 60 (30∼60 minute), 90 (60∼90 minute), 120 (90∼120 minute), 180 (150∼180 minute), and 240 (210∼240 minute) minutes after saline or tramadol administration were used to quantify the EEG. The Hanning-windowed 2.5-second epochs (1.25-second overlap) were converted to power spectra using a fast Fourier transform algorithm and then averaged to power spectra. Relative band powers: Power spectra were cut into nine frequency bands: delta1, 1∼2.5 Hz; delta2, 2.5∼4.0; theta1, 4∼6; theta2, 6∼8; alpha, 8∼13; beta1, 13∼21; beta2, 21∼ 32; gamma, 32∼50; and total, 1∼50 Hz.

None of the experimental dogs showed any paroxysmal discharges in the EEG tracing, and EEG artefacts were eliminated as much as possible. In the non-treated group, electrical burst were noticed especially around the C4-A2 with amplitude of 325.8 ± 0.8μv^2/Hz Mean ± SE and speed of 30mm/s (Fig 4.27) and the T4 –A2 aspect of the brain (Fig 4. 28). At incision however, spiked to 350.5± 0.5μv^2/Hz (wave amplitudes) and speed of 30mm/s (Fig 4.29) and a total of 654 EEG waves out of which we had 38 sharp spike waves, 18 at the point of incision alone. The predominant waves were the delta waves of that range from 0.3-3.8Hz (Fig 4.29) this indicated a lot of activities in the right cerebral hemisphere which is one of the area where there were somatosensory and pain activities. This activities were highest when surgical incisions, ligations and suturing were been performed.

The paracetamol groups exhibited activities in the T3, T4, C3 and C4 montage sites. The activities observed were not however as high as that observed in the none treatment group with amplitudes of 286.9± 0.56 μv^2/Hz Mean ± SEand speed of 30mm/s (Fig 4.31 and Fig 4.32).At intrasurgical incision, the amplitude of 1000± 0.56 μv^2/Hz and a total of 1088 waves on the EEG tracing with all were slow wide waves.

Ketoprofen treated groups had a total of 311 waves throughout the period of study with 5 spike waves, 3 sharp waves and the rest were wide waves. The mean amplitude of the spikes was13.2± 2.56 μv^2/Hz observed mainly at the O2 – A2 aspect. Mild activities were also seen at the T4 – A2, O1 – A1 and C4 – A2 aspects of the brain especially during intrasurgical incision period with spike amplitude 14.9 ± 2.56 μv^2/Hz (Fig 4. 38).

The mono-therapy of tramadol (TRA) gave a total pathologic wave report of 248 waves of which we had 2 spike waves and 2 sharp waves and 244 slow wide waves. The mean amplitude of the waves was 100.1± 4.13 μv^2/Hz and the highest activity was seen at the C4 – A2 aspect of the brain during incision (Fig 4.41). At rest however this activity was minimised.

The pathologic wave report for morphine (MOR) indicated a total of 236 waves with no spike wave but have 5 sharp waves and 231 slow wide waves. At rest there were minimal activities seen throughout the all the aspects of the brain (Fig. 4.46). The mean amplitude of the waves was 40.2± 4.13 μv^2/Hz with most activities at incision was seen around the FP2 – A2 region of the brain (Fig. 4.46). These activities noticed are not so obvious.

The multimodal therapy of tramadol/ paracetamol gave a total wave of 286. Out of these, there was 1spike wave,2 sharp waves, 1 spike slow wave and 281 slow wide waves. At rest, activities were not observed. All the spike, sharp, and spike slow waves

were observed at the incision and suturing period of the study. The mean amplitude of the waves was 10.1± 1.23 μv^2/Hz with most activities around the T4 – A2, C4- A2 and the O2 – A2 aspect of the brain (Fig 4.44 and Fig 4.45).

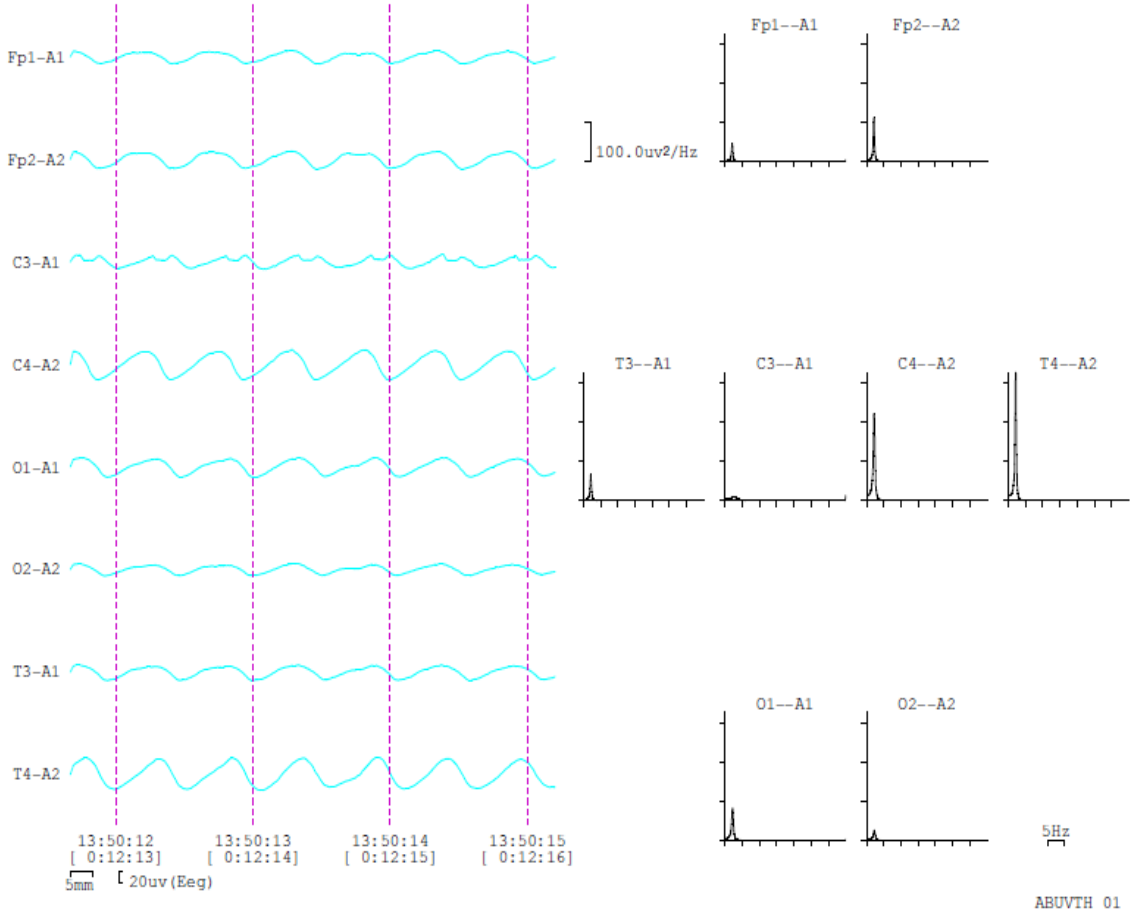


Fig. 4.27: The power spectrum graph for the non-analgesic group before intrasurgical incision. Note. Amplification is 5mm/50uv and Speed: 30mm/s

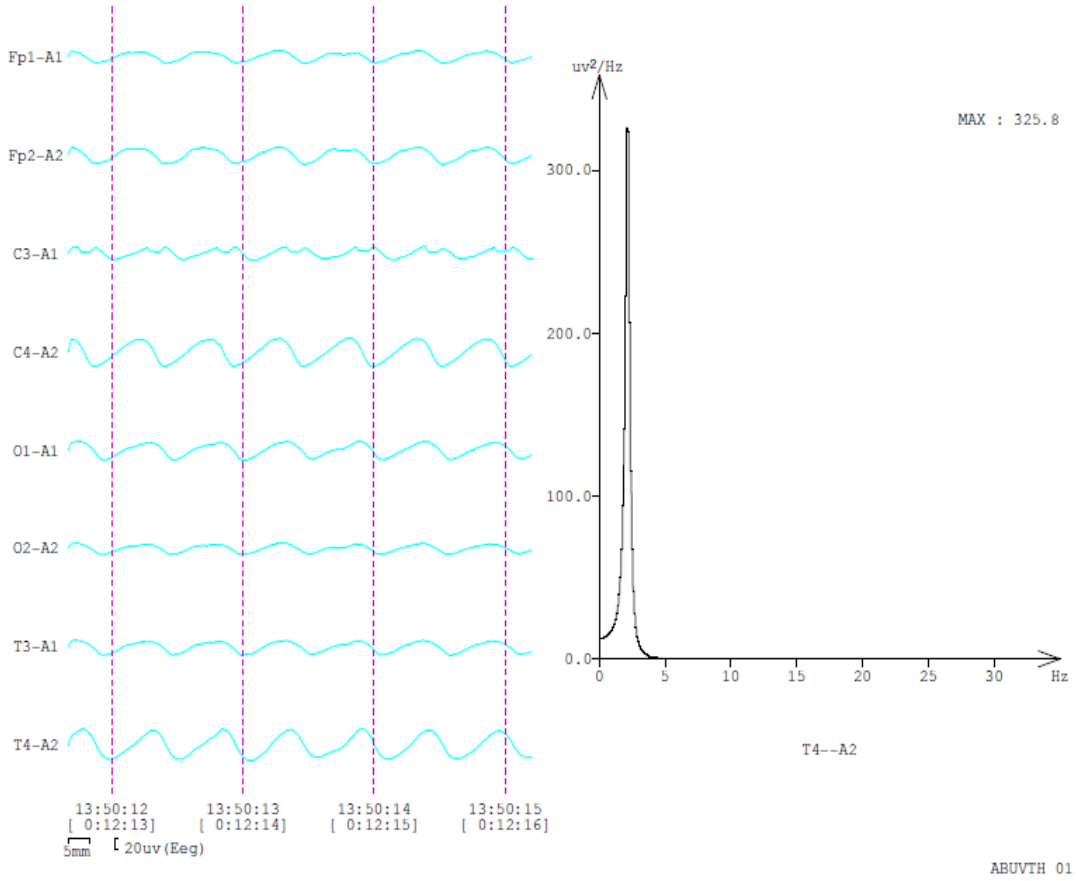


Fig. 4.28: The power spectrum graph for the non-analgesia group before intrasurgical incision showing the T4- A2 power spectrum graph. Note. Amplification is 5mm/50uv and Speed: 30mm/s

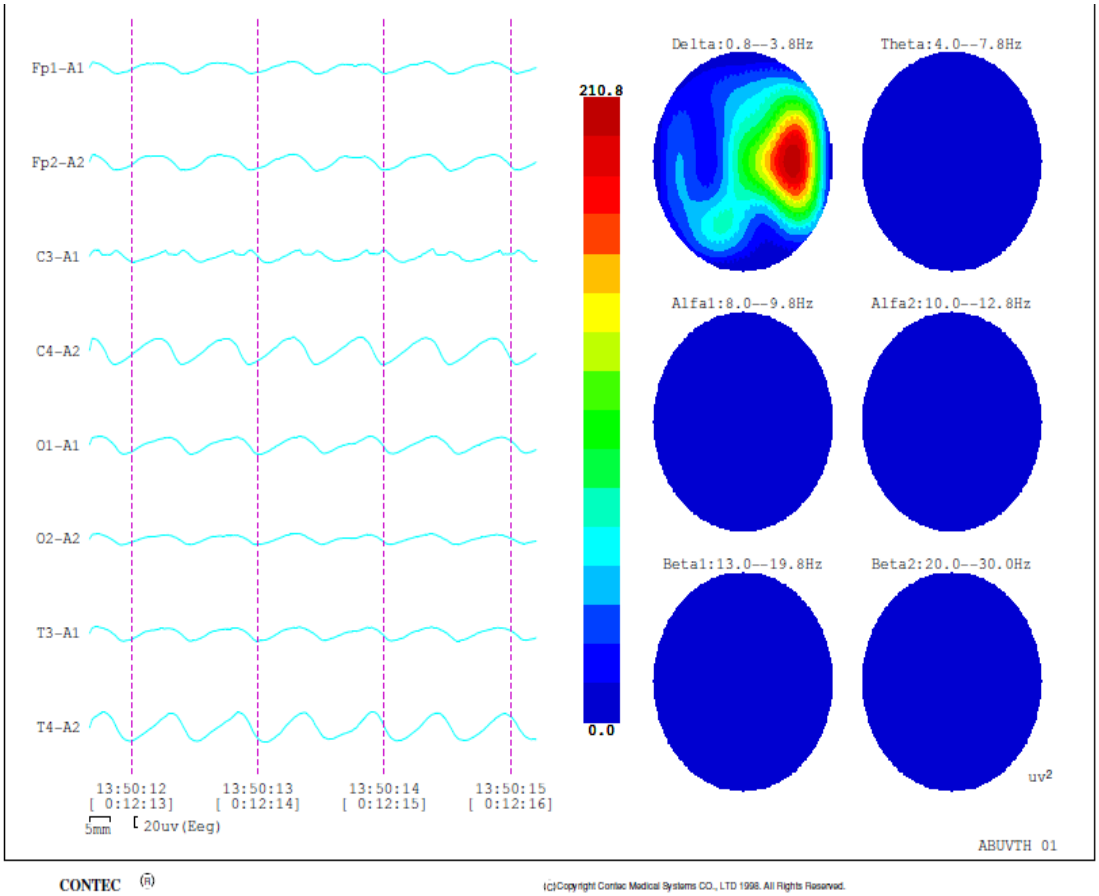


Fig. 4.29: The beam spectrum graph for the non-analgesia group before incision. Note.amplification is 5mm/50uv and Speed:30mm/s

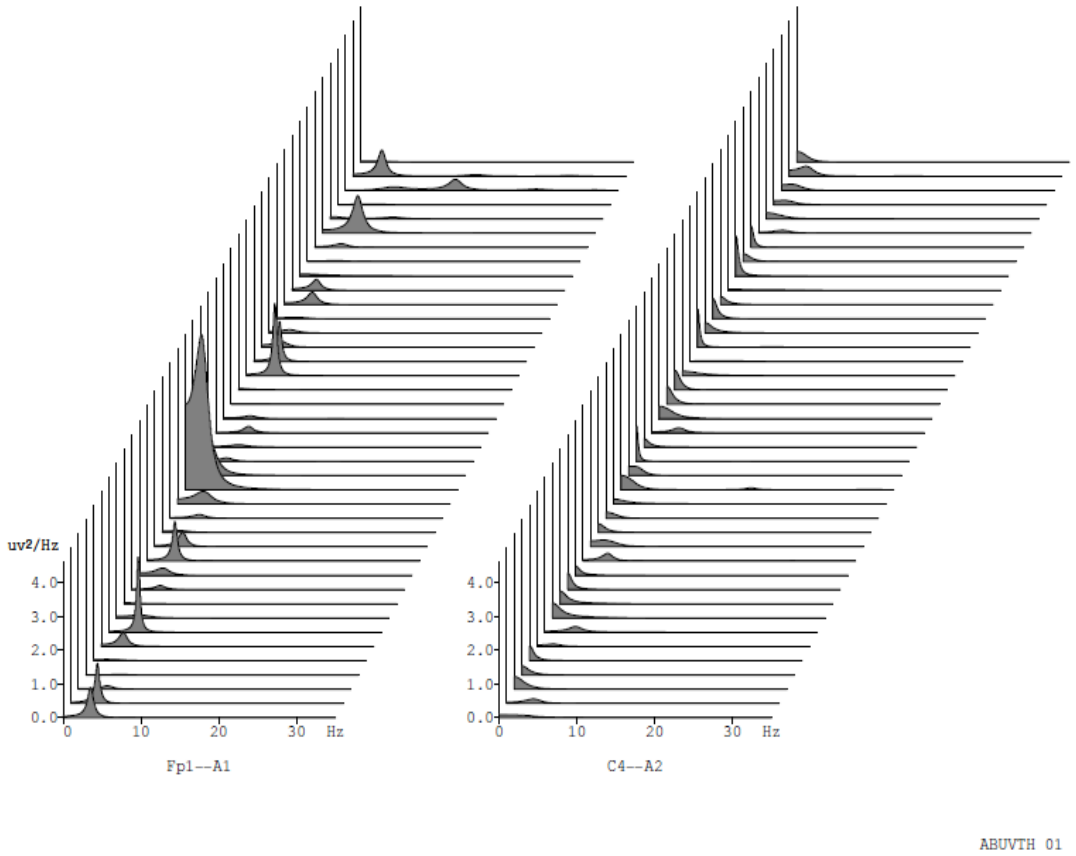


Fig. 4.30: Compressed power spectrum graph for the non-analgesia group before intrasurgical incision, Showing the Fp4- A1 and C4-A1 compressed power spectrum graph. Note. Amplification is 5mm/50uv and Speed: 30mm/s

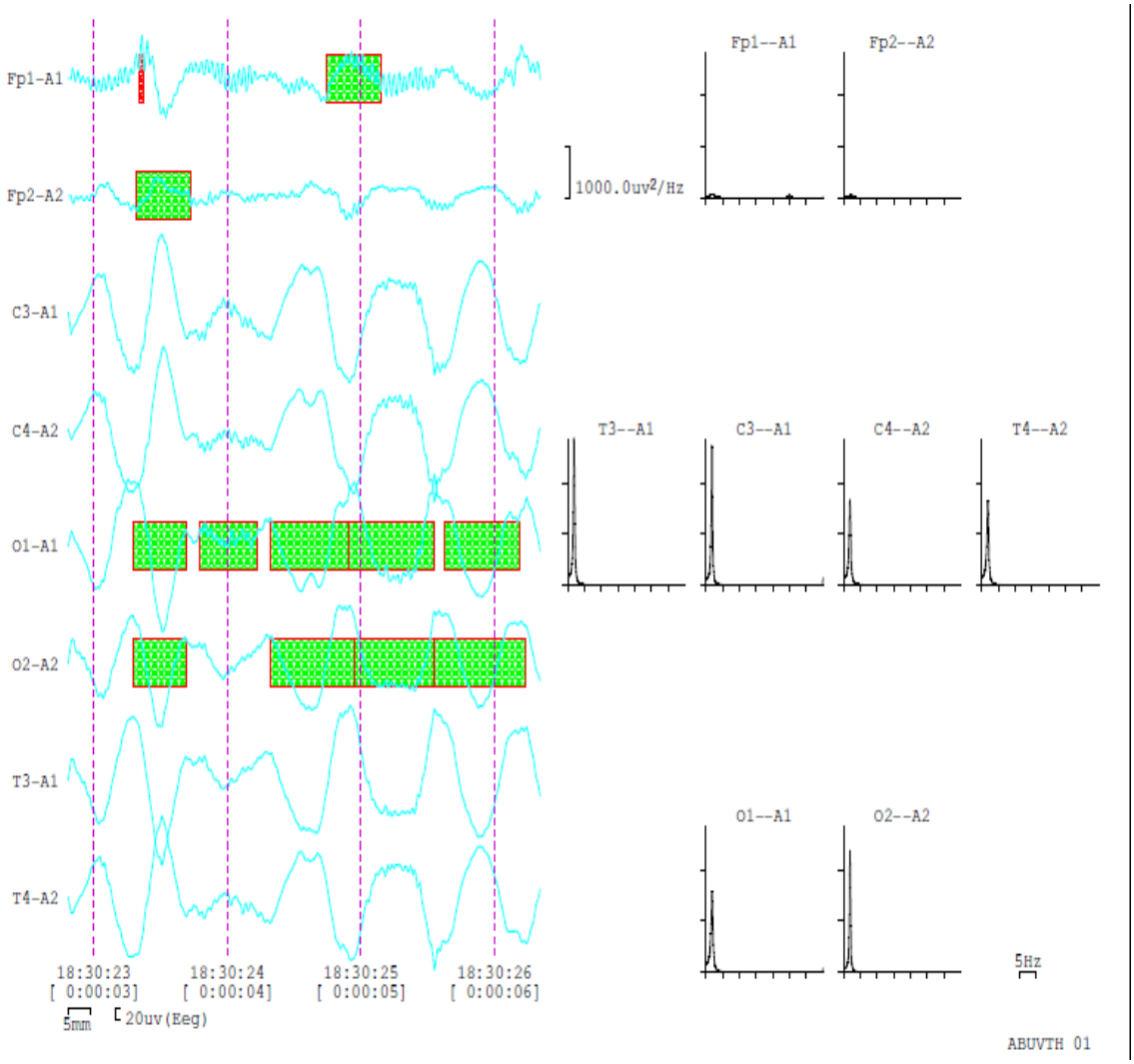


Fig. 4.31: Power spectrum graph for the paracetamol group at resting stage. Note. Amplification is 5mm/50uv and Speed: 30mm/s.

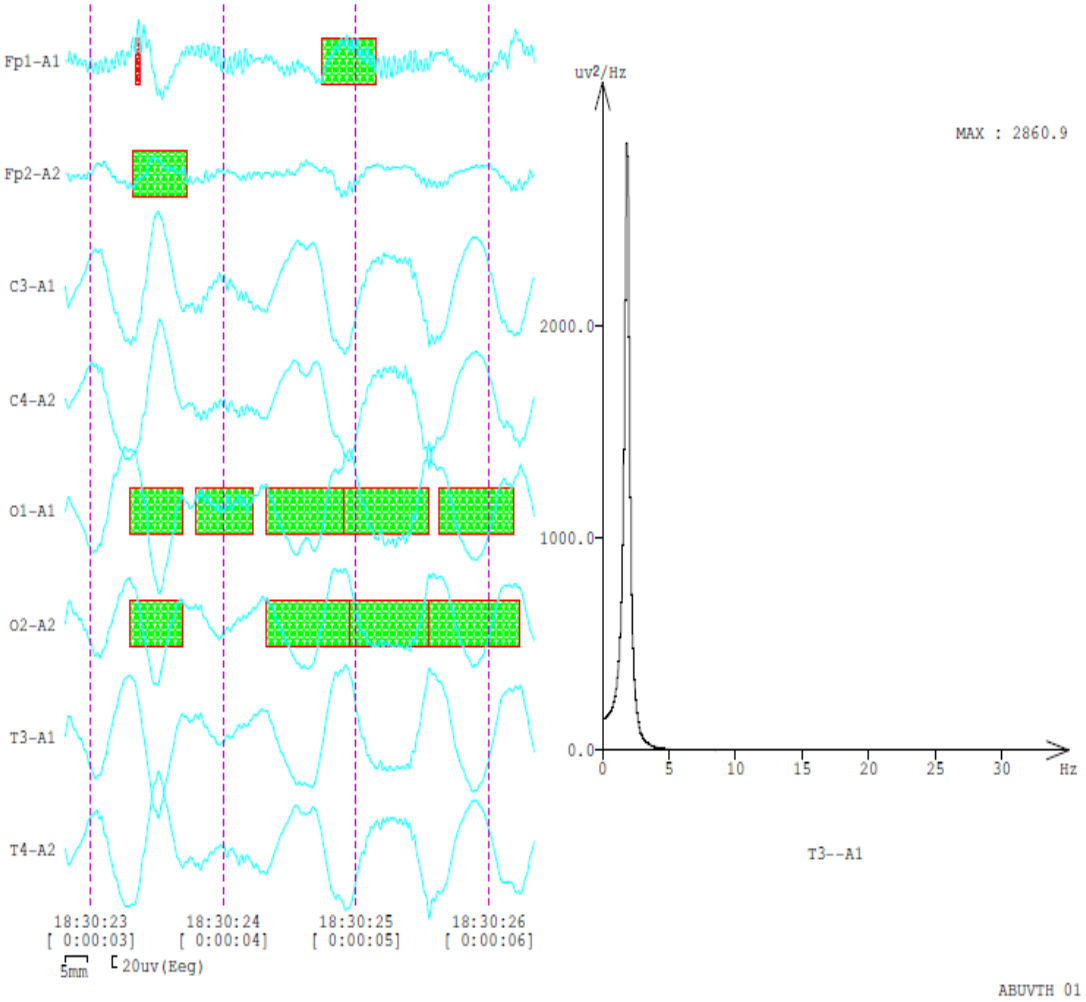


Fig. 4.32: Power spectrum graph for the paracetamol group at resting stage showing the T3-A1 spectrum. Amplification is 5mm/50uv and Speed:30mm/s.

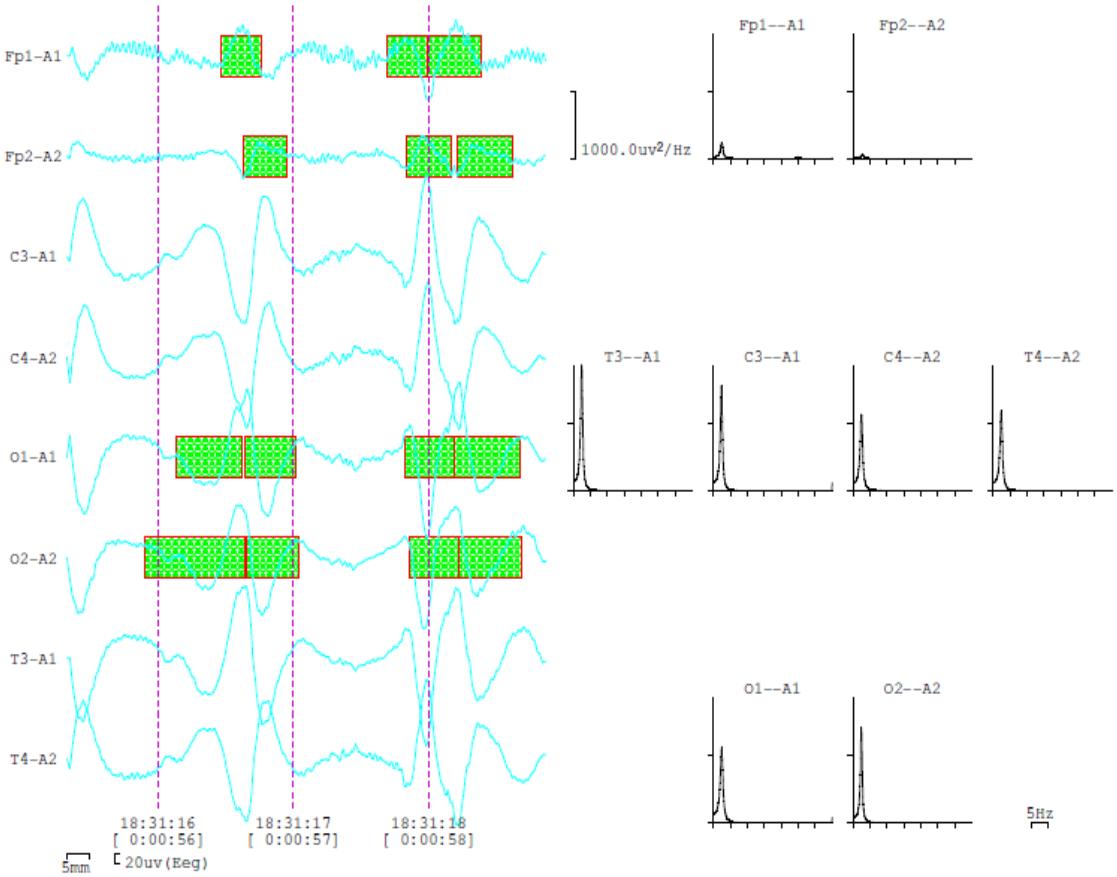


Fig. 4.33: Power spectrum graph for the paracetamol group at intrasurgical incision. Note. Amplification is 5mm/50uv and Speed:30mm/s

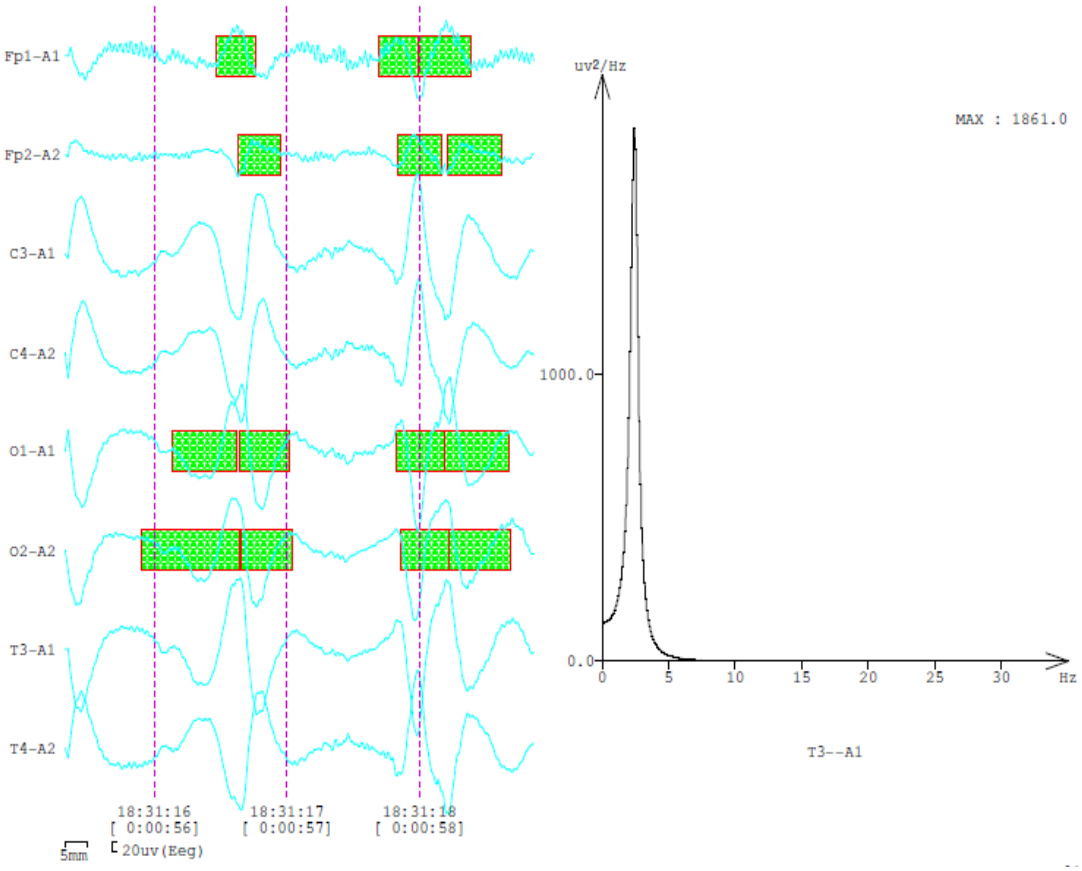


Fig. 4.34: Power spectrum graph for the paracetamol group at resting stage showing the T3-A1 aspect of the spectrum .Note the maximum amplitude 1861. Note. Amplification is 5mm/50uv and Speed:30mm/s.

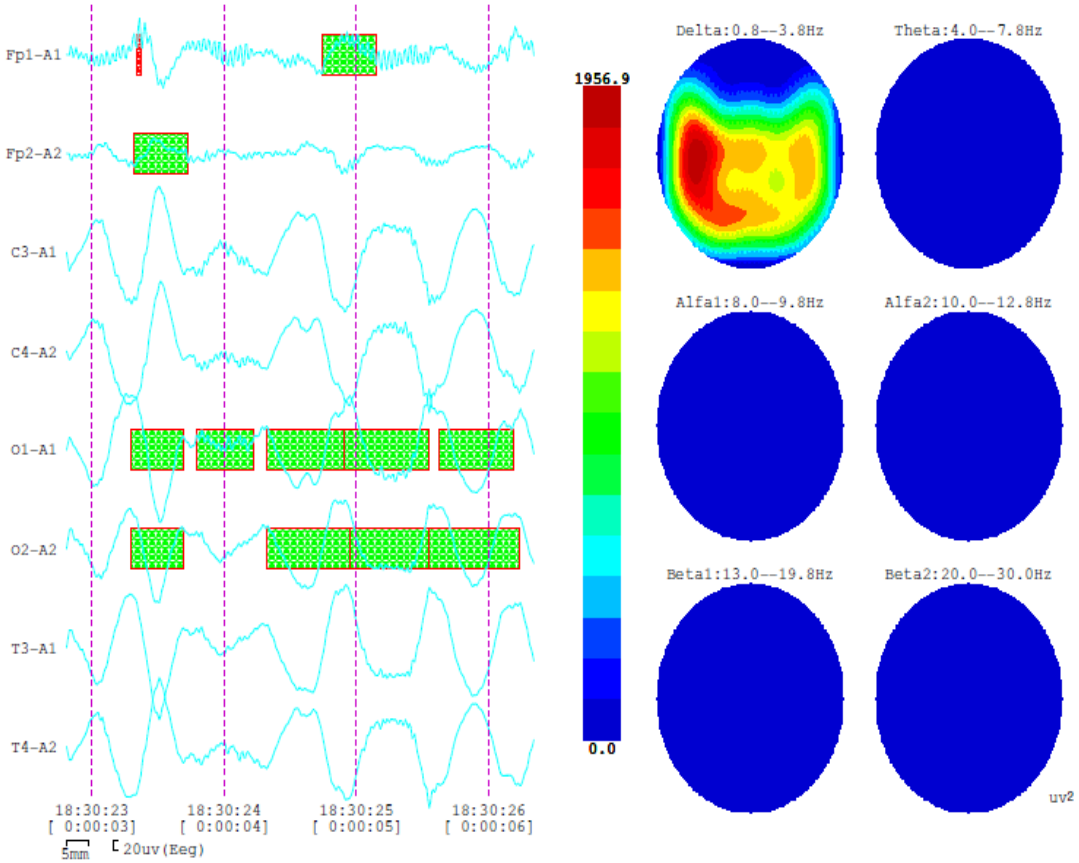


Fig. 4.35: Beam wave for the paracetamol group at rest.Note: The frequency of delta. Note. Amplification is 5mm/50uv and Speed:30mm/s

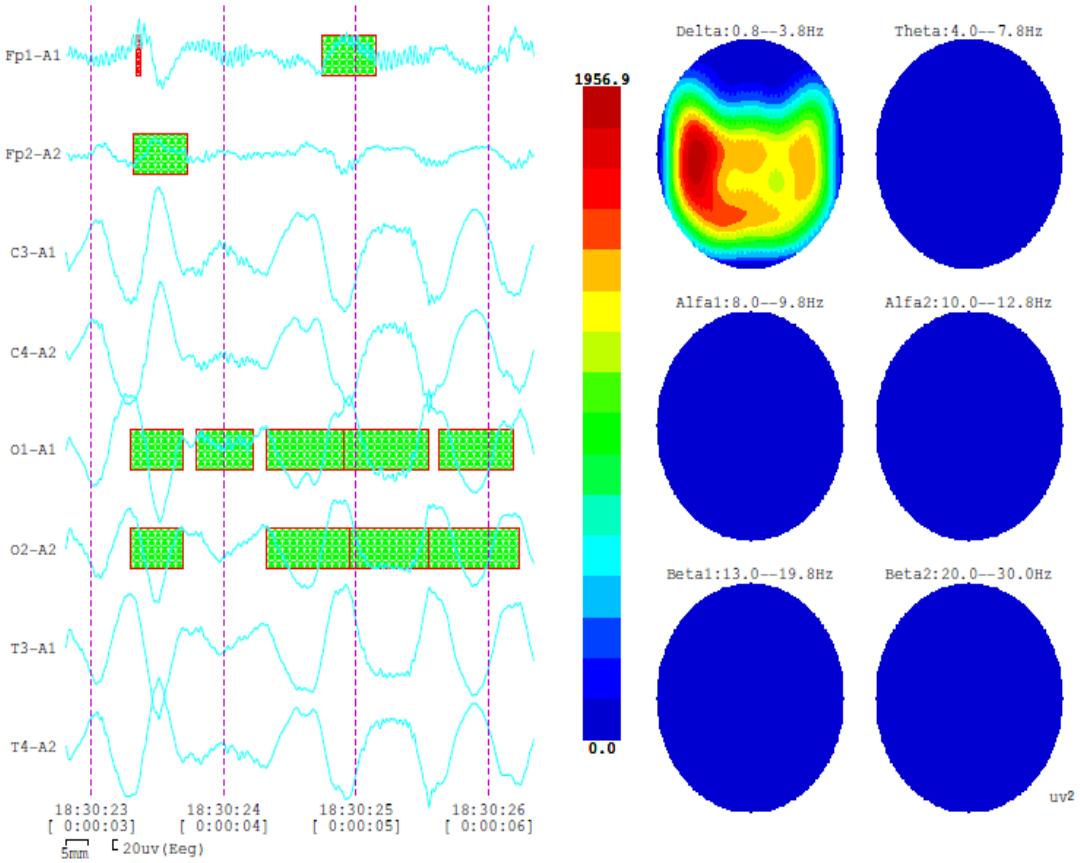


Fig. 4.36: Beam wave for the paracetamol group at intrasurgical incision. Note: The frequency of delta. Note. Amplification is 5mm/50uv and Speed:30mm/s

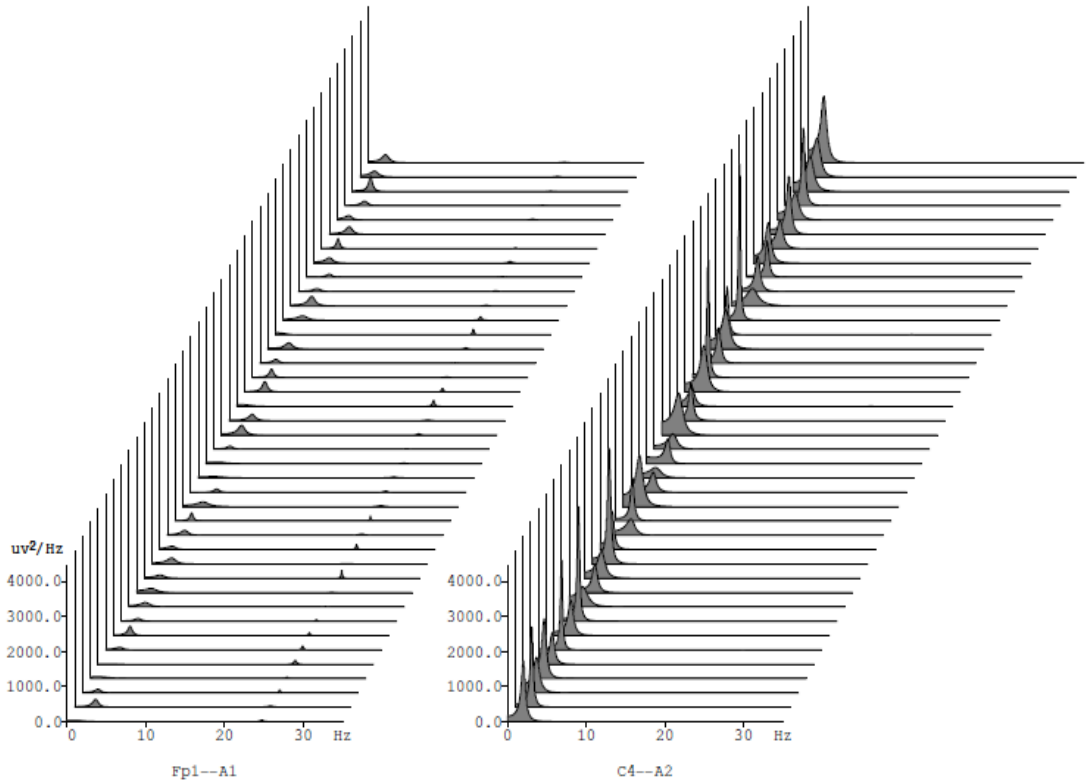


Fig. 4.37: Resting compressed spectrum graph of the digital EEG for paracetamol treated group.

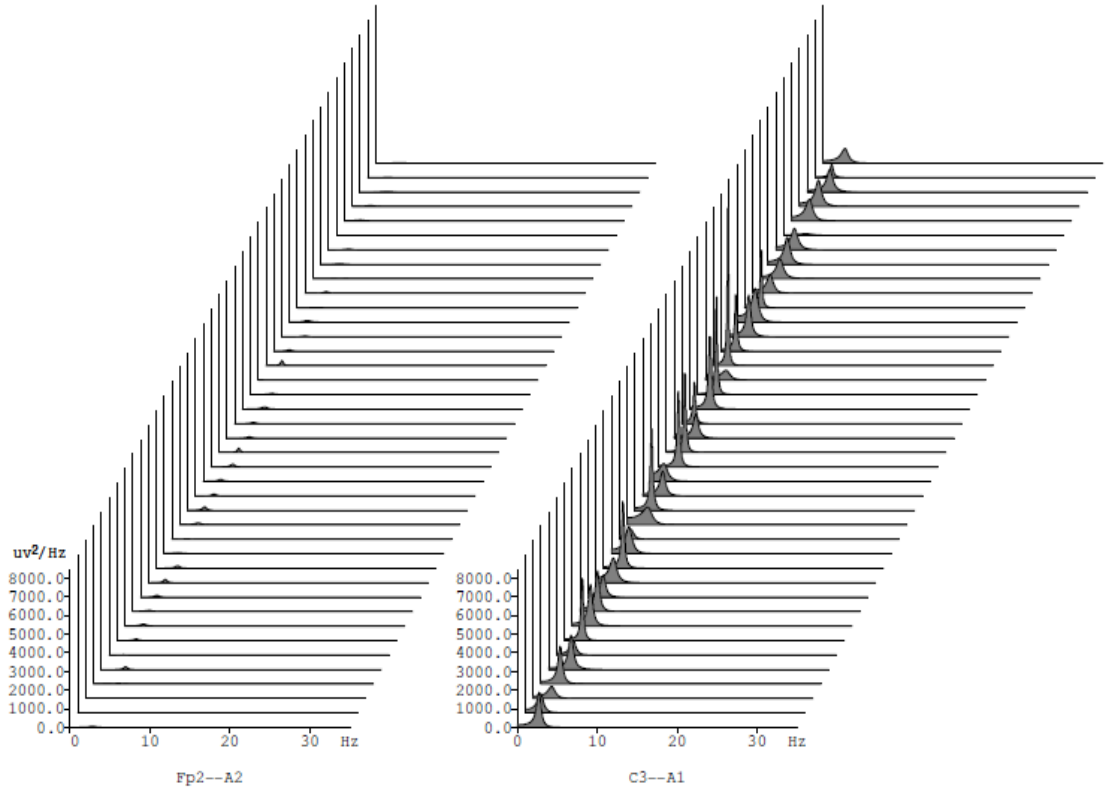


Fig. 4.38: Compressed spectrum graph of the digital EEG for keoprofen treated group during intrasurgical incision.

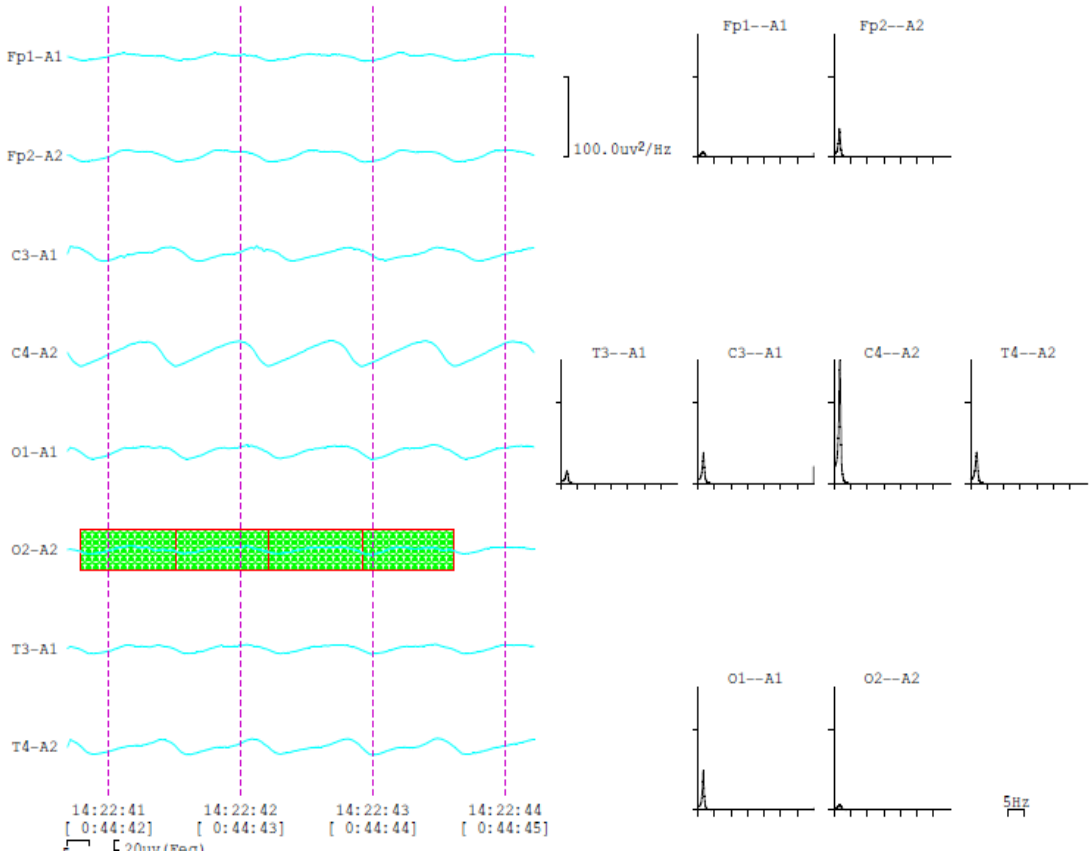


Fig. 4.39: Thepower spectrum graph for the Tramadol group before intrasurgical incision. Note. Amplification is 5mm/20uv and Speed:30mm/s

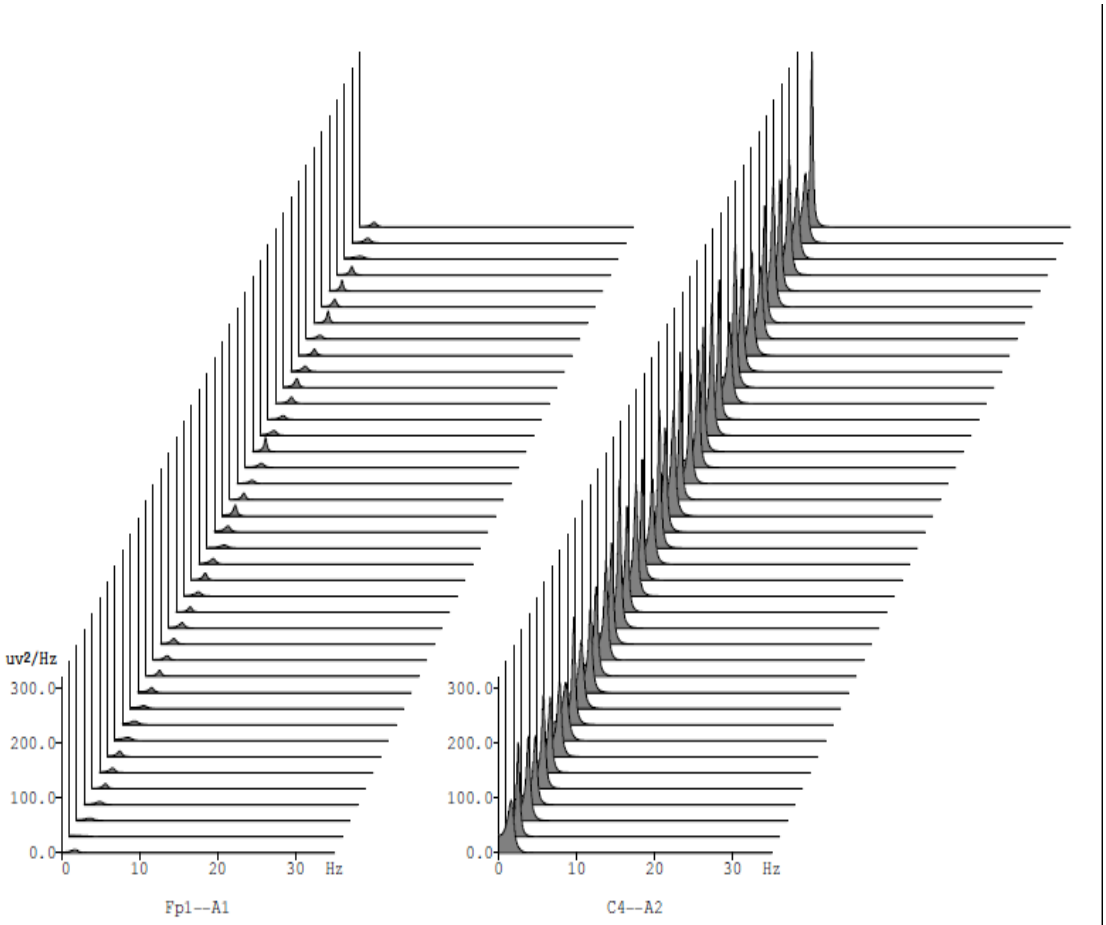


Fig.4.40:Compressed spectrum graph for the Tramadol group before intrasurgical incision. Note. Amplification is 5mm/50uv and Speed:30mm/s

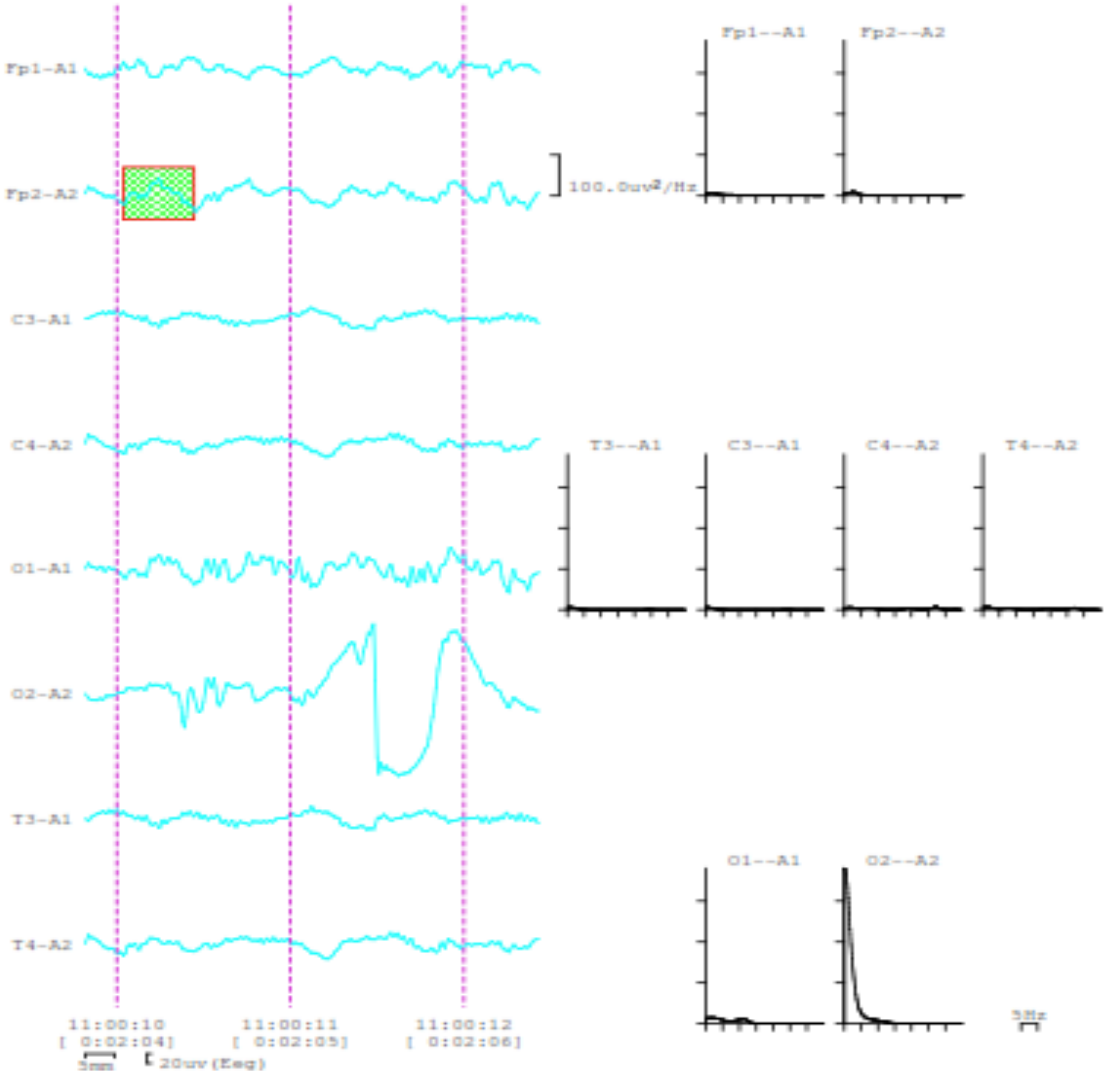


Fig. 4.41: Power spectrum graph of ketoprofen treated group (resting period)

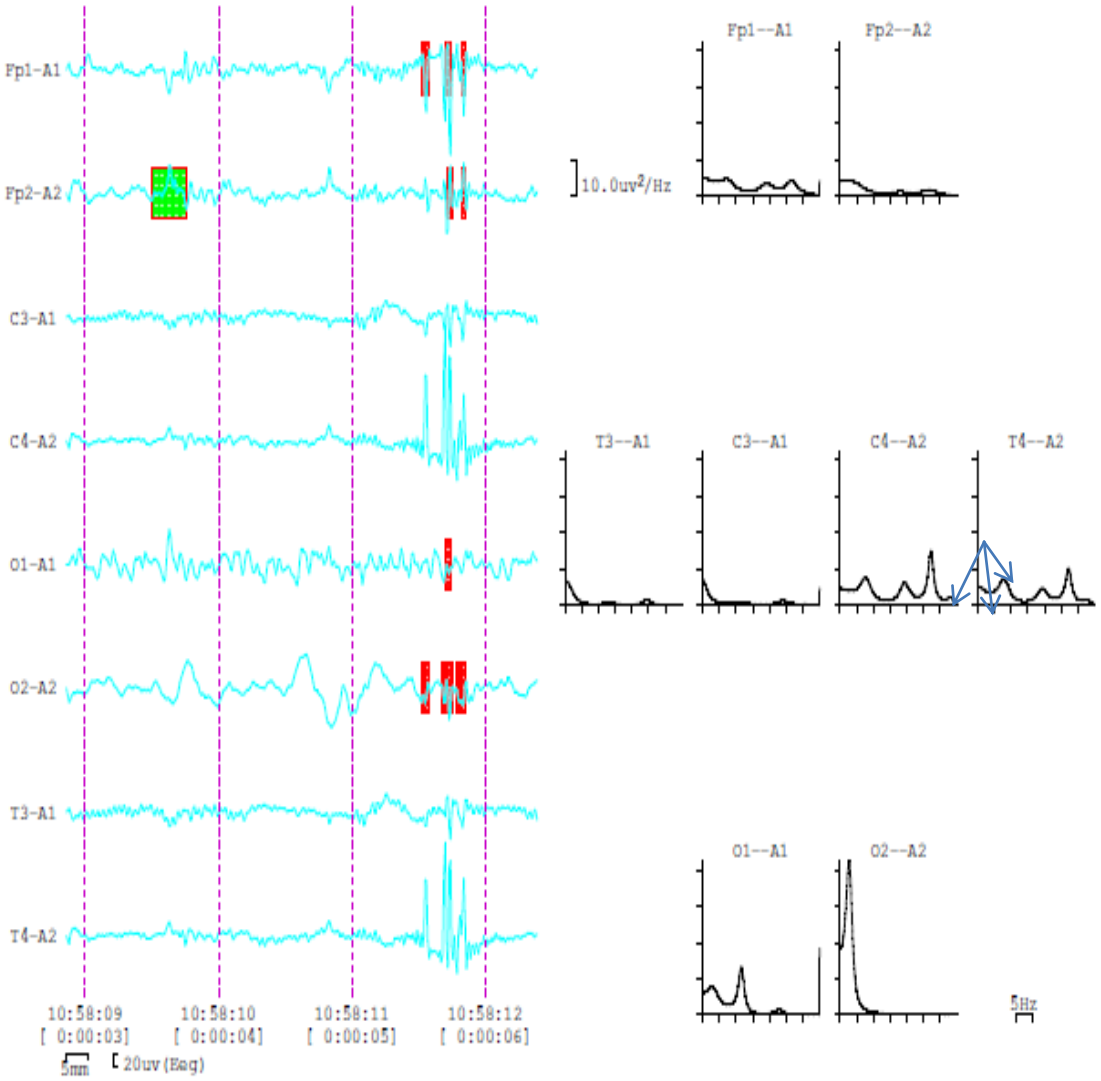


Fig. 4.42: Power spectrum graph of ketoprofen treated group at intra surgery incision period. Note. Multiple spikes at the c4 – A2 and the T4 –A2 reference montage placement.

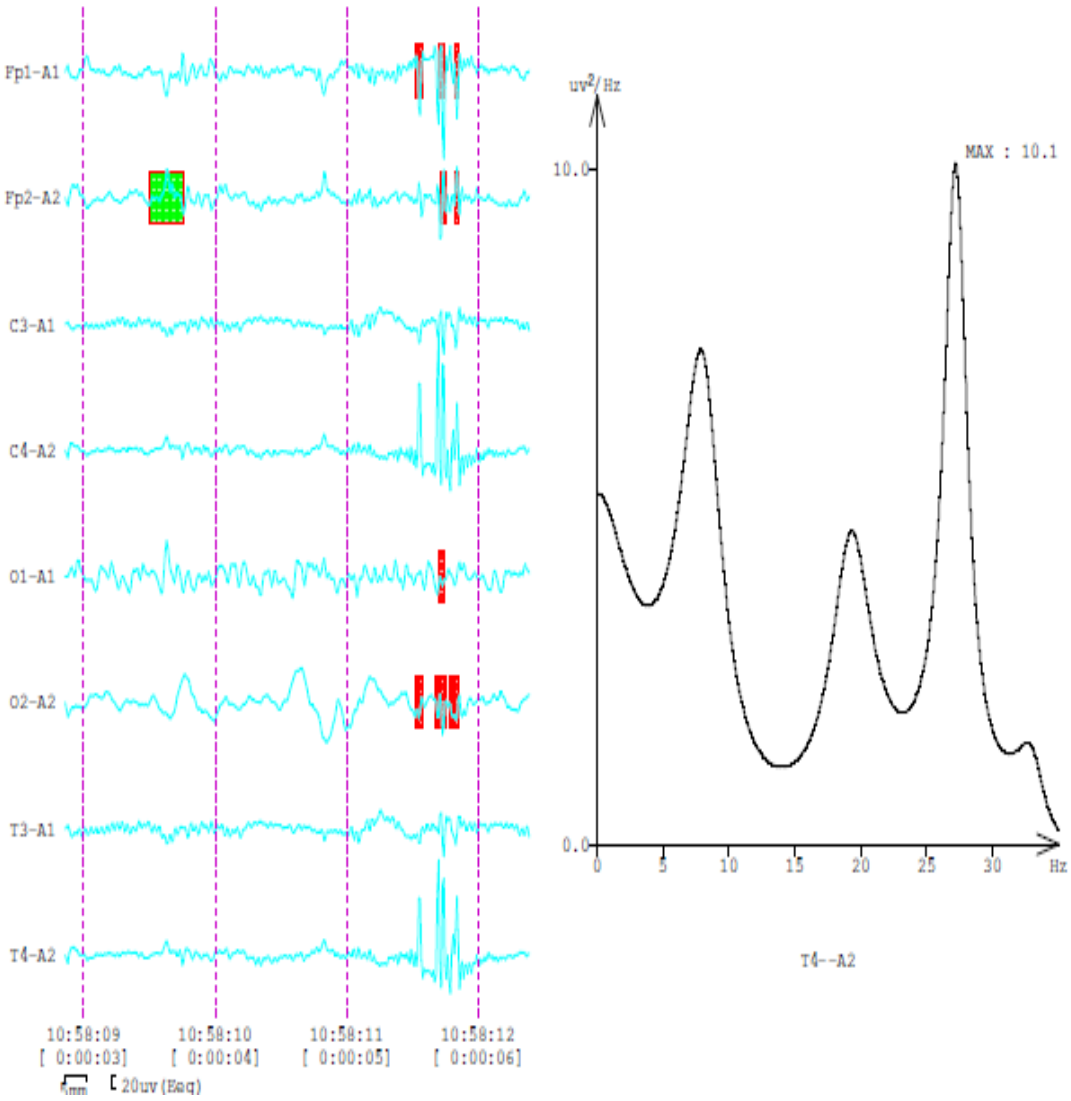


Fig 4.43: Power spectrum graph of ketoprofen treated group at intra surgery incision period, Note the T4-A2 graph pattern.

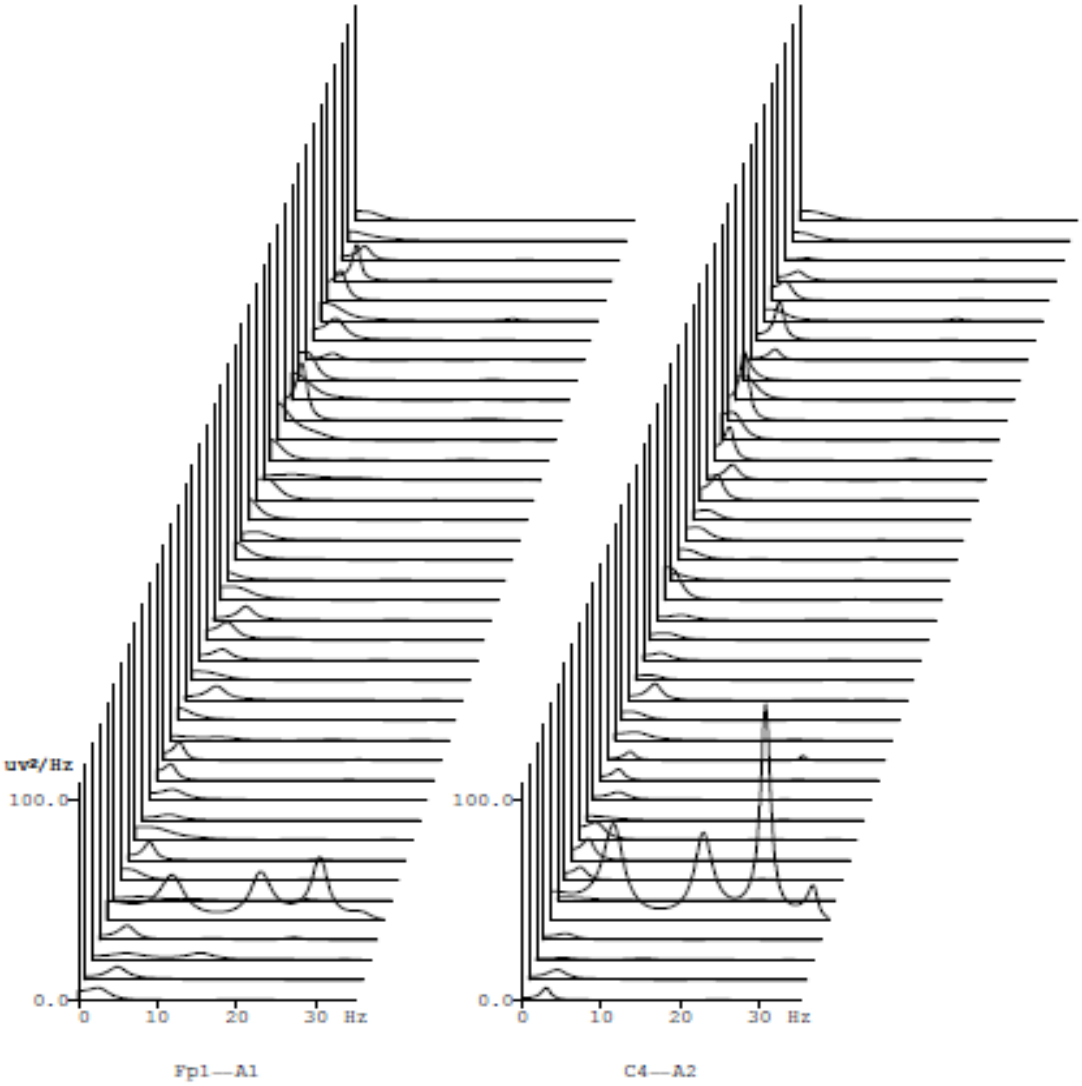


Fig. 4.44: Compression spectrum graph of tramadol/paracetamol treated group at resting period, Note the FP1-A1 and C4-A2 graph pattern.

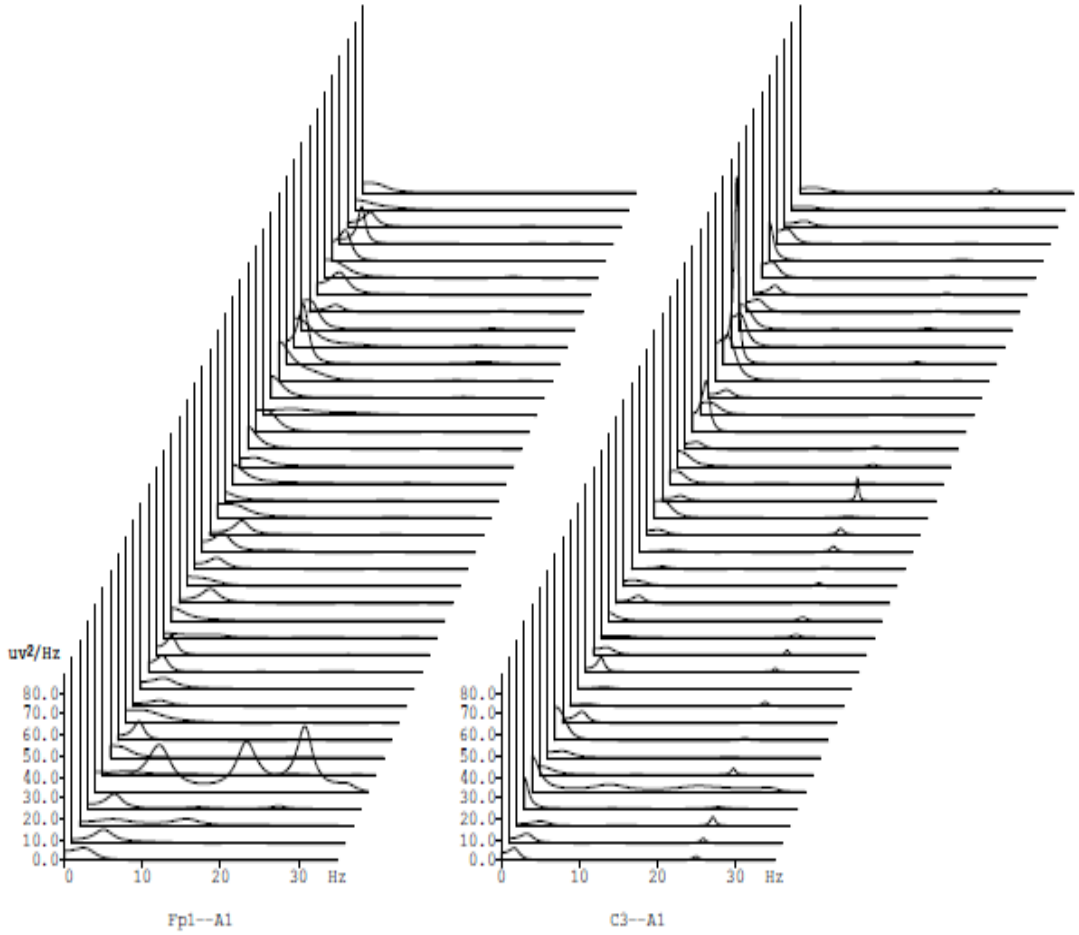


Fig. 4.45: Compression spectrum graph of tramadol/paracetamol treated group at intra surgical incision period, Note the FP1-A1 and C3-A1 graph pattern.

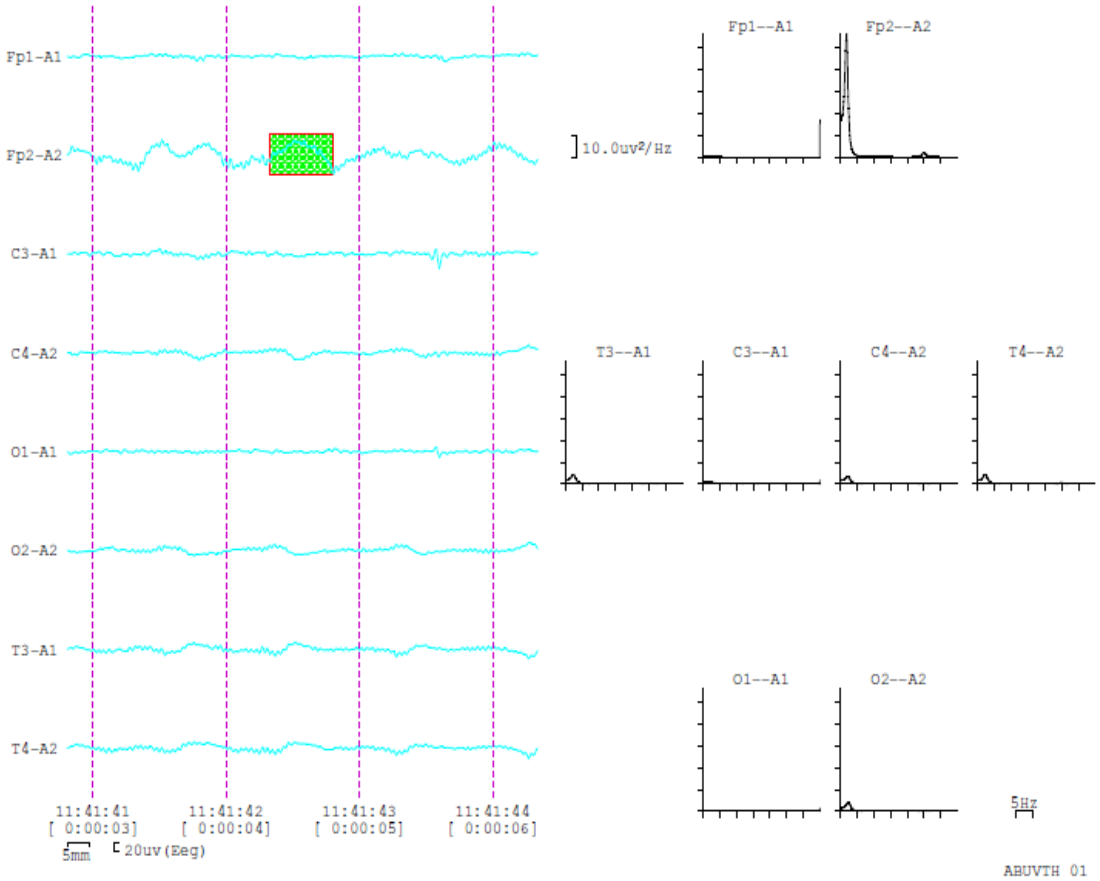


Fig. 4.46: Power spectrum graph for morphine treated group at the anesthetized presurgical stage.

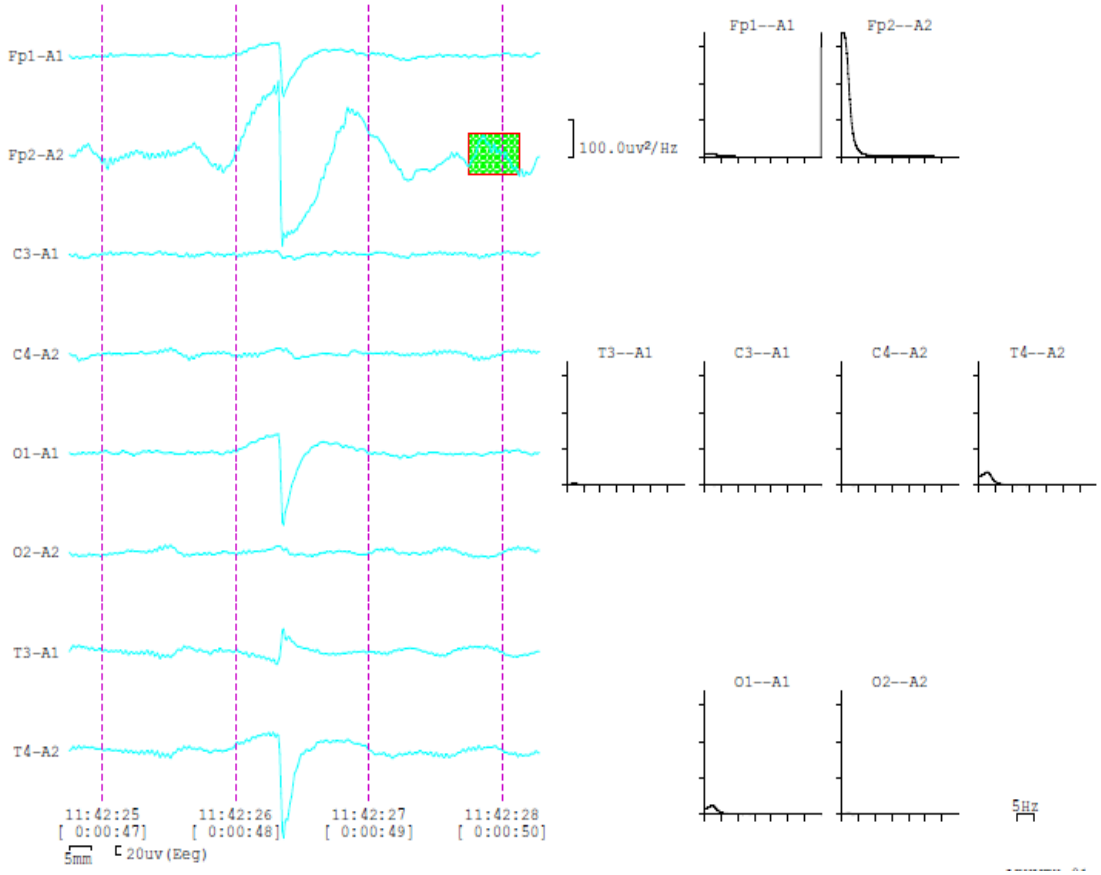


Fig. 4.47: Power spectrum graph for morphine treated group at the anesthetizedsurgical incision stage.

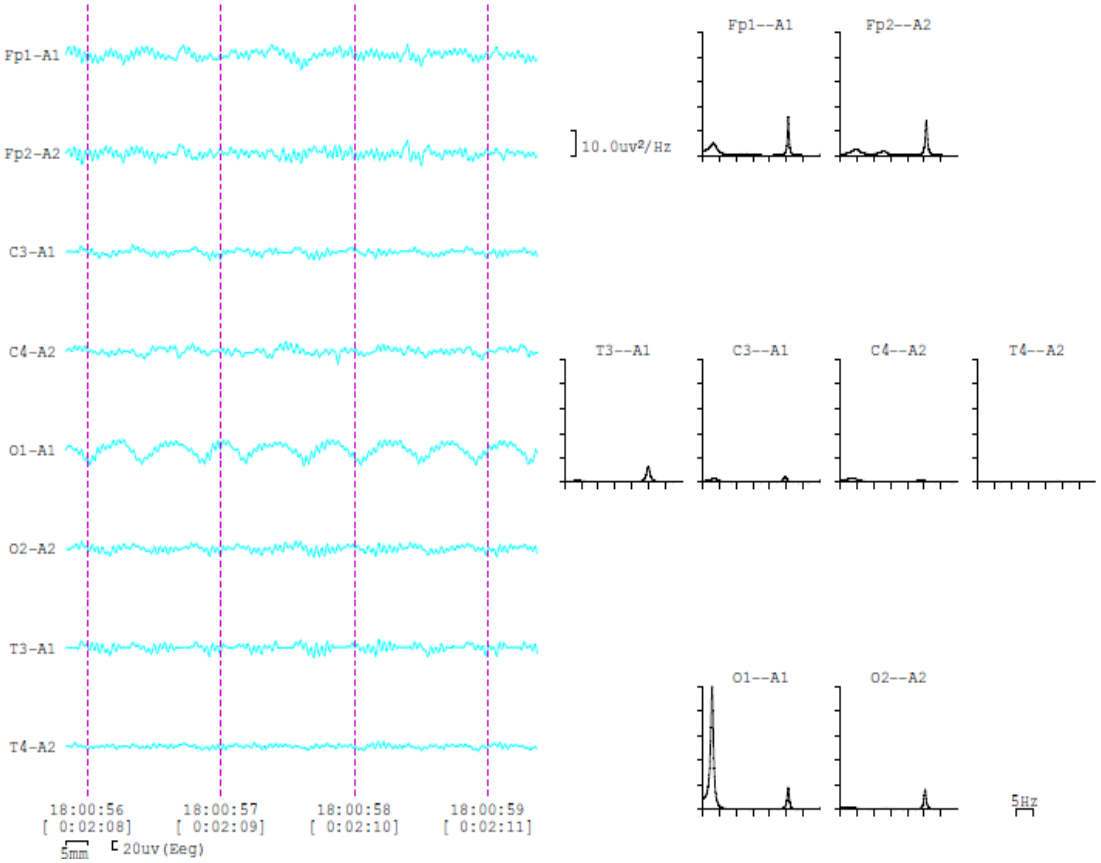


Fig. 4.48: Power spectrum graph for morphine and ketoprofen combination treated group at the anesthetized presurgical stage.

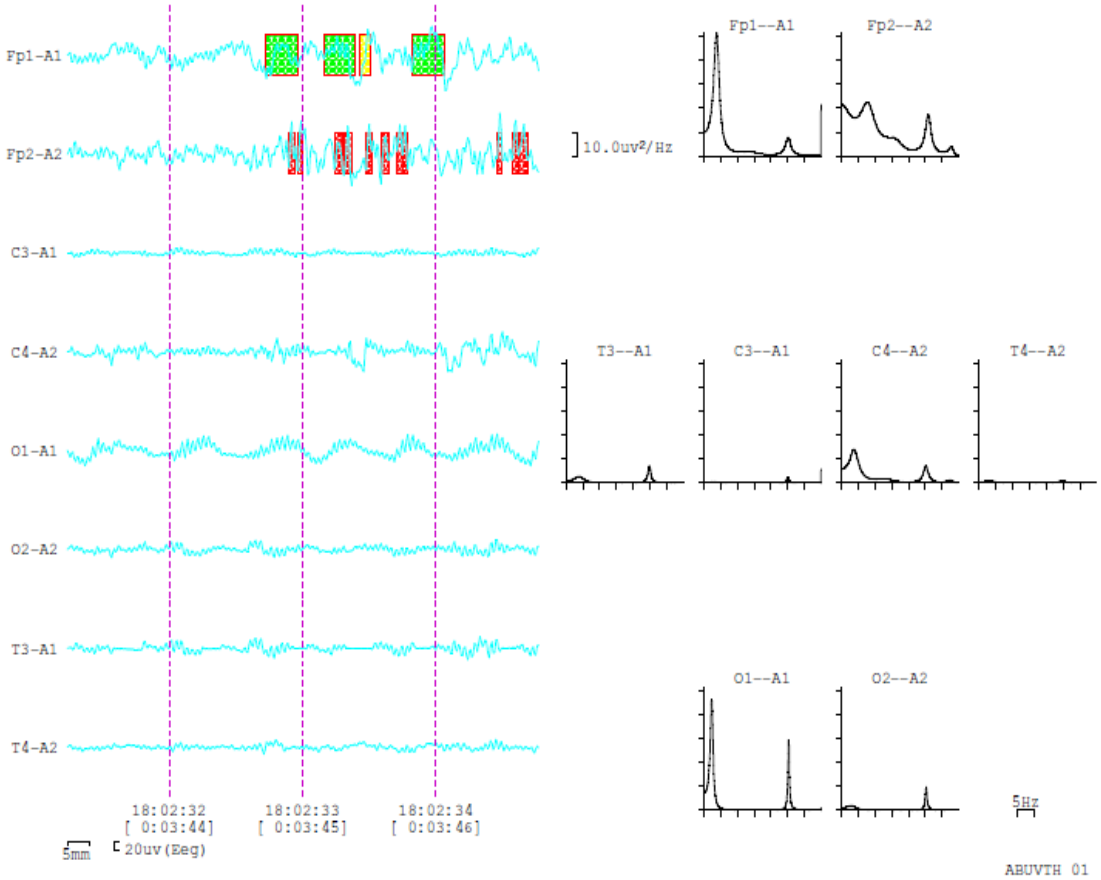


Fig. 4.49: Power spectrum graph for morphine and ketoprofen combination treated group at the anesthetized surgical incision stage.

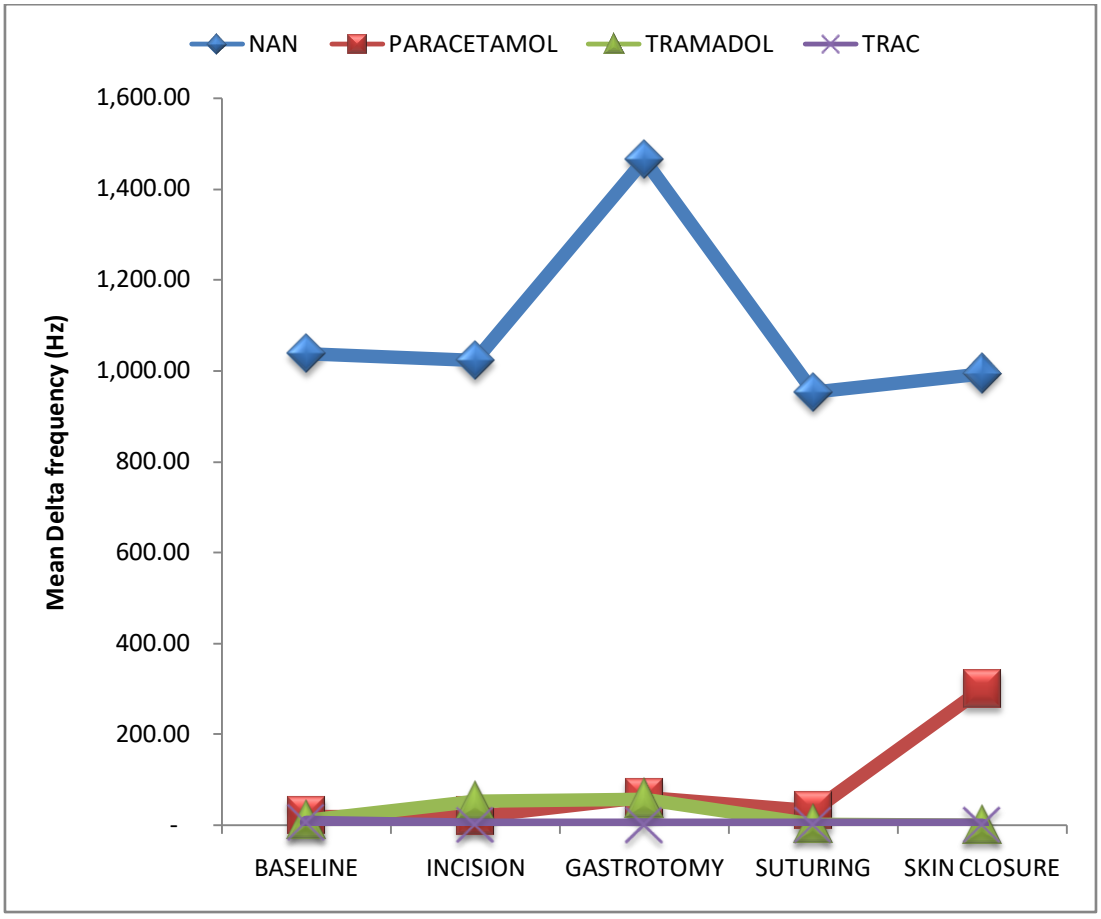


Fig. 4.50: Mean Delta wave frequency pattern of the cerebral cortex and frontal lobes of the in the experimental dogs for the non-analgesic (NAN), Paracetamol, Tramadol and the tramadol/ paracetamol combination therapy

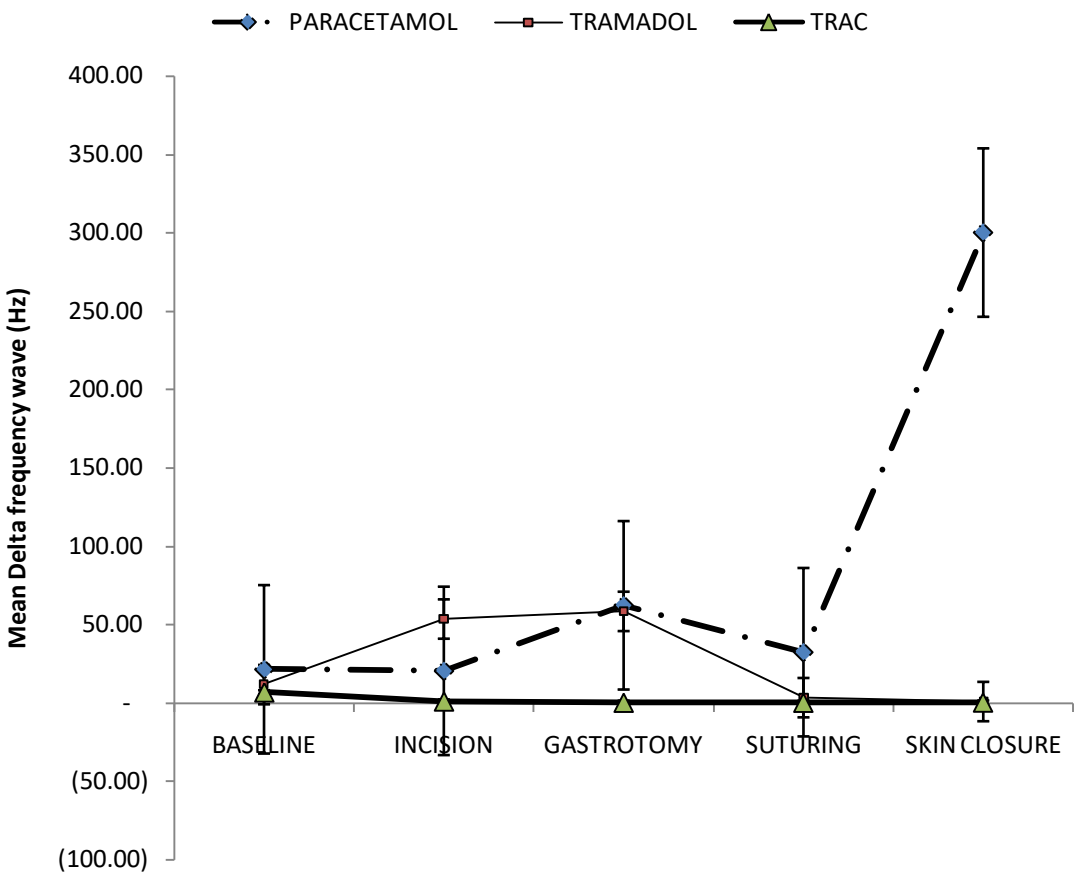


Fig. 4.51: Mean Delta wave frequency pattern of the cerebral cortex and frontal lobes of the in the experimental dogs for the paracetamol (ACE), tramadol (TRA) and the combination of tramadol and paracetamol (TRAC) combination.

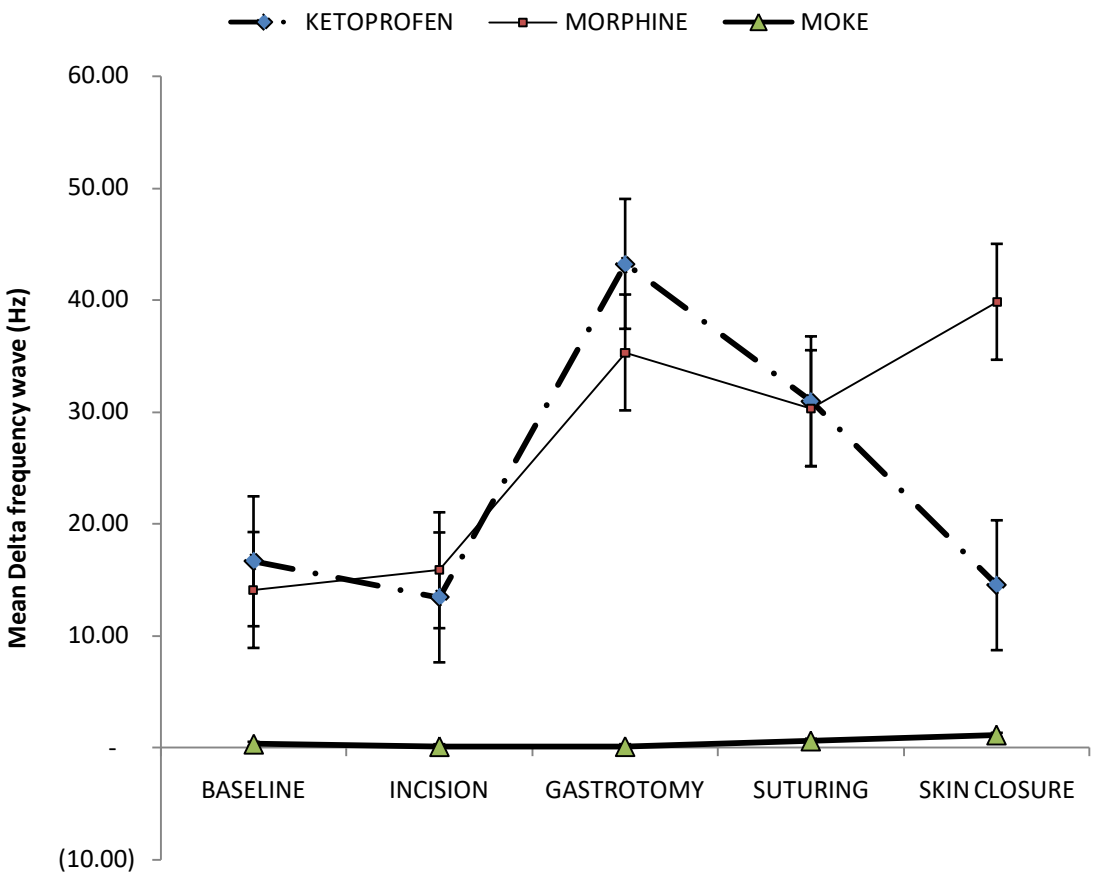


Fig. 4.52: Mean Delta wave frequency pattern of the cerebral cortex and frontal lobes of the in the experimental dogs for the ketoprofen, morphine and morphine and ketoprofen combination therapy

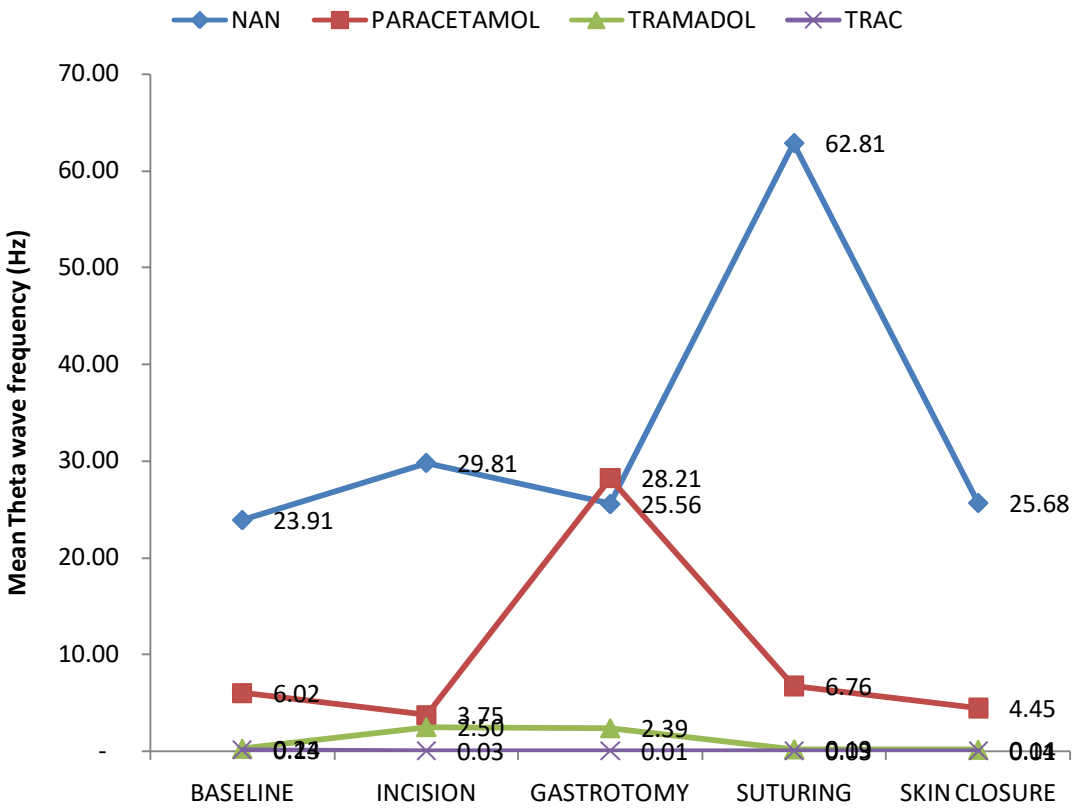


Fig. 4.53: Mean Theta wave frequency pattern of the cerebral cortex and frontal lobes of the in the experimental dogs for the non-analgesic (NAN), Paracetamol, Tramadol and the tramadol/ paracetamol combination therapy

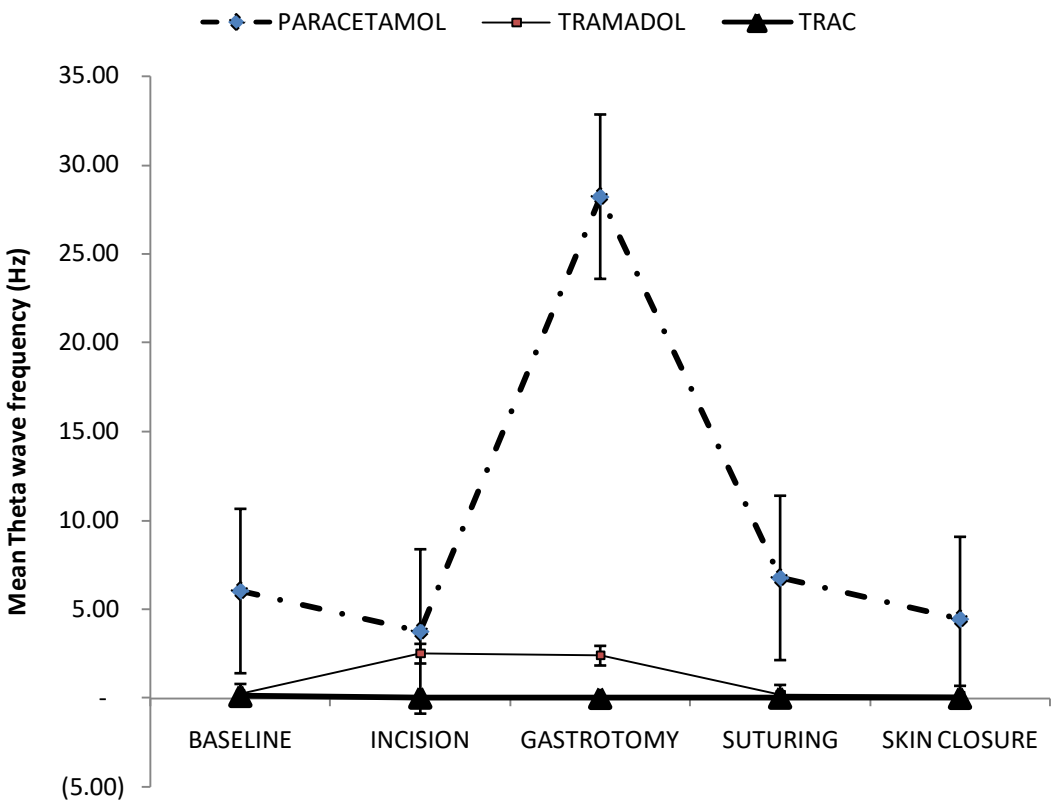


Fig. 4.54: Mean Theta wave frequency pattern of the cerebral cortex and frontal lobes of the in the experimental dogs for the paracetamol, tramadol and the tramadol/ paracetamol combination therapy

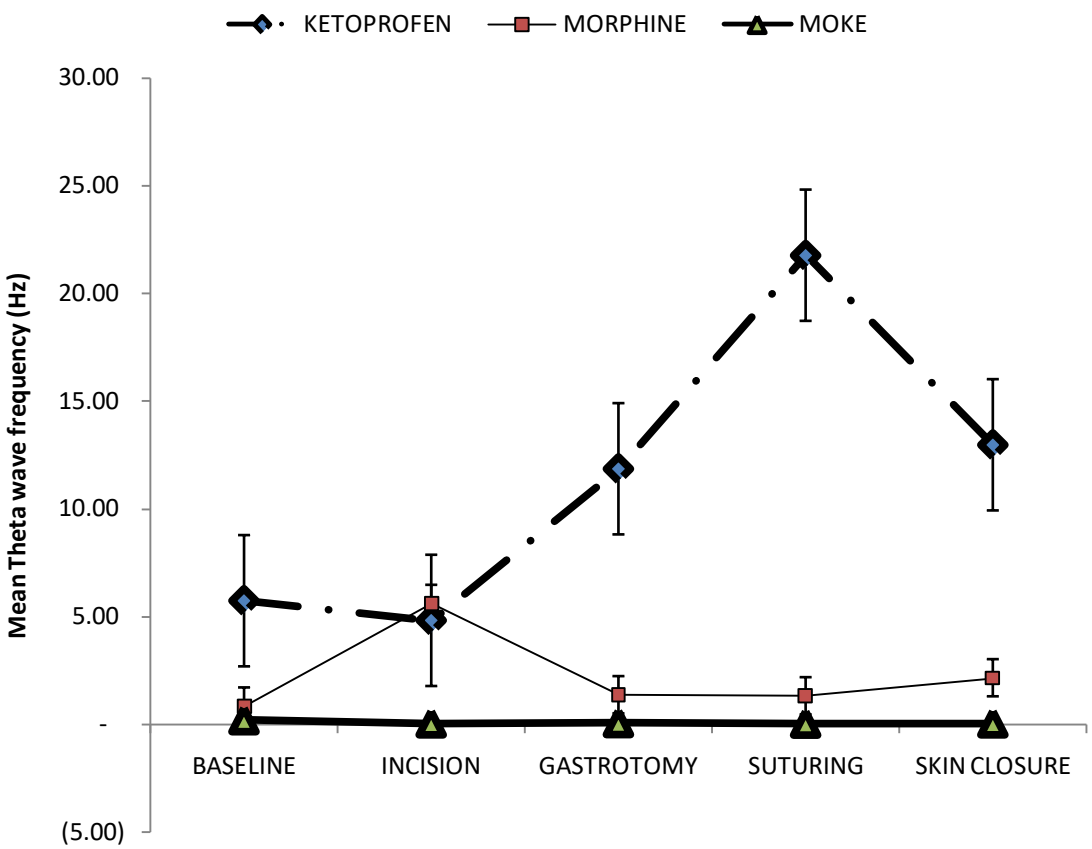


Fig. 4.55: Mean Theta wave frequency pattern of the cerebral cortex and frontal lobes of the in the experimental dogs for the ketoprofen, morphine and the ketoprofen/morphine combination therapy.

CHAPTER FIVE

DISCUSSION

Pain control is an important part of peri-operative patient care (Breivik 1998). Cyclooxygenase (COX) inhibitors and opioids are agents often used in post-operative pain management(Bennett *et al.,* 2003). Many studies have reported the use of injectable cyclooxygenase (COX) inhibitors and other analgesic as effective but they have been accompanied by numerous side effects in both human and animals (Süleyman*et al.,* 2007). This days the use of multimodal analgesic therapies are been advocated (Bennett *et al.,* 2003). This study compares the efficacy of the single administration of paracetamol, ketoprofen, tramadol and morphine and the multimodaltherapy of tramadol/paracetamol and morphine/ketoprofen.

The reliability of the virtual analogue scale (VAS) when compared to the numeric analogue scale in pain assessment in small animals is high andresearch points to the fact that the result so derived could be reproducible (Holton *et al*., 1998; Bijur*et al.,* 2001). When the virtual analogue scale (VAS) was used, it was noted that there was significant ($P< 0.05$) efficacy observed in the analgesic treated groups as compared to the group that was not treated with analgesic.Single drug therapy of dogs treated with tramadol and with paracetamoldid not show a significant difference in the pain intensity.Similar results were reported byPerrot*et al.,* (2006). The multimodal administration of tramadol and paracetamol in this study was significantly ($P< 0.05$) lower in the pain score this is similar to the result obtained by McClellan and Scott (2003) when the administered these drugs to human patients with chronic and acute pain conditions. The multimodal administration of paracetamol and tramadol in human had also been reported (Bennett *et al.*, 2003; Schnitzer, 2003; Dhillon, 2010).The combination has the advantages of better tolerability and lower hepato-toxic when compared to tramadol and paracetamol alone

(Schnitzer, 2003).Also the risks of patient developing gastro intestinal and cardiovascular crises as seen in COX inhibitors are minimized (Dhillon, 2010).

Similarly, single intramuscular administration of ketoprofen and morphine gave results that were not significantly different when compared to the multimodal therapy of morphine and ketoprofen. Ketoprofen is a COX II agent which has a rapid unset of action (30min) when administered intramuscularly and peak effect at 1 to 2 hours.Like the other NSAIDs, it has the potential risk of hypersensitivity reactions, nephrotoxicity, hepatotoxicity and gastrointestinal complications,while morphine administration alone. The multimodal therapy of the two drugs at lower doses results in reduced pain intensity and absence of the attendant side effects which is similar to the findings of Hanna (2003).

While physiological parameters alone might not be adequate to assess pain in human (Nancy *et al.*,2008), in veterinary practice however, there are varied opinion on the use of physiologic parameters.Additional employment of biochemical analysis and evaluation of pain threshold through the virtual analogue scaleare veritable tools in the assessment of pain (Matičić *et al.*,2010).This concept agrees largely with the values we obtained in our study.

Paracetamol single dose therapy though comparable to the non-treatment group exhibited significant reduction in rectal temperature when compared to the non-treatment group.There was also increase in the respiratory rates, blood pressure, heart rate and the saturation of peripheral oxygen (SPO2) of the body but the changes in these data were not statistically significant, especially when compared with the other drugs

that were used. Other research work also corroborates the antipyretic activities of this drug (Schuitmaker*et al.,* 1999).

The respiratory rate in the paracetamol administered increased significantly when compared to the other treatment groups.A similareffect was also reported by Satav and Bhattacharya, (1997) when they administered paracetamol to rats.They attributed this to the effect of this drug on the respiratory function of the kidney mitochondria.It was further postulated that paracetamol bound to the surface of the mitochondrial protein covalently (Zezi, 2006).

Tramadol, a weak synthetic opioid has a dual mechanism of action as a serotonin and as a norepinephrine reuptake inhibitor (Li*et al.,* 2011). However there was no significant increase or depression of the heart rate when compared to both the non-treatment group and paracetamol treated group. A similarreportabout its effect on the heart rate was madeby Natalini and Robinson(2003) where they mentioned that tramadol does not have any effect on the heart rate.Tramadol does not significantly change the respiratory rate and saturated oxygen concentration, but the significant changes observed in the rectal temperature and the blood pressure were similar to the findings of Yoshimi, *et al.*(2010) where they observed a decrease in blood pressure in rat models treated for arthritis with tramadol and the animal exhibited significant increase in their pain threshold (Poulsen *et al.,* 1996).

The change in rectal temperature, saturated oxygen pressure, mean arterial pressure (MAP) and the respiratory rates was not significant for ketoprofen dog treatment group. The multimodal therapy of tramadol and paracetamol on the other hand showed a significant decrease in the mean arterial pressure as well as the rectal temperature. The

multimodal therapy of morphine and ketoprofen produced better analgesia with a significant decrease in the values obtained for respiration, MAP, and rectal temperature when the single drug administration is compared to its use as multimodal therapy. This combination however gives a relatively stable respiratory rate as compared to the single drug administration.

For most of the time during monitoring of the experimental dogs, there were normal ECG tracing pattern for all the drugs either administered singly or in combination.However, immediately after drug administration or when surgical pain is inflicted through incision or suturing some abnormal tracings were noticed.

When paracetamol was administered at therapeutic doses used in this study, there was normal cardiac sinus tracing. Similar report had been observed by Jaques-Robinson *et al*.(2008) where they noticed that paracetamol hadcardio-protective againstproperties hydrogen peroxide in the cardiac myocardium which could be responsible for the normal tracings observed.Merrill *et al*.(2007) also reported the anti-arrhythmic properties of paracetamol. In addition,Rork *et al*.(2004) observed thatthe myocardium of the guinea pigs heart was easily re-perfused even when ischemia was induced when paracetamol was administered, all these agreed with the findings in this study.

Tramadol gave a normal ECG sinus tracing for most part of this study except at surgical incision. The present study observed a significant increase in the T - wave amplitude, unlike Raina*et al*., (2008), who revealed a significant decrease in the T - wave amplitude.The reason for the variation observed could be based on the difference in the species used in study,while theyusedgoats fortheir study, the present study used dogs. Furthermore in this study, the P wave and the QRS wave amplitudes observedwere similar to those seen by Shipton et al. (2003) and Choi et al.(2011) this effect was as a result of the sodium and potassium channel blockage of the myocardia muscles. The

sinus tracing observed for anaesthetized dogs in this study also showed muscular tremors and similar result was reported by Zahedi, (2004) where he studied the comparison between pethidine and tramadol in human cataract conditions.

The administration of Ketoprofen revealed a transient electrical altenans. A similar result was obtained by Kockskamper and Blatter (2002).This effect is as a result of the transient delay in Ca^{2+} ion inflow which resulted in changes in the ventricular electrical axis thus leading to the narrowing of the AV junctional and re-enterant tachycardia (Kockskamper and Blatter, 2002). In spite of this, ketoprofen is fast becoming the drug of choice in the management of acute and chronic pain either as a single drug or multimodal drug administration. The administration of Morphine and morphine/ ketoprofen combination also gave an initial alternans tracing similar to that seen in the ketoprofen treated group only, and when they had been stabilized due to the uniform distribution of the drug in the body system, the ECG sinus tracing also stabilized with only sporadic episodes of muscular tremors.

It was observed that in all treatment groups, there were relative decreasesin the serum cortisol levels with the decreasesignificantly more in tramadol, paracetamol and morphine/ketoprofen drug treatment groups.It is surprising however, that the single administration of morphine and ketoprofen study groups did not show any significant decrease in the cortisol serum levels. Earley and Crowe(2002) while evaluating the effect of ketoprofen and ketoprofen in combination with local anaesthetic noticed a decrease in plasma cortisol level in calves that were surgically castrated and thus concluded that ketoprofen was capable of modulating the serum cortisol level.The difference in the current finding could be as a result of interspecies differences.

The serum urea levels for the drugs were evaluated to determine renal clearance and possible renal toxicity. In the current study none of the experimental dogs treated with the different analgesic exceeded the normal range of serum ureavalues. Itwas however observed that tramadol had a significant post-surgical renal clearance of urea after 45 minutes of its administration. Other treatment groups such as paracetamol, multimodal therapy of tramadol and paracetamol and the multimodal therapy of morphine and ketoprofen exhibited insignificant ($P < 0.05$)increased serum urea levels in both the pre and 45 minutes post-surgical periods. Immer *et al.*, (2003) observed a short-lastingelevation of serum urea level in tramadol, this slight elevation however returned to normalwithin four days. If samples were taken for a longer period of time it is possible that the values obtained would have been reversed to normal just as it was reported by Immer *et al.*(2003). Earlier report by El-Gaafarawi, (2006) also reiterated the effect of prolonged use of tramadol on the hepatic, renal toxicity and the possible sexual dysfunction this drug could cause. This may not however be relevant to single use of the drug.

This study demonstrated that basic serum electrolytes such as sodium, ionized calcium blood pH and serum anion gap were not significantly affected in all the drugs evaluated except in paracetamol which showed a significant difference in the serum sodium level. Serum potassium levels were also affected in morphine, the combination therapy of morphine and ketoprofen and the combination of tramadol and paracetamol. In most of the drugs used the potassium level remained within the normal range. It was also observed that there was actually lowered serum potassium which indicated that there was some degree of renal involvement which may not be toxic if these drugs were

administered at their therapeutic doses but could be toxic when administered at doses above the normal therapeutic doses. This result is in consonance with earlier reports byPakravan *et al*.(2004) and Anderson and Day (2008).Further to this Pakravan *et al*.(2007) while evaluating the dose dependent effect of paracetamol on renal function noticedincreased serum paracetamol concentration and decrease serum potassium concentration. Also revealed in this study was no significant difference in the serum chloride level that is seen in the group that was treated with a multimodal therapy of morphine and ketoprofen (Krummel *et al.*, 2000).Apart from this all the other treatments did not give any significant effect on the serum chloride, as earlier reported by Kinjavdekar *et al.* (2000).

Inthe current study,brain activities over the somatosensory cortex were evaluated using the power spectrum, beam spectrum and compressed spectra mapping of the EEG.Recordings for pain modulated effects on dogs tested with some analgesics and compared with dogs that were not administered with any of the drugs. Filters were also applied to eliminate artefact that may arise during the course of the recording.

The negative control group showed evidence that there were pain sensation noticed especially in the alpha and much more on the delta waves with evidence much of the pain sensation were noticed in the thalamus and the cerebral cortex. Higher alpha spikes in the thalamus and the cortical brain section were noticed in the paracetamol treament groups, this could be as a result of the toxicity of this drug as it may have some effect on the brain cells, Poirier*et al*.(2008)also reported a similar case in profuse transcriptional de-regulation of the retrosplenial cortex.

Groups that were treated with ketoprofen indicated stability in the effect of the drug on the compressed spectral graph.However greater activities with multiple frequency

revealing spikes between the cortical region with highs at the 10, 20 and 30Hz was noticed during incision and suturing of the wounds.This was also observed at the fronto-parietal region with similar spikes. The power spectrum graph in addition were observed for activities at the right temporal region of the brain.

Tramadol on the other hand only showed a single frequency spike very close to the 0Hz frequency line on the compressed spectrum recording indicating dull pain sensation around the right cortical region which is even lesser on the left. In almost all treatment, there weremore activation of cell that assembles on the right cortical and fronto-perietal region than on the left which is in agreement with the result obtained by Sitges *et al.*(2010) where the analysis of fractal dimension revealed significantly higher values at P4 than P3 when pain patients were viewing unpleasant pictures.

Technological advances increased ability of encephalography to read brain activity data from the entire head simultaneously (Todor *et al.*, 2000). Quantitative EEG (qEEG) applies multi-channel measurements that can better determine spatial structures and localize areas with brain activity or abnormality. The qEEG evaluation revealed that the multi-drug administration of morphine and ketoprofen and tramadol and paracetamol manifested a stable delta and theta response to nociceptive stimuli perioperatively. This is evidenced in the stability seen during incision, suturing and rest periods in the surgery.

CHAPTER SIX

6. 1. CONCLUSION AND RECOMMENDATIONS

This work has used behaviour, physiologic, serologic parameters and electroencephalogram toevaluate the effect of single drug administration of paracetamol, ketoprofen and single drug administration of tramadol and morphine (opioid) as perioperative analgesics in dogs.

Neither the opioids, COX inhibitors nor the combination drugs have significant effects on SPO2, serum calcium, chloride, blood pH and serum anion gap (AG).

a. Paracetamol and ketoprofen produce tremendous analgesia but not as much as that of the opioids.
b. Ketoprofen is safer and produced a better result but not readily available in the market. Tramadol though may not be as effective as the morphine, it is more available in the market because it is not a controlled drug and is a ready substitute for morphine in perioperative surgical pain.
c. The combination of low dose opioids as pre-operative and reduced dose of COX inhibitors as intraoperative and post-operative analgesics produced smoother, longer and better analgesia with reduced side effects of both drugs than the single administration of these drugs in gastrotomy of the dogs.
d. Tramadol (15mg/kg) / paracetamol (0.5mg/kg) combination showed superior efficacy to that of morphine (0.1mg/kg) /ketoprofen (20mg/kg) in dogs during gastrotomy.
e. The EEG and the qEEG give early detection of analgesia and pathology in patients under anaesthesia and can aid in early intervention on surgical risk patients.

f. Perioperative administration of paracetamol and ketoprofen cannot completely abolish the afferent nociceptive transmission to the extent of morphine and better still the multimodal therapy of morphine-ketoprofen combination and tramadol paracetamol combination, in response to a standard electrical stimulus to become a useful tool for measuring anti-nociceptive efficacy. EEG needs however, a stable plane of anaesthesia.

6. 2. RECOMMENDATIONS

While this study evaluated the efficacy of some selected COX inhibitors and opioids as single and multi-drug and administration perioperatively for 72 hours using various indices as parameter to evaluate their efficacy, furtherresearch work needs to be done in the following areas:

i. There is need to re-evaluate the long-term use and toxicity of these drugs monitored over a period of one month or more though the measurement of BUN and possibly organ biopsy.

ii. There is need to commit a larger dog population to investigate the efficacy of these analgesics administered in different dose rates and times of surgery, for optimal postoperative analgesia.

iii. Other biomarkers such as blood glucose may also be explored.

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Appendix

Appendix I: Sample of the Pain evaluation form

AHMADU BELLO UNIVERSITY
DEPARTMENT OF VETERINARY SURGERY AND RADIOLOGY, SMALL ANIMAL UNIT
PAIN EVALUATION CHART – DOGS

Patient name:	*Case number:*
Analgesic(s) used:	Date:

Please tick the answer that you feel is appropriate to the dog you are assessing. From outside the kennel, look at the dog's behaviour and answer the following questions.

	ASSESSMENT CRITERIAS	LOW	MILD	SEVERE
1.	**Look at the dog's posture, does it seem…**			
	Rigid			
	Hunched or Tense			
	Neither of these			
2.	**Does the dog seem to be…**			
	Restless			
	Settled			
3.	**If the dog is vocalising, is it…**			
	Screaming			
	Groaning			
	Crying or whimpering			
	Not vocalising/none of these			
4.	**Look at the dog's chart, has it…**			
	Not eaten anything			
	Picked at its food			
	Eaten well			
5.	**If the dog is paying/trying to pay attention to its wound (even if it has a collar on), is it…**			
	Chewing			
	Licking			
	looking			
	Rubbing			
	Ignoring the wound			
6.	**Does the dog seem to be…**			
	Aggressive			
	Depressed			
	Disinterested			
	Nervous, anxious or fearful			
	Quiet or indifferent			
	Happy and content			
	Happy and bouncy			
7.	**During this procedure did the dog seem to be…**			
	Stiff			
	Slow/reluctant to rise or sit			
	Lame			
	None of these			
	Assessment not carried out			
8.	**When touched did the dog…**			
	Snap			
	Growl or guard the area			
	Cry			
	Flinch/become tense			
	Look round sharply			
	None of these			
9.	**In your opinion, would you classify the dog as…**			
	Painful			

	Uncomfortable			
	Comfortable			
GENERAL COMMENTS:				

Appendix II: Sample of the surgical consent form

Veterinary Surgical Consent Form

AHMADU BELLO UNIVERSITY VETERINARY TEACHING HOSPITAL

Your pet should not have any food after 8 pm the night before surgery.
A little water is okay.

Owner's Name_____

Pet's Name_____ Age_____

Scheduled Procedure _____Date_____

Drop Off Time_____
IS YOUR PET ON ANY SUPPLEMENTS? PLEASE INFORM US OF ANY and ALL SUPPLEMENTS._____

Pre-Anaesthetic Blood Testing: Our greatest concern is the wellbeing of your pet. We will be using a multi-parameter patient monitoring your pet during surgery. This technology along with pre-anaesthetic blood screening reduces many of the risks of surgery. Before putting your pet under anaesthesia, we recommend pre-anaesthesia blood work. Many conditions including disorders of the liver, kidneys and blood may not be detected unless blood testing is performed. For these reasons, we strongly recommend that all patients receive blood work before such procedures. ***Mandatory blood work is required for all animals of all ages.*** The total cost of these tests: N_____

☐ **Yes,** I want my pet to have a blood test performed before anaesthesia

☐ **No,** I decline this blood test and **have been informed of the risks**

Pain Management: While undergoing and after surgery, your pet will receive a pain injection. In most cases that injection will not have long lasting effects. Additional pain medication can effectively control your pets discomfort during the recovery at home and aid in your pet's recovery. **Specific procedures, such as cat declaws can be very painful and take home pain medication will be sent home automatically.**

☐ I'm not sure, please allow Dr to suggest if my pet needs it

☐ **Yes,** I want my pet to take pain medication home. ☐ **No,** I decline pain medication

Misc. Services: While your pet is under anaesthesia, we are able to perform many convenient procedures such as nail trims, general ear cleaning or vaccinations.

☐ **Yes,** I want my pet's nails trimmed ☐ **Yes,** Clean my pets ears ☐ **Yes,** update vaccines

Elizabethan Collar: To ensure that your pet will not chew or licks open a new surgical site, please prepare N200.00 to purchase a modified Elizabethan collar. This small investment could save you the added cost to have the site repaired.

☐ **Yes,** please purchase one collar for me ☐ **No,** I will buy one collar by myself.

I, being responsible for the above animal, have the authority to grant you my consent to receive treatment, prescribe for and or operate upon my pet as noted above. You are to use all responsible precautions against injury, escape or death of my pet, but you will not be held liable or responsible in any matter, as I thoroughly understand I assume all risks. I agree to pay for in full for the services rendered.

Client Signature _____Date_____
In case of an emergency where can we reach you?

Phone _____Cell_____

Appendix III**:** Paired sample T test for visual analogue pain score for paracetamol, tramadol and paracetamol/tramadol drug combination therapy

Paired Samples Test

Time (hours)			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
						Lower	Upper			
-1.00	Pair 1	NAN - ACE	1.53250	.33049	.16525	1.00661	2.05839	9.274	3	.003
	Pair 2	NAN - TRA	1.59500	.40137	.20069	.95633	2.23367	7.948	3	.004
	Pair 3	NAN - TRAC	1.62500	.42477	.21239	.94909	2.30091	7.651	3	.005
0.50	Pair 1	NAN - ACE	2.55250	.34490	.17245	2.00368	3.10132	14.801	3	.001
	Pair 2	NAN - TRA	2.55250	.34490	.17245	2.00368	3.10132	14.801	3	.001
	Pair 3	NAN - TRAC	2.46000	.30800	.15400	1.96990	2.95010	15.974	3	.001
2.00	Pair 1	NAN - ACE	3.16750	.53587	.26794	2.31481	4.02019	11.822	3	.001
	Pair 2	NAN - TRA	3.99750	.52073	.26036	3.16890	4.82610	15.353	3	.001
	Pair 3	NAN - TRAC	4.26000	.37974	.18987	3.65575	4.86425	22.437	3	.000
4.00	Pair 1	NAN - ACE	2.64500	1.33902	.66951	.51433	4.77567	3.951	3	.029
	Pair 2	NAN - TRA	4.16750	.75734	.37867	2.96241	5.37259	11.006	3	.002
	Pair 3	NAN - TRAC	4.60500	.69983	.34992	3.49141	5.71859	13.160	3	.001
6.00	Pair 1	NAN - ACE	3.03250	.99864	.49932	1.44343	4.62157	6.073	3	.009
	Pair 2	NAN - TRA	4.44000	.77602	.38801	3.20519	5.67481	11.443	3	.001
	Pair 3	NAN - TRAC	4.95250	.69916	.34958	3.83998	6.06502	14.167	3	.001
24.00	Pair 1	NAN - ACE	4.63750	.41844	.20922	3.97167	5.30333	22.166	3	.000
	Pair 2	NAN - TRA	4.70000	.36414	.18207	4.12057	5.27943	25.814	3	.000
	Pair 3	NAN - TRAC	5.01250	.59724	.29862	4.06216	5.96284	16.786	3	.000
48.00	Pair 1	NAN - ACE	4.89750	.35957	.17979	4.32534	5.46966	27.241	3	.000
	Pair 2	NAN - TRA	4.89750	.35957	.17979	4.32534	5.46966	27.241	3	.000
	Pair 3	NAN - TRAC	5.27000	.36120	.18060	4.69525	5.84475	29.180	3	.000

Appendix IV:One way analysis of variance (ANOVA) for rectal temperature showing p values

		Sum of Squares	df	Mean Square	F	Sig.
NAN	Between Groups	3.375	12	.281	.342	.976
	Within Groups	32.870	40	.822		
	Total	36.245	52			
ACE	Between Groups	20.422	12	1.702	12.435	.000
	Within Groups	5.474	40	.137		
	Total	25.897	52			
KET	Between Groups	6.026	12	.502	.726	.718
	Within Groups	27.668	40	.692		
	Total	33.693	52			
TRA	Between Groups	26.884	12	2.240	4.326	.000
	Within Groups	20.717	40	.518		
	Total	47.601	52			
MOR	Between Groups	10.336	12	.861	2.184	.032
	Within Groups	15.772	40	.394		
	Total	26.108	52			
TRAC	Between Groups	4.188	12	.349	18.382	.000
	Within Groups	.760	40	.019		
	Total	4.948	52			
MOKE	Between Groups	2.649	12	.221	18.867	.000
	Within Groups	.468	40	.012		
	Total	3.117	52			

Appendix V: Paired Samples Test

		Paired Differences					T	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	MOR - MOKE	.22000	.06708	.03000	.13671	.30329	7.333	4	.002
Pair 2	KET - MOKE	.26400	.08355	.03736	.16026	.36774	7.066	4	.002

Appendix VI: PairedSamples Correlations

		N	Correlation	Sig.
Pair 1	MOR and MOKE	5	.988	.002
Pair 2	KET and MOKE	5	.978	.004

Appendix VII: Paired Samples "T" Test for the pain scoring scale

		Paired Differences					T	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	TRA - TRAC	.25600	.10922	.04885	.12038	.39162	5.241	4	.006
Pair 2	ACE - TRAC	.32400	.16072	.07187	.12444	.52356	4.508	4	.011

Appendix VIII: Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	TRA and TRAC	5	.963	.008
Pair 2	ACEand TRAC	5	.943	.016

Appendix IX: Analysis of variance (ANOVA) for respiratory rate

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
NAN	Between Groups	9592.286	13	737.868	4.794	.000
	Within Groups	4309.333	28	153.905		
	Total	13901.619	41			
ACE	Between Groups	1375.167	13	105.782	5.940	.000
	Within Groups	498.667	28	17.810		
	Total	1873.833	41			
KET	Between Groups	228.667	13	17.590	.927	.539
	Within Groups	531.333	28	18.976		
	Total	760.000	41			
TRA	Between Groups	352.976	13	27.152	.402	.957
	Within Groups	1890.000	28	67.500		
	Total	2242.976	41			
MOR	Between Groups	1168.476	13	89.883	.859	.601
	Within Groups	2930.000	28	104.643		
	Total	4098.476	41			
TRAC	Between Groups	218.405	13	16.800	1.164	.353
	Within Groups	404.000	28	14.429		
	Total	622.405	41			
MOKE	Between Groups	52.952	13	4.073	.279	.991
	Within Groups	408.667	28	14.595		
	Total	461.619	41			

Appendix X:Means cortisol level in nmol/l for the various test groups.

DRUGS	**Time (Mins)**	
	0	**30**
NAN	2.50 ± 0.00	3.60 ± 0.27
ACE	2.67± 0.12	1.33± 0.12*
KET	3.23± 0.53	2.43 ±0.41
TRA	5.20± 0.00	2.67± 0.20*
MOR	5.17± 1.18	7.33± 0.24
MOKE	4.30± 0.69	2.35 ± 1.10*
TRAC	5.67± 0.60	4.03± 0.52

Note: The above results are Mean ±SEM. *Where values P≤ 0.05 and CI= 95%

Appendix XI: Analysis of variance (ANOVA) for serum cortisol evaluation

		Sum of Squares	df	Mean Square	F	Sig.
NAN	Between Groups	2.420	1	2.420	5.672	.055
	Within Groups	2.560	6	.427		
	Total	4.980	7			
ACE	Between Groups	3.556	1	3.556	64.000	.000
	Within Groups	.333	6	.056		
	Total	3.889	7			
KET	Between Groups	1.280	1	1.280	1.419	.279
	Within Groups	5.413	6	.902		
	Total	6.693	7			
TRA	Between Groups	14.580	1	14.580	174.960	.000
	Within Groups	.500	6	.083		
	Total	15.080	7			
MOR	Between Groups	9.389	1	9.389	3.250	.121
	Within Groups	17.333	6	2.889		
	Total	26.722	7			
TRAC	Between Groups	5.336	1	5.336	1.626	.249
	Within Groups	19.693	6	3.282		
	Total	25.029	7			
MOKE	Between Groups	7.605	1	7.605	6.064	.049
	Within Groups	7.525	6	1.254		
	Total	15.130	7			

Appendix XII:Paired Samples Student T Test for the Blood urea nitrogen (BUN) Test

Paired Samples Test

Drugs			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
						Lower	Upper			
ACE	Pair 1	Pre - Post surgical	.86667	3.15331	1.82056	-6.96658	8.69991	.476	2	.681
KET	Pair 1	Pre - Post surgical	.03333	1.65025	.95277	-4.06612	4.13279	.035	2	.975
TRA	Pair 1	Pre - Post surgical	.03333	.45092	.26034	-1.08683	1.15349	.128	2	.910
MOR	Pair 1	Pre - Post surgical	1.00000	1.15326	.66583	-1.86485	3.86485	1.502	2	.272
TRAC	Pair 1	Pre - Post surgical	.26667	.25166	.14530	-.35849	.89183	1.835	2	.208
MOKE	Pair 1	Pre - Post surgical	-.36667	.80829	.46667	-2.37457	1.64124	-.786	2	.514

Appendix XIII: Paired Samples Student T Test for the serum potassium (K^+) test

Drugs		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
ACE	Presurgical - Postsurgical	.07000	.10817	.06245	-.19870	.33870	1.121	2	.379
KET	Presurgical - Postsurgical	.56000	.68432	.39509	-1.13996	2.25996	1.417	2	.292
TRA	Presurgical - Postsurgical	.02000	.38000	.21939	-.92397	.96397	.091	2	.936
MOR	Presurgical - Postsurgical	-2.15667	.71059	.41026	-3.92186	-.39147	-5.257	2	.034[a]
TRAC	Presurgical - Postsurgical	-.60667	.76559	.44202	-2.50851	1.29517	-1.373	2	.304
MOKE	Presurgical - Postsurgical	-.65000	.15000	.08660	-1.02262	-.27738	-7.506	2	.017[a]

a. P≤0.05

Appendix XIV: Paired sample T test for serum Sodium level in the experimental dogs

Paired Samples Test

Time			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
						Lower	Upper			
ACE	Pair 1	Presurgical - Postsurgical	-3.75000	8.85000	5.10955	-25.73462	18.23462	-.734	2	.539
KET	Pair 1	Presurgical - Postsurgical	-4.20000	.65574	.37859	-5.82896	-2.57104	-11.094	2	.008[a]
TRA	Pair 1	Presurgical - Postsurgical	-5.23333	12.00014	6.92828	-35.04333	24.57666	-.755	2	.529
MOR	Pair 1	Presurgical - Postsurgical	2.28333	24.35438	14.06101	-58.21630	62.78297	.162	2	.886
TRAC	Pair 1	Presurgical - Postsurgical	.05000	5.75000	3.31976	-14.23379	14.33379	.015	2	.989
MOKE	Pair 1	Presurgical - Postsurgical	-2.50000	5.50000	3.17543	-16.16276	11.16276	-.787	2	.514

Appendix XV: Result of the paired sample T test for serum Chloride ions for the experimental groups

Time			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
						Lower	Upper			
ACE	Pair 1	Presurgery - Postsurgery	1.10000	2.10000	1.21244	-4.11669	6.31669	.907	2	.460
KET	Pair 1	Presurgery - Postsurgery	-6.66667	7.93242	4.57979	-26.37190	13.03856	-1.456	2	.283
TRA	Pair 1	Presurgery - Postsurgery	-2.00000	5.30000	3.05996	-15.16593	11.16593	-.654	2	.580
MOR	Pair 1	Presurgery - Postsurgery	4.00000	12.16511	7.02353	-26.21982	34.21982	.570	2	.626
TRAC	Pair 1	Presurgery - Postsurgery	.80000	3.50000	2.02073	-7.89448	9.49448	.396	2	.730
MOKE	Pair 1	Presurgery - Postsurgery	4.00000	3.00000	1.73205	-3.45241	11.45241	2.309	2	.147

Appendix XVI: Analysis of Variance (ANOVA) for ionized serum Calcium

		Sum of Squares	df	Mean Square	F	Sig.
Paracetamol	Between Groups	.034	1	.034	1.183	.390
	Within Groups	.058	2	.029		
	Total	.092	3			
Ketoprofen	Between Groups	.038	1	.038	.376	.602
	Within Groups	.202	2	.101		
	Total	.240	3			
Tramadol	Between Groups	.003	1	.003	1.389	.360
	Within Groups	.004	2	.002		
	Total	.006	3			
Morphine	Between Groups	.070	1	.070	1.376	.362
	Within Groups	.102	2	.051		
	Total	.172	3			
Tramadol+paracetamol	Between Groups	.000	1	.000	.000	1.000
	Within Groups	.119	2	.059		
	Total	.119	3			
Morphine+Ketoprofen	Between Groups	.010	1	.010	.573	.528
	Within Groups	.035	2	.017		
	Total	.045	3			

Appendix XVII: Paired student T test for ionized serum Calcium

Time			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
						Lower	Upper			
Paracetamol	Pair 1	Presurgical - Postsurgical	-.18500	.12021	.08500	-1.26503	.89503	-2.176	1	.274
KET	Pair 1	Presurgical - Postsurgical	.19500	.30406	.21500	-2.53683	2.92683	.907	1	.531
MOR	Pair 1	Presurgical - Postsurgical	.26500	.43134	.30500	-3.61039	4.14039	.869	1	.545
TRAC	Pair 1	Presurgical - Postsurgical	.00000	.14142	.10000	-1.27062	1.27062	.000	1	1.000
MOKE	Pair 1	Presurgical - Postsurgical	.10000	.07071	.05000	-.53531	.73531	2.000	1	.295

a. No statistics are computed for one or more split files

Appendix XVIII: Analysis of Variance (ANOVA) for serum pH

		Sum of Squares	df	Mean Square	F	Sig.
Paracetamol	Between Groups	.003	1	.003	.111	.771
	Within Groups	.054	2	.027		
	Total	.057	3			
Ketoprofen	Between Groups	.181	1	.181	.426	.581
	Within Groups	.847	2	.424		
	Total	1.028	3			
Tramadol	Between Groups	.011	1	.011	.073	.812
	Within Groups	.300	2	.150		
	Total	.311	3			
Morphine	Between Groups	.912	1	.912	1.918	.300
	Within Groups	.951	2	.476		
	Total	1.863	3			
Tramadol+paracetamol	Between Groups	.023	1	.023	9.000	.095
	Within Groups	.005	2	.003		
	Total	.028	3			
Morphine+Ketoprofen	Between Groups	.010	1	.010	2.000	.293
	Within Groups	.010	2	.005		
	Total	.020	3			

Appendix XIX: Paired sample T test (ANOVA) for serum pH

Drug			Paired Differences					t	df	Sig. (2-tailed)
			Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
						Lower	Upper			
ACE	Pair 1	Presurgical - Postsurgical	-.05500	.23335	.16500	-2.15152	2.04152	-.333	1	.795
KET	Pair 1	Presurgical - Postsurgical	-.42500	1.19501	.84500	-11.16174	10.31174	-.503	1	.703
TRA	Pair 1	Presurgical - Postsurgical	.10500	.64347	.45500	-5.67632	5.88632	.231	1	.856
MOR	Pair 1	Presurgical - Postsurgical	-.95500	1.12430	.79500	-11.05643	9.14643	-1.201	1	.442
TRAC	Pair 1	Presurgical - Postsurgical	-.15000	.07071	.05000	-.78531	.48531	-3.000	1	.205
MOKE	Pair 1	Presurgical - Postsurgical	-.10000	.14142	.10000	-1.37062	1.17062	-1.000	1	.500

Appendix XX: Analysis of Variance (ANOVA) for serum anion gap (AG)

		Sum of Squares	df	Mean Square	F	Sig.
Paracetamol	Between Groups	2.103	1	2.103	.388	.597
	Within Groups	10.825	2	5.412		
	Total	12.928	3			
Ketoprofen	Between Groups	5.063	1	5.063	1.163	.394
	Within Groups	8.705	2	4.353		
	Total	13.768	3			
Tamadol	Between Groups	1.823	1	1.823	.143	.742
	Within Groups	25.505	2	12.753		
	Total	27.328	3			
Morphine	Between Groups	68.063	1	68.063	.989	.425
	Within Groups	137.605	2	68.803		
	Total	205.668	3			
Tramadol+Paracetamol	Between Groups	20.703	1	20.703	1.361	.364
	Within Groups	30.425	2	15.212		
	Total	51.128	3			
Morphine+Ketoprofen	Between Groups	.490	1	.490	.097	.785
	Within Groups	10.090	2	5.045		
	Total	10.580	3			