THE EFFICIENCY OF PCSO-524 ON FELINE OSTEOARTHRITIS ASSOCIATED WITH CHRONIC KIDNEY DISEASE.

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A Thesis Submitted in Partial Fulfillment of the Requirements
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ประสิทธิภาพของพีซีเอสโอ-ห้าสองสี่ในแมวที่เป็นโรคข้อเสื่อมร่วมกับโรคไตเรื้อรัง

น.ส.เปมิกา ดุลยประพันธ์

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เปมิกา ดุลยประพันธ์ : ประสิทธิภาพของพีซีเอสโอ-ห้าสองสี่ในแมวที่เป็นโรคข้อเสื่อมร่วมกับโรคไตเรื้อรัง. (THE EFFICIENCY OF PCSO-524 ON FELINE OSTEOARTHRITIS ASSOCIATED WITH CHRONIC KIDNEY DISEASE.) อ.ที่ปรึกษาหลัก : กัมปนาท สุนทรวิภาต

การศึกษานี้ประกอบไปด้วยแมวที่เป็นโรคข้อเสื่อมร่วมกับโรคไตเรื้อรังจำนวน 26 ตัว แบ่งออกเป็น 2 กลุ่มได้แก่ กลุ่มควบคุม (12ตัว) ได้รับยาหลอก และ กลุ่มทดลอง (14ตัว) ได้รับพีซีเอสโอ-ห้าสองสี่ ต่อเนื่องกันเป็นเวลา 60 วัน แมวทุกตัวได้รับการวินิจฉัยว่าเป็นโรคไตเรื้อรังระยะที่ 2 มีการติดตามและประคองอาการโรคไตเรื้อรังจากโรงพยาบาลสัตว์เล็ก จุฬาลงกรณ์มหาวิทยาลัย หรือ โรงพยาบาลสัตว์เอกชนในบริเวณกรุงเทพมหานคร มาไม่ต่ำกว่า 3 เดือน หลังจากนั้นแมวจะถูกนำไปถ่ายภาพรังสีบริเวณสะโพก โดยต้องพบรอยโรคข้อเสื่อมที่บริเวณข้อสะโพก อย่างน้อย 1 ข้าง ก่อนการศึกษา แมวจะต้องได้รับการ ตรวจเลือด ปัสสาวะ ตรวจวัดความดัน ประเมินอาการขากะเผลก ประเมินความเจ็บปวดเฉียบพลันและเรื้อรังโดยใช้แบบสอบถาม วัดเส้นรอบวงต้นขา วัดมุมต้นขา ทดสอบการกระโดด หลังจากนั้นจะได้รับการประเมินติดตามอาการ ทุกวันที่ 14, 28, 42 และ 60 มีเพียง ส่วน ภาพถ่ายรังสี แบบสอบถาม วัดเส้นรอบวงต้นขา วัดมุมต้นขา จะทำการประเมินก่อนการศึกษา (วันที่0) และ วันสิ้นสุดการศึกษา ผลการศึกษาพบว่า ค่าครีเอทินีนในเลือดจากแมวกลุ่มทดลอง ลดลงอย่างมีนัยสำคัญ การทดสอบการกระโดด มีพัฒนาการที่ดีขึ้นอย่างมีนัยสำคัญในแมวกลุ่มทดลอง และมีความเจ็บปวดเรื้อรังลดลงอย่างมีนัยสำคัญ จากการศึกษานี้กล่าวได้ว่าพีซีเอสโอ-ห้าสองสี่มีประสิทธิภาพที่ดีในการลดความเจ็บปวดเรื้อรังจากโรคข้อเสื่อมและมีแนวโน้มที่ดีในการลดค่าครีเอทินีนในเลือด การควบคุมอาหารและการจัดการภาวะแห้งน้ำอย่างเหมาะสม ร่วมกับการปรับปรุงสิ่งแวดล้อมที่บ้าน จะช่วยส่งเสริมคุณภาพชีวิตของสัตว์ที่เป็นโรคข้อเสื่อมร่วมกับโรคไตเรื้อรังได้ดียิ่งขึ้น

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Twenty-six osteoarthritic cats concurrent with chronic kidney disease (CKD) enrolled in this study. All cats were divided randomly into 2 groups; control group (n=12) received placebo and treatment group (n=14) received PCSO-524 for 60 days. Cats had verified stable CKD stage II and had treated and followed up for CKD more than 3 months were included in our study. Before starting the study (day 0), all cats were taken the coxofemoral joint radiographic imaging. Only cats with the radiographic osteoarthritic lesion(s) were recruited. All of them had blood profile check-up, urinalysis, blood pressure measurement, lameness score assessment, acute and chronic pain assessment, thigh circumference measurement, range of motion (ROM) measurement, and jump test every day 14, 28, 42, and 60. Only radiographic imaging, pain questionnaire, thigh circumference measurement, ROM measurement were assessed at day 0 and 60. In the treatment group, this study revealed significantly declined in blood creatinine concentration and chronic pain score while jump test score found significant rising. In conclusion, PCSO-524 gained high efficiency in coping with chronic pain from osteoarthritis in CKD cats. It also showed a great tendency to decrease blood creatinine level. Dietary restriction and water management together with environmental modification, help promote a better quality of life in osteoarthritic cat concurrence with CKD at its best.

Field of Study: Veterinary Surgery Student's Signature .....

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Pemika Dulyapraphant

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CHAPTER I

INTRODUCTION

Important and rationale

Nowadays, in general practice, feline osteoarthritis remains an under-diagnosed disease which causes chronic pain in cats as it does in humans. As a self-protective mechanism, cats tend to hide their feelings from pain. Fortunately, there is an increasing awareness of feline OA in the last decade. Many studies found the higher prevalence of Osteoarthritis (OA) in the feline population (Lascelles et al., 2010; Rodan et al., 2011; Bennett et al., 2012a; Klinck et al., 2012; Tomas et al., 2015). One of the random studies of cats in different age groups, 91% had radiographic evidence of OA, occurring as early as 6 months of age, and the signs seem to worsen with ages (Lascelles et al., 2010). Nowadays, OA is an incurable disease. Long-term nonsteroidal anti-inflammatory drugs (NSAIDs) and neuropathic pain-controlled medication were suggested to control the central and peripheral sensitisation in order to decrease pain and improve quality of life. Even though NSAIDs are effective in controlling inflammation and pain, cat patients are at higher risk for adverse drug reactions (ADRs). One of the specific ADRs on the long-term application of NSAIDs is renal effects (Marcum and Hanlon, 2010). Due to their adverse effects, NSAIDs usually limited in CKD patients in every species. Both OA and CKD are the degenerative disease which concurrent often occurred and were found in 44% of CKD cats affected with OA in all ages, especially elder. (Marino et al., 2014). Nutraceuticals are the closest ideal to manage joint pain (Ameye and Chee, 2006; Akhtar and Haqqi, 2012). They could offer a safer alternative avoiding of NSAIDs adverse effects. In this study, PCSO-524 (New Zealand green-lipped mussel extract) will be applied to detect clinical improvement and to raise the quality of life in cats with OA and CKD. Since, many studies in dogs show the experienced improvements in clinical lameness along with owner preference (Mongkon and Soontornvipart,

2012; Soontornvipart et al., 2015; Kwananocha et al., 2016) but still no scientific study has been done in cats.

CHAPTER II

LITERATURE REVIEW

2.1 Feline Osteoarthritis

Osteoarthritis (OA) is degenerative and progressive disease appears on any diarthrodial joint. It once thought to be rare in cats but actually, it is commonly found in feline species (Lemetayer and Taylor, 2014). There are two types for this disease - Primary and secondary. Frequently, the feline OA is appeared to be primary, cannot be identified for the initial cause. As we have seen in clinical practices, feline OA occurs with no noticeable factor, usually referred to age-related cartilage degeneration (Lascelles, 2010). Feline OA has more complicated compared to canine, which OA usually occurs secondary to some other abnormalities (hip dysplasia, elbow dysplasia, cranial cruciate ligament ruptures). There are some cat breeds have a higher risk for feline OA due to previous musculoskeletal abnormalities (table 1)

Table 1 Cat breed predisposing to orthopaedic-related disease.

Disease	Breed predisposing	Reference
Hip dysplasia	Maine Coon	(Perry, 2016; Loder and Todhunter, 2018)
Osteochondrodysplasia	Scottish Fold	(Chang et al., 2007; (Selting et al., 2019)
Mucopolysaccharidoses (MPS)	Siamese	(Lyons et al., 2016)
Patellar luxation	Abyssinian and Devon Rex cats	(Harasen, 2006)

There were high prevalence reports in hip and elbow for appendicular and thoracic vertebral for axial OA (Godfrey, 2005; Lascelles et al., 2010; Slingerland et al., 2011; Kranenburg et al., 2012) (table 2,3)

Table 2 Prevalence of appendicular OA in some previous reports.

Studies	Carpus (%)	Elbow (%)	Shoulder (%)	Tarsus (%)	Stifle (%)	Hip (%)
(Godfrey, 2005)	0	55.45	0.9	1.82	24.55	17.28
(Lascelles et al., 2010)	15	35	14	40	50	65
(Slingerland et al., 2011)	2	27	37	13	8	49

Table 3 Prevalence of axial OA in some previous reports.

Studies	Cervical (%)	Thoracic (%)	Lumbar (%)	Lumbosacral (%)	notes
(Lascelles et al., 2010)	20	43	26	29	
(Kranenburg et al., 2012) spondylosis deformans	lowest	highest	2nd high	3rd high	Did not report in percentage

Degenerative joint disease (DJD) and OA had so much in similar but in the definitions of DJD is also included spondylosis deformans of the intervertebral disc or axial joints, some degenerative lesions such as enthesophytes, degenerative soft tissue mineralisation within joints which might not be considered as OA , and traumatic arthritis (Bennett et al., 2012a; Stadig, 2017).

The molecular changes in OA include the matrix proteins expression, proteoglycans, collagens, metalloproteinases and their inhibitors in both cartilage and bone which pattern of molecular changes are dependence on the species and stage of the disease progression although broad similarities in patterns of differential gene expression in end-stage OA are observed between species (Ryan et al., 2013). In mammal species, articular cartilage thickness is related to species size and weight. Accordingly, the feline cartilage is relatively thin (Ryan et al., 2013). Osteoarthritis is the consequence of the chondrocytes are less able to maintain homeostasis between synthesis and degradation (Man and Mologhianu, 2014). Which exactly initiates the cascade of the imbalance is still left unknown. The breakdown of collagen and proteoglycan molecules, also taken up by synovial macrophages, cause releasing of proinflammatory cytokines such as TNFα, IL-1, and IL-6. After that, proinflammatory cytokines bind to chondrocyte receptors lead more release of metalloproteinases and inhibition of collagen type II production, resulted in further cartilage deterioration. Disruption of this homeostasis arises in increased water content and decreased proteoglycan in the extracellular matrix, weakening of the collagen network due to reducing the synthesis of collagen type II and increasing of collagen breakdown. Furthermore, apoptosis of chondrocytes is also increased (Man and Mologhianu, 2014). The matrix metalloproteinases (MMPs) of the collagenase, gelatinase, and stromelysin families received much attention about their specifically degrading both collagens and proteoglycans. An initial cascade is activated by plasmin, a serine protease, which enhanced stromelysin (MMP-3), an activator of collagenases. Only IL-1 or together with TNF-a help stimulate the synthesis of all of these proteinases. MMPs have been localised where cartilage degradation and have been detected in synovial fluids and cartilage from OA patients. The increased levels of the tissue of inhibitors of metalloproteinases (TIMPs) in OA synovial fluids may alter the response of active MMPs growing levels (Goldring, 2000). The collagenases allied with cartilage collagen degradation, including collagenases 1, 2, and 3 (MMP-1, 8, 13) and membrane type I (MT1)-MMP (MMP–14). The expression of MMP-13 in osteoarthritic cartilage and its ability to more effectively degrade type II collagen suggested the leading role for this enzyme in cartilage degradation. Other products of

the inflammatory process produced by chondrocytes when stimulated by IL-1 alone or with TNF-α include nitric oxide synthetase (iNOS), cyclooxygenase-2 (COX-2), and phospholipase A2 (sPLA2) empirically. Products of nitric oxide (NO) and prostaglandins E (PGE), promote chondrocyte functions related to matrix synthesis and degradation either positively or negatively (Goldring, 2000).

The development of subchondral bone pathology in OA is shown a critical role in the pathogenesis and progression of the disease (Ryan et al., 2013). The thickness of the subchondral bone plate and density of trabeculae in the subchondral bone increases in naturally occurring OA and consequently, it is undergoing low-grade inflammation resulting in varying degrees of pain and swelling of the affecting joints (Langley-Hobbs, 2014).

2.2 Osteoarthritic pain

OA is also associated with the inflammatory mediators' inflation, such as NO and prostanoid, prostaglandin E2 (PGE2) (Cason, 2014). It is directly related to painful conditions, arisen from free axonal endings in the synovium, periosteum, tendons, and bones, but not in the cartilage. The nociceptive message, act as a neuromediators, associate in regulating factors such as neuronal growth factor (NGF) and central modification of pain pathway. OA pain is considered a mixed phenomenon which nociceptive and neuropathic mechanisms are involved at the peripheral and central levels. OA pain perception is influenced by multiple factors; environmental, psychological, or constitutional factors as example (Perrot, 2015).

Infiltrations of inflammatory cells release chemical mediators then initiation of the arachidonic acid (AA) cascade by phospholipase-A2 (PLA2) and subsequent eicosanoid production are followed. It seems that the inflammatory process has its dominant role in activating more silent nociceptors, which releasing substance-P (S-P). A pronociceptive peptide neurotransmitter can increase the afferent input to the spinal cord, accompanied by an increased pain response for a given stimulus that would typically elicit less pain (hyperalgesia) referred to peripheral sensitisation (Goldring, 2000).

OA pain pathophysiology includes four cascades of the pain pathway (Perrot, 2015).

1) Transduction: painful stimuli induced energy conversion into electrical energy by specific receptors. In the joint, local inflammation together with the release of phospholipases, cyclooxygenases, lipo-oxygenases, leukotrienes, free radicals, and NO are involved in pain mechanisms. Transient receptor potential vanilloid receptors (TRPV) is playing a leading role in neuropathic pain; they present in many joint structures and can be the target of descending inhibitory mechanisms. At the joint level, there are four types of sensory organs. Type I and type II receptors, these are mechanoreceptors with low threshold, active in every joint position, transmitting the message by myelinic fibres. Type III receptors, they were found at superficial of the joints and ligaments. Type IV receptors, they could be found in all structures except in the cartilage and could not be activated in the normal situation. In an inflammatory condition, Type III and IV receptors are involved in pain sensation induced by joint lesions. They are also sensitised by increased intra-articular pressure and by local chemical changes.
2) Transmission
3) Perception: Perception plays its part in the brain cortical zones.
4) Modulation by the brain and spinal cord, by inhibiting and modifying, this is a pivot part of minimising the pain sensation.

2.2.1 Chronic pain in cats

Chronic pain is defined when the pain lasts longer than 3-6 months (Ellen Goldberg, 2017). It resulted from central and peripheral sensitisation in which pain is persistent nociceptive activities even nociceptive inputs have subsided. Neuropathic pain, chronic pain subunit, arises as a result of defects of the somatosensory nervous system either in the peripheral nervous system (PNS) or central nervous system (CNS) (Baron et al., 2010).

There are three essential phenomena intrinsic to neuropathic pain development (Mathews, 2008):

1. Central sensitisation: wind-up procession resulted in transcriptional changes at the dorsal horn, leading to synaptic neurotransmitter alteration.

2. Central disinhibition: It defines as an imbalance between the excitation and inhibition of the nervous system and this imbalance can occur instant or in a period of time.

3. Phenotypic change of mechanoreceptive Aβ-fibres (light-touch-sensitive) toward substance-P production, an electrical input from them is noticeable as pain. Thus, typical pain perception is changed into an aberrant process.

OA causes significant chronic pain. Chronicity of pain is correlated with changes in the CNS. Central sensitisation is explicit as pain hypersensitivity, particularly dynamic tactile allodynia, secondary punctate hyperalgesia, and enhanced temporal summation (TS). The early phase of wind-up phenomena goes to TS, N-methyl-D-aspartate (NMDA) receptor-dependent in both animals (Dickenson and Sullivan, 1987) and humans (Price et al., 1994). TS involves impulse conduction via Ad and C-fibers in the dorsal horn. Nevertheless, even wind-up and central sensitisation shared a similar pathway, where wind-up initiates and preserves central sensitisation, but they are not considered as the same phenomena (Guillot et al., 2014).

2.3 Clinical signs and diagnosis

OA is generally painful and suitable treatments are required to promote the animal's quality of life, so It is necessary for the clinicians to actively observe these cases in the patient population (Bennett et al., 2012a). Lameness is not the most common clinical signs of feline OA because of their self-protection behaviour (Langley-Hobbs; from https://www.langfordvets.co.uk/media/1225/osteoarthritis.pdf).

Radiographic lesion identification is recognised as disease confirmation, but it could be problematic. Feline joint radiographic interpretation is hard for interpreters who are not familiar with, and it might see no bony change in early OA (Bennett et al., 2012a). Radiographic features for evaluation and considerate indication of OA in appendicular joints including joint effusion (not scored for the hip), osteophytes, enthesophytes, joint-associated mineralisation, sclerosis, subluxation, subchondral

bone erosions and cysts, presence of intraarticular mineralisation, and new bone formation in the intertarsal and tarsometatarsal joints. (Lascelles et al., 2010)

The most common radiographic features of feline hip OA is osteophytes (Freire et al., 2011). Moreover, hip subluxation, inadequate development of the craniolateral acetabular edges, loss of the arched shape of the cranial subchondral acetabular bones, shallowed acetabulum, and secondary degenerative changes at the femoral heads and necks were also recorded as radiological findings in the affected cats (Patsikas et al., 1998).

It was time-consuming for OA lesion development on radiographic imaging. The study from Clarke and Bennett in 2006 reported that cats could suffer from OA without any specific notable radiographic changes (Clarke and Bennett, 2006).

Apart from using x-ray as the diagnostic tool, completing history taking is the key to help diagnose feline OA. The characteristic signs of pain in animals is a change in their behaviours which seems to be the first indication to detect the pain (Members et al., 2007; Rodan et al., 2011; Slingerland et al., 2011). In most cases, the shifted behaviour usually associated with the cat's decreased fluidity movements and reluctance jumping up and down (Langley-Hobbs, 2014). Altered gait, posture, or carriage were also reported. Many cats also decreased playfulness, less tolerance for handling, changed in grooming habit, had overgrown nails, changed in lying down and sleeping area, changed in mood and energy level, changed in little box habits, and even decrease appetite (Robertson and Lascelles, 2010; Bennett et al., 2012a)

2.4 Multimodal management for feline OA

OA is an incurable disease nowadays. Multimodal management plays a huge part in OA management as they have the main focused at coping the pain and slow disease progression including weight control, environmental modification, rehabilitation, surgery, medical, and nutrition treatments.

Environmental modification is an essential one. Since the cats had a sedentary lifestyle, providing them with more convenient access to litter boxes, beddings, food, and water. Vertical dimension is considered very important in cats' behaviour, putting little steps and ramps helps them assess perches. An enriched

environment can promote some exercise, which can help maintain muscle mass and tone, and decreasing pain possibly. Different toys, hidden food, and towers benefit to mental health, and they could promote foraging, hunting, and playing behaviours. (Bennett et al., 2012)

Rehabilitation and physical therapies aim at pain management and enhance function. Passive range of motion (PROM) and home massage can be useful for stress and muscle pain reduction. These methods can be performed at home by the owner. (Lascelles and Robertson, 2010). Swimming, underwater treadmills, cold and heat therapy, laser, ultrasound, and shock wave are other optimal therapies which could be considered even though the scientific study in cats is little. Acupuncture, as some cats tolerated well with this technique, has gained some benefits for relieving pain in arthritis cat. Though it may take several sessions before detecting improvement.

Nonsteroidal anti-inflammatory drugs (NSAIDs), usually considered the gold standard medical therapeutic regimen in feline OA due to their pain management effects and diminished inflammation adequately. NSAIDs provide analgesia effectively by competitive inhibitors of cyclooxygenase (COX)(Zarghi and Arfaei, 2011). COX is the enzyme responsible for the bioconversion of cell membrane-derived arachidonic acid to prostaglandins. Prostaglandin E_2 is a potent nociceptor stimulus that contributes to the pain associated with inflammation. COX isoforms have been described in the periphery as well as in the spinal cord, where upregulation may contribute to chronic pain. Many NSAIDs are available, with varying ratios of inhibitory capacity for the COX-1 and the COX-2 isoenzymes. Several recommended NSAIDs are available in cats that have been safely provided for long-term usage at appropriate doses, including Meloxicam and Robenacoxib.

Meloxicam is broadly known for long-term treatment in animal with locomotors disorder (Cross et al., 1997; Doig et al., 2000; Gunew et al., 2008) and provide good outcomes in many study (Lascelles et al., 2001; Gunew et al., 2008; Guillot et al., 2013; Sul et al., 2014) except patients who classified for allodynia, the response is poor (Guillot et al., 2014). Long-term treatment (more than six months) in

aged cats (7 years and above) with oral meloxicam did not reduce the lifespan of stable CKD cats, even for cats in IRIS stages 2 and 3. (Gowan et al., 2012)

Robenacoxib shows high selectivity for the cyclooxygenase-2 (COX-2) enzyme in rats, cats, and dogs. It was tolerated well when administered daily dose 1.0-2.4 mg/kg for a month in cats with osteoarthritis, including some with verified a concurrent CKD as there was no clinical indication of damage to the gastrointestinal tract, kidney or liver (King et al., 2016)

Although, NSAID use in cats with concurrent CKD is highly concerned; both Meloxicam (Metacam®) and Robenacoxib (Onsior®) gained some indicated safety at lower doses in cats with stable stage1 or 2 CKD. There was an efficiency comparing study between Robenacoxib versus Meloxicam in cats. The result showed both treatments were effective (table 4). There was no significant difference in frequencies of reported adverse events, clinical observations and haematology or clinical chemistry variables between the groups.

Table 4 Efficacy comparisons between Robenacoxib versus Meloxicam in post-operation.

Study	**Animals (number of animals)**	**Doses and administrations**	**Pain assessment**	**Outcomes**
(Bendinelli et al., 2019)	Dogs (26) 13 each	Pre-operative s.c. injection meloxicam (0.2 mg/kg), robenacoxib (2 mg/kg)	1,6,12,18,24 hours	Meloxicam was more effective
(Speranza et al., 2015)	Cats (147) Robenacoxib 101 Meloxicam 46	Pre-operative s.c. injection robenacoxib (2 mg/kg) followed by robenacoxib tablets	9 days	3 - 22 hours post-operative assessment found no statistically non-inferior to

		(1–2.4 mg/kg) administered post-operatively Pre-operative s.c. injection meloxicam (0.3 mg/kg), followed by placebo tablets		meloxicam, No significant differences during the follow-up treatment with robenacoxib tablets compared with placebo
(Kamata et al., 2012)	Cats (96) Robenacoxib 67 Meloxicam 29	single s.c. injection of robenacoxib (2 mg/kg) meloxicam (0.3 mg/kg)	22 hours	Robenacoxib gain a faster good outcome
(Gruet et al., 2011)	Dogs (140) Robenacoxib 97 Meloxicam 43	An initial dose robenacoxib, 2 mg/kg; meloxicam, 0.2 mg/kg) via SC injection before surgery and daily doses per oral robenacoxib, 1 to 2 mg/kg; meloxicam, 0.1 mg/kg	15 days	similar adequate pain control

Feline OA frequently diagnosed when it was late, so the cat may already develop central sensitisation. Hence, other drugs such as gabapentin, amantadine, and tramadol play increasing importance roles in OA management.

2.5 Feline Chronic Kidney Disease (Feline CKD)

Among kidney disease in cats, CKD is the most common (Reynolds and Lefebvre, 2013). CKD is the persistent loss of kidney function over time, causing mobility and mortality in cats (Spark, 2006) as healthy kidneys perform many crucial tasks as filtering blood and maintaining normal excretory function.

CKD was defined when renal function has an irreversible deterioration of more than 50% of the glomerular filtration rate (GFR) at least three months (Polzin, 2011; Piyarungsri and Pusoonthornthum, 2017). This disease report prevalence approximately 4% in the UK (Sparkes et al., 2016) and 0.6% of the feline patient presented in a small animal hospital in Thailand. Ten-year collected data (June 2004 – November 2014) from Small Animal Hospital, Faculty of Veterinary Science, Chulalongkorn University, and veterinary hospitals in the Bangkok Metropolitan area found male was two times at risk for CKD compare to female (Piyarungsri and Pusoonthornthum, 2017).

Feline CKD is common, especially in aged cats as ageing is considered a risk factor for this disease (Brown et al., 2016; Relford et al., 2016; Sparkes et al., 2016; Piyarungsri and Pusoonthornthum, 2017; van den Broek et al., 2017). Another risk factor for developmental CKD included systemic hypertension, cardiovascular disease, primary hyperaldosteronism, and urinary tract infections (UTIs) (Reynolds and Lefebvre, 2013). The evidence for breed-associated risk in CKD is low and gender is not a risk factor for the developmental CKD (Paepe and Daminet, 2013), although most cases have nonspecific renal lesions. Tubulointerstitial infiltration of inflammation (lymphocytes and macrophages) is considered an early feature of CKD as tubular damage occurs early before azotemia. The presence of interstitial fibrosis lesion is the strongest histomorphometric predictor of renal function (Chakrabarti et al., 2013; Reynolds and Lefebvre, 2013) and anaemia could enhance interstitial fibrosis by aggravating renal hypoxia (Chakrabarti et al., 2013). Regardless, from the initial cause, chronic renal inflammation is believed to play a critical role in the pathophysiology of CKD (Lopez-Novoa et al., 2011). Chronic inflammation produced pro-fibrotic growth factors and chemokines from activated epithelial and endothelial cells. Both leukocytes and macrophages infiltration have been suspected of

fibrogenesis promotion in feline CKD at the end (Lawson et al., 2015). T-cells are the factors modulate myofibroblast activation, not only by direct effects on fibroblasts but also inducing macrophages and tubular cells to produce more pro-fibrotic cytokines and growth factors (Nikolic-Paterson, 2010).

In overall, the pathophysiology of CKD could be considered at the level of organ and systemic disorder. It is including; declined in glomerular filtration rate, hormonal disturbances, and compensatory mechanism. CKD in cats differs from dogs, where proteinuria is more frequently occurring, the progressive loss of renal function tended to be more common, linear, and relatively fast compared with cats. Cats may show stable condition for a very long period (months up to years) but then experience an abrupt, unpredictable in renal function decreases, or they may present slowly progressive disease over the years (Grauer; from http://www.iris-kidney.com/education/proteinuria.html).

The clinical presences of feline CKD are non-specific and may show no signs detected in the early stage. According to clinical symptoms, CKD cat (>50%) found dehydration, lethargy, anorexia, and weight loss (Reynolds and Lefebvre, 2013; Piyarungsri and Pusoonthornthum, 2017). Optimal monitoring strategies for cats with CKD had to be done in every patient. International renal interest society (IRIS; http://www.iris-kidney.com) launched guideline of staging feline CKD in 2005 based on fasting blood creatinine concentration and assessed on at least two times in the stable patient (table 4). Another suggestion based on Symmetric dimethylarginine (SDMA) concentrations in blood plasma or serum as it may be a more sensitive biomarker of renal function.

Renal biomarkers for early detection were reported including

- SDMA: a methylated arginine amino acid, releasing into the cytoplasm after proteolysis. The strong relationship between SDMA and creatinine concentration supports the fact that SDMA is primarily excreted by the kidneys (Jepson et al., 2008). A further advantage of SDMA over serum creatinine is SDMA is not affected by muscle mass, so it may be help diagnosed in CKD cats with low muscle mass (Hall et al., 2015). SDMA was also increasing in cats with calcium

oxalate uroliths (Hall et al., 2017). However, in people SDMA is elevated by several non-renal diseases such as sepsis, cardiac disease and hepatic disease (Koch et al., 2013) and further research is needed into the specificity of raised SDMA in cats.

- Neutrophil gelatinase-associated lipocalin (NGAL) (Piyarungsri, 2017)

Renal biomarkers for tubular dysfunction were also reported including

- N-acetyl-ß-D-glucosaminidase (NAG)
- Cystatin C
- Cauxin (Piyarungsri, 2017)

Other renal markers for kidney damage (table 5)

Table 5 Markers of kidney damage, modification of (Polzin, 2011)

Blood markers	**Urine markers**
Azotaemia	Impair urine concentrating ability
Hyperphosphatemia	Proteinuria
Hyper or Hypokalaemia	Cylindruria
Metabolic acidosis	Renal hematuria
Hypoalbuminemia	Inappropriate urine pH
Abnormalities on imaging	Inappropriate glucosuria
	Cystinuria

Moreover, patients should be monitoring their clinical presenting and condition. The assessment for the circumstance of hypertension, proteinuria, hypokalaemia, hyperphosphataemia, primary hyperaldosteronism, cardiovascular disease, UTIs, anaemia and CKD-associated mineral bone disorder as they might contribute to the development of the renal disease.

For cats with CKD, if proteinuria is showed, dietary protein restriction is beneficial as proteinuria induces inflammatory and fibrogenic pathways and increases

oxidative stress the minimum dietary protein requirement suggested is 24% of a dry-matter basis. The cat, an absolute carnivore, is unable to down-regulation of the hepatic enzyme activity associated with protein catabolism even when dietary protein intake is low. High-quality protein sources are needed to prevent essential amino acid deficiency. The cat's body weight, lean muscle mass, body condition score, serum albumin, BUN and cholesterol should be monitored. If protein malnutrition becomes visible, then the amount of protein consumption should be increased until signs are no longer apparent. Cat with sarcopenia, frequently seen in geriatric and CKD cats, may require more protein than a general renal diet could provide. Hence, routinely monitoring and adjustment will be necessary for these cats.

Nevertheless, there were many useful parameters for monitoring chronic kidney disease, i.e. blood press measurement, urinalysis, ultrasound (for gross lesion), phosphorus and UP/C ratio

2.6 Serum creatinine

Creatinine is a nitrogenous bases waste product from the catabolism of phosphocreatine and filtered mainly by the kidney. Serum creatinine test reflects the amount of creatinine in the blood; any changes in the level of creatinine concentration are related to excretion as it is the most commonly used as an indirect indicator for kidney function.

Serum creatinine measurement has many limitations. Many factors can be influenced the results such as the method of analysis; Jaffe's reaction, enzymatic and bench-top, and laboratory calibration. One of the most disconcerting of interpretation of blood creatinine is the high variation in reference intervals between laboratories; these could lead to false-positive and false-negative azotaemia (Grauer; from http://www.iris-kidney.com/education/utility_creatine_early_diagnosis_ckd.html). Furthermore, its defective limitations including low sensitivity as it only exceeds the normal range when renal tissue is deteriorated approximately 75% and low specificity due to the endogenous synthesis of creatinine interfere by muscles making muscle mass, breed and sex an influencing factors of serum creatinine. Also, it could be affected by hydration and diet as well. The muscle mass and serum creatinine

relationship can be a particular problem for the interpretation of the results in elder CKD cats because these cats usually had muscle mass decreased (sarcopenia) such that their normal range for creatinine value may be lower than it should be (Finch et al., 2016).

Serum creatinine elevation and decline GFR are not straight-line relationships. Initially, the dramatic dropped in GFR reflects in a small amount of creatinine increasing. Whilst in late disease, a minor change in GFR could have much more effective. This may imply that whether apparently healthy cats (i.e. IRIS stage 1 and early stage 2) with little amount creatinine concentration from the normal range may indicate a significant deterioration in kidney function. Serial measurements for each animal are useful to maintain animal health status (Canon, 2016).

2.7 Urinalysis

Urine specific gravity (USG) is the concentration measurement of particles in urine and urine density compared with water density. Measuring USG is non-invasive and convenience but the development of isosthenuria is not much better in diagnosing CKD, as its appearance signifies a 68-70% decreased in renal function. Also, multiple conditions will affect USG such as endocrine disease, afternoon urine sample, diet. Cats with CKD have persistently reduced USG (<1.035), and it tends to decrease further as CKD progression, but in the early stages (IRIS stages 1 and 2) most of them could maintain their concentrating ability. Frequently, their USG is above the isosthenuric range (>1.015).

Urine strip test does not seem to be a proper diagnosis tool, so measuring the urine protein/creatinine (UP/C) ratio is required. Moreover, since lower urinary inflammation and bacterial infection are commonly found in CKD cats, the evaluation of urine sediment is an essential procedure before interpreting elevated UP/C as renal proteinuria.

2.8 Blood pressure measurement

Systemic hypertension associated with progression CKD has a reported prevalence of 19–40% in primary care practices (Sparkes et al., 2016). Consequences

of sustained systemic hypertension are the damage of target organs, most notably the eye, heart, brain and kidney (Brown et al., 2007). Cats with CKD are often hypertensive due to changes in their neurohormonal and fluid homeostatic mechanisms. The burden of remaining nephrons in order to maintain GFR followed by the dilation of the afferent arterioles and vasoconstricting the efferent arteriole. An extended period of work leads protein leaking into the tubular interstitium and associated with more rapidly progressive kidney disease.

Thus, blood pressure measurement is essential for feline CKD and in routine healthcare of elder cats. Moreover, stress-induced can increase blood pressure, also called white coat effect or white coat hypertension. In general practices, initial therapy is applied in a patient with evidence of target-organ-damage, if reliable measurements of blood pressure indicate that systolic blood pressure exceeds 160 mm Hg

The definition and classification of systemic hypertension in cats has recently been reviewed and refined by the IRIS (table 6)

Table 6 IRIS substaging of blood pressure in dogs and cats

Substaging	**Systolic blood pressure (mmHg)**
Normal	<140
Pre-hypertension	140-159
Hypertension	160-179
Severe hypertension	180

Nowadays, Amlodipine is the treatment of choice in cats. Cats with hypertension (sustained systolic blood pressure 160 mmHg and above) should be treated and routinely monitored, with the aim of blood pressure reduction to <150–160 mmHg.

2.9 Nutraceuticals for feline OA

The pathological changes in OA induce pain by repeating the release of inflammatory mediators which not only direct nociceptor excitation but also increase

sensitivity to afferent nerve stimuli then primary hyperalgesia is followed (peripheral sensitization) (Kidd, 2012). The effective pain-killers using worldwide are NSAIDs but some specific ADRs with the chronic use of NSAIDs lead adverse effects in body system including gastrointestinal, renal, cardiovascular, cerebrovascular, and central nervous system (Marcum and Hanlon, 2010).

Because of drug limitation in patient contain both OA and CKD, which usually aged animals, the model of pain control has changed for patient safety. Nutraceuticals are becoming an alternative for pharmaceutical. Nutraceutical is a combination of nutrition and pharmaceutical. Nutraceuticals, in general, are fortified food or dietary supplements having a symbolic performance in modifying and sustaining regular physiological function that maintains the body in good conditions (Das et al., 2012).

Many products used as nutraceuticals can be categorized as dietary fibre, polyunsaturated fatty acids, prebiotics, probiotics, and antioxidants as example. Nutraceuticals are benefited in facing some of the major health problems such as obesity, cardiovascular diseases, cancer, osteoarthritis, diabetes (Das et al., 2012). In the animal with OA, nutraceuticals are the closest ideal to manage joint pain (Ameye and Chee, 2006; Akhtar and Haqqi, 2012); which offer a safer alternative avoiding of NSAIDs adverse effects.

Nutraceuticals used in the management osteoarthritis are included glucosamine and chondroitin sulphate, free radical scavenger, Methyl-sulfonyl-methane, Pentosan polysulfate, Polysulfate glycosaminoglycan, Omega-3 fatty acid. The omega-3 fatty acid has outstanding potential in anti-inflammatory and anti-oxidant effect. (Simopoulos, 2002; Mori and Beilin, 2004; Wall et al., 2010).

Glucosamine and chondroitin sulphate, once broadly famous in managing OA, showed a good result in many *in vitro* studies for their chondroprotective effect but for *in vivo* studies, it seems to be controversy.

PCSO-524®, a patented marine oil lipid derived from the New Zealand green-lipped mussel (Perna canaliculus), is rich in omega-3 fatty acids.

It has the polyunsaturated fatty acids (PUFAs); which consist of 5,9,12,15-octadecatetraenoic acid (OTA), 5,9,12,16-nonadecatertraenoic acid, 7,11,14,17-eicosatetraenoic acid (ETA), eicosapentaenoic acid (*EPA*) and docosahexaenoic acid (DHA), and 5,9,12,15,18-heneicosapentaenoic acid. ETA, EPA and DHA have a similar structure to arachidonic acid (AA), also known as the precursor to the inflammatory agents, prostaglandins, and leukotrienes. The interrupted bond positioning of these structural analogues of AA can be an explanation for their anti-inflammatory (AI) behaviour, by competitively inhibiting the active site of enzymes using AA as a substrate. This combination of omega-3 fatty acids is unique and cannot be found in other marine livings. Moreover, in the studies of fish oil are usually used large dosages of standardised EPA and DHA fish oil compared with studies using extracted oil from *Perna canaliculus* to accomplish in inflammatory markers reductions (Zawadzki et al., 2013). Strong evidence has been shown to diminish inflammation in both animal studies and human patient trials with no harmful effect (Jamikorn and Yibchok-anun, 2013; Zawadzki et al., 2013). A safety study report in cats in 20007 showed no adverse effect when administrated 1 tablet per day, only found lipemia when treated with 6 tablets per day and this condition is reversible (Pusoonthornthum, 2017). In dogs, many studies showed the experience of clinical lameness improvement as well as owner preference (Mongkon and Soontornvipart, 2012; Soontornvipart et al., 2015; Kwananocha et al., 2016). However, there is no scientific study has been done in cats. Therefore, this study aims to detect clinical improvement and to rise up the quality of life in cat patients.

CHAPTER III

MATERIALS AND METHODS

3.1 Animals

Twenty-six adult indoor cat patients (age>1year) with a clinically-healthy presentation. Cats found normal on orthopaedic and neurologic examinations (except subtle or overt lameness). Cats had confirmed OA at hip joint, had stabled CKD with blood creatinine concentration between1.6 - 2.8 mg/dl (repeated measurement every 2 weeks for 3 times if the patient fell in the same stage they would concern stable CKD), had treated and followed up for CKD more than 3 months at Small Animals Hospital Chulalongkorn University, private pet hospitals in Bangkok Metropolitan area. Continue feeding with renal® (Appendix 1) or k/d® prescription diet (Appendix 2) at least a month. Obtain urination by voiding (mid-stream voiding) and perform a urinalysis. Their urinalysis results showed inactive sediment (not found white blood cells, blood, cast), Urine specific gravity <1.035 and blood pressure below 180 mmHg

All cats must have haematocrit > 20, systolic blood pressure ≤ 180 mmHg if over 160 mmHg, UP/C will be evaluated, Urine specific gravity <1.035 (animal status = normal hydration) and had no other concurrence systemic disease can be detected from blood profile. Not in term of pregnancy or lactation. Owners were able to give patients medicine daily.

Cats had UP/C above 0.4, continued calcium antagonist, Angiotensin-converting enzyme (ACE*)* inhibitors, Angiotensin receptor blockers (ARB), corticosteroid, antibiotics, NSAIDs, Beta blockers *and* hypertension drugs, received omega-3 supplementation, had urinary tract infection (within a month), found white blood cells from urinalysis, found other detectable systemic diseases, urolithiasis, neoplasia, kidney cyst, abscess and pyelonephritis were confirmed, need any

therapeutic drugs during the study, died or disappeared while the study was carried out was excluded from this study.

Owners signed a consent form to permit their cats enrolled in this double-blinded study. This study followed the guidelines for the care and use of laboratory animals and approved by the Animal Care and Use Committee of the Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand.

3.2 Study designs

3.2.1 IRIS staging

Based on the International Renal Interest Society (IRIS) staging of CKD (table 7), cats with CKD were graded depending on blood creatinine. After that, all the CKD cats would separate into two groups, one receives PSCO-524 (n=14), and the other receives placebo, which contained olive oil (n=12).

Table 7 Staging of CKD in cats based on blood creatinine concentration from IRIS in 2015

Stage	Blood creatinine (mg/dl)
1	<1.6
2	1.6-2.8
3	2.9-5.0
4	>5.0

3.2.1.1 Treating protocol of feline CKD stage 2

1) If possible, all potentially nephrotoxic drugs should be discontinued.
2) Measure blood pressure at right radius
3) All the cats will be feed with prescription renal diet.

Management of dehydration:

These patients have decreased urine concentrating ability and will receive the standard conservative CKD treated with

1) Correct clinical dehydration/hypovolemia with isotonic, polyionic replacement fluid solutions (e.g., lactated ringer's) via intravenous or subcutaneous as needed.
2) All-time available fresh water.

3.2.2 Radiographic findings

Hip joints were required taking ventrodorsal (VD) (figure 1) to diagnose osteoarthritis. In this study, all the cats must have found evidence of osteoarthritis at least one from the followings

- Osteophytosis
- Enthesophytosis (morgan's line)
- Subchondral sclerosis
- Intra-articular mineralisation
- Subluxation score 1 and above

After that, veterinary radiologist, who did not become familiar with the cat patients, interpreted and scored a grade of severity (modified from Takahashi's scoring system (table 8, figure 2-6) and subluxation (modification of (Dennis, 2012)) (table 9) (figure 7-13) of all radiographic images.

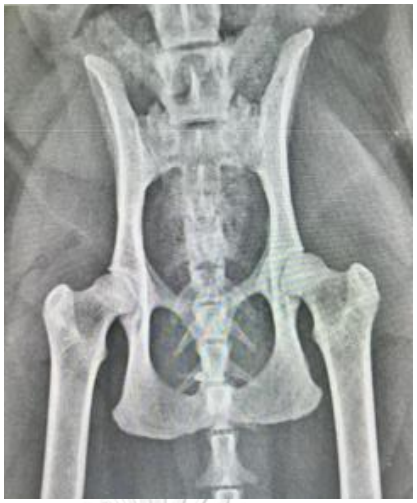


Figure 1 Hip joint in ventrodorsal extended coxofemoral projection (VD).

Table 8 Modified Takahashi's score system

	Grade	Radiographic findings
0	Normal	Not affected
1	Mild	Little osteophytes
2	Moderate	Obvious osteophytes and subluxation
3	Severe	Multiple osteophytes, some sclerosis with possible bone contour deformity, and subluxation
4	Very severe	Large osteophytes and sclerosis, bone contour deformity, and subluxation

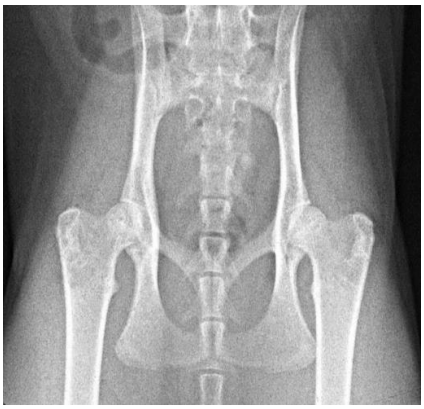


Figure 2 Grade 0 normal (Coulson and Lewis, 2002)

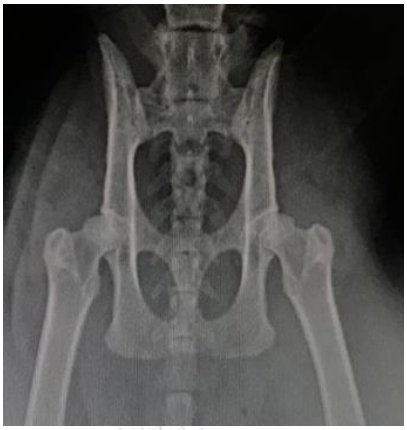


Figure 3 Grade 1 mild, little osteophytes.

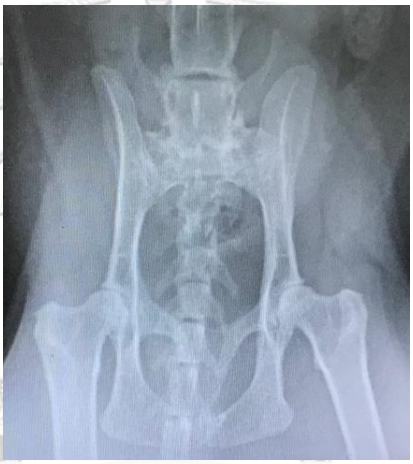


Figure 4 Grade 2 moderate, obvious osteophytes and subluxation.

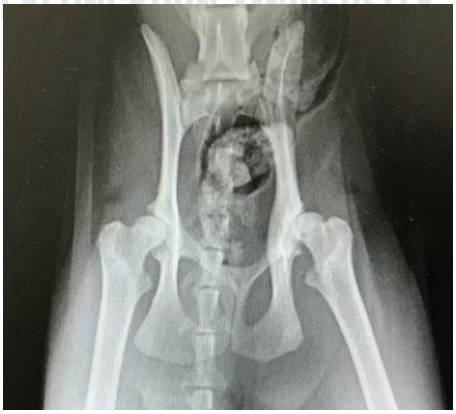


Figure 5 Grade 3 severe, multiple osteophytes, some sclerosis with possible bone contour deformity, and subluxation.

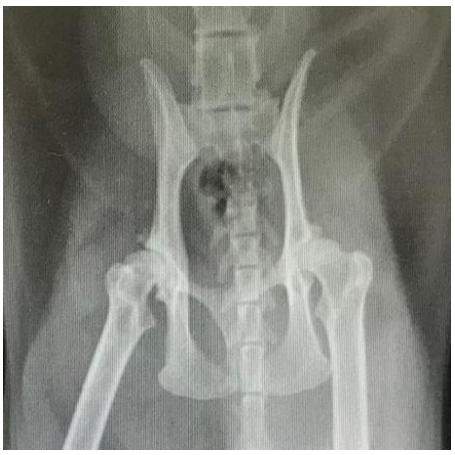


Figure 6 Grade 4 very severe, large osteophytes and sclerosis, bone contour deformity, and subluxation.

Table 9 Subluxation score (modification of Dennis, 2012)

score	subluxation
0	Centre of the femoral head fits well in acetabulum
1	Centre of the femoral head lies medial to the dorsal acetabular edge (DAE)
2	Centre of the femoral head lies superimposed on DAE
3	Centre of the femoral head lies lateral to DAE + only half of the femoral head intact in the acetabulum.
4	Centre of the femoral head lies lateral to DAE + only quarter of femoral head intact in the acetabulum.
5	Centre of the femoral head lies lateral and touches the DAE
6	Completely dislocated

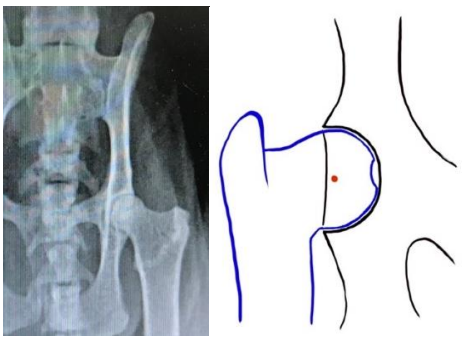


Figure 7 Subluxation score 0, the centre of the femoral head fits well in acetabulum

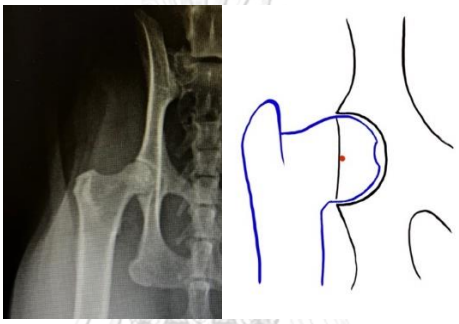


Figure 8 Subluxation score 1, the centre of the femoral head lies medial to DAE

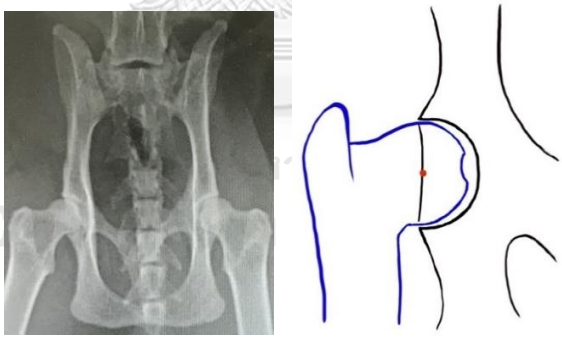


Figure 9 Subluxation score 2, the centre of the femoral head lies superimposed on DAE

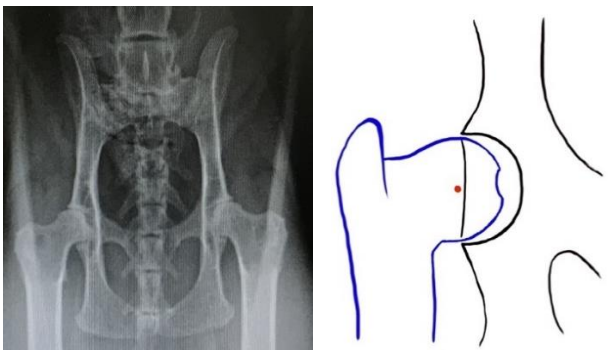


Figure 10 Subluxation score 3, the centre of the femoral head lies lateral to DAE + only half of the femoral head intact in the acetabulum.

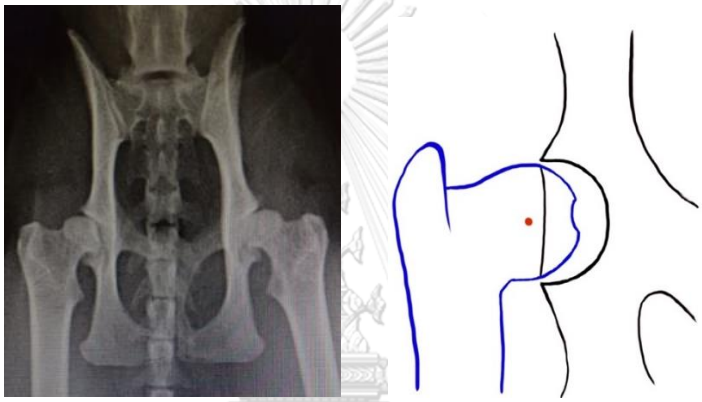


Figure 11 Subluxation score 4, the centre of the femoral head lies lateral to DAE + only quarter of femoral head intact in the acetabulum.

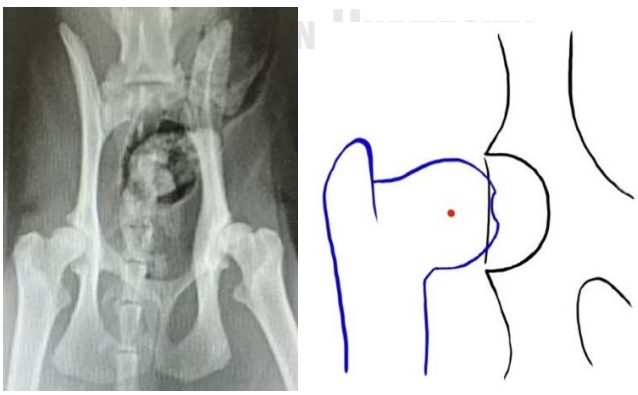


Figure 12 Subluxation score 5, the centre of the femoral head lies lateral and touches the DAE.

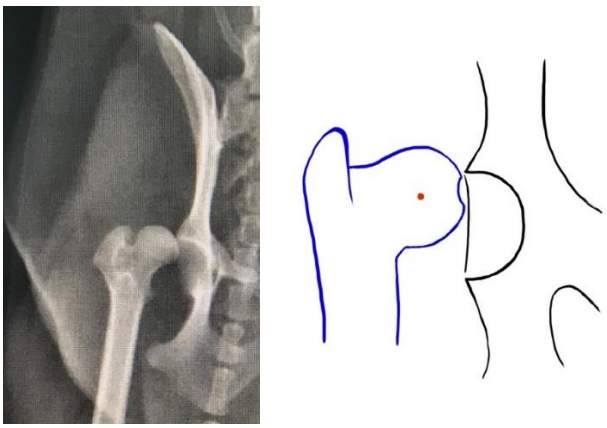


Figure 13 Subluxation score 6, completely dislocated.

3.3 Clinical evaluation

Blood profile, urinalysis, lameness score, blood pressure measurement and jump test were performed at day 0, 14, 28, 42 and 60 of treatment respectively. Thigh circumference measurement, range of motion (ROM), owner questionnaire, pain scores were performed at day 0 and 60 of the treatment (figure 14). The diagnosis of chronic kidney disease was performed on the basis of clinical signs, complete history taking, urinalysis, elevation of serum creatinine and urea concentration.

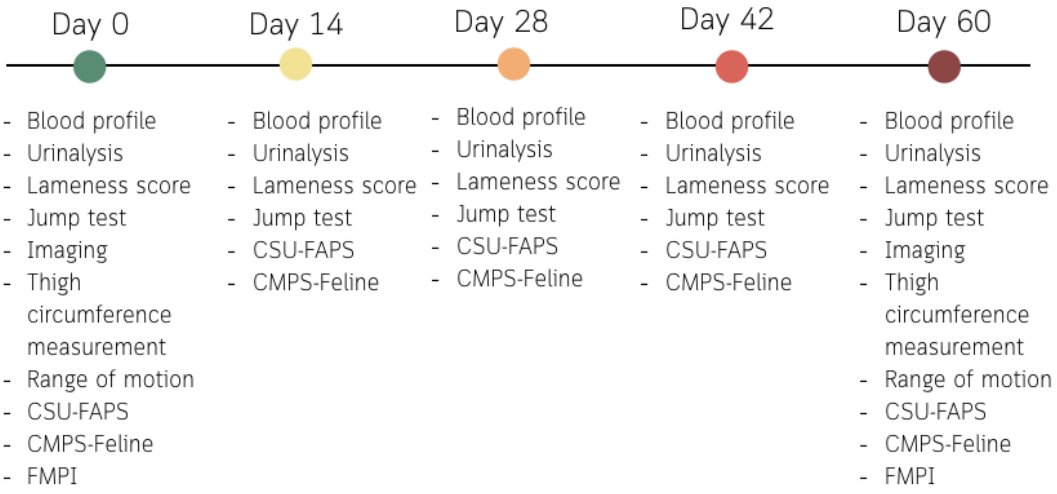


Figure 14 Timeline of clinical assessment

To avoid bias; x-ray, jump test, lameness score, CSU-FAPS and CMPS-feline were scored by a clinician who did not familiar with cat patients and all imaging was graded by veterinary radiologist.

3.3.1 Blood collection protocol

Blood sample was collected in the morning before receiving fluid replacement to evade diuretics effect. 3 millilitres blood samples of the forty cats (n=26) are drawn from the cephalic or saphenous vein into two test tubes which contain additive, one is heparin and another one is EDTA to inspect blood morphology, blood chemistry respectively. This experiment needs all of these blood chemistry values: Alanine aminotransferase (ALT), *Alkaline phosphatase* (ALP), Blood urea nitrogen (BUN), Creatinine, and Total protein (TP).

3.3.2 Urinalysis

Obtain urine samples by voiding. There are 3 steps for complete urinalysis. 1) General observation i.e. colour, turbidity, and measured urine specific gravity by using a refractometer.

2) Performing a chemical analysis using a urine strip test (Combur Test®) (figure 15). To measure Urine pH, Protein, Glucose and Ketones, Bilirubin, Urobilinogen, Blood and Nitrites values.

3) Centrifuging the urine samples and examining the urine sediment under a microscope such as white blood cells, bacteria, crystals and casts.

Figure 15 Combur Test® (F. Hoffmann-La Roche Ltd.)

3.3.3 Blood pressure measurement

Blood pressure of cat patients was measured by using the same doppler devices. Throughout the study, the measurements were measured from the same veterinarian and the same assistances. The cuff width should be approximately 30–40% of the radial circumference. Five measurements per session were taken. After that, the highest and the lowest value for systolic blood pressure were discarded. Average measurement was calculated from the remaining three values (as long as all systolic blood pressure results are within 20 mm Hg of each other). In case the remaining systolic blood pressure differs by more than 20 mm Hg, the measurement session would be repeated.

3.3.4 Thigh circumference measurement

Thigh circumference measurement was performed by palpating grater trochanter as a bony landmark then measured the length to lateral femoral condyle using tape measurement (figure 16). Then, multiplies the measured value by one third and then add 3 centimetres from the distal end, respectively. The quadriceps circumference was measured by using Gulick's tape measurement, a spring-tensioned device, (figure 17) put some pressure until one ball was clearly seen before procedure and day 60 of the procedure (figure 18).

Thigh circumference = 1/3 (Length from the greater trochanter to femoral condyle) + 3 centimetres from the distal

The measurement was repeated three times and calculated the average.

Figure 16 Gulick's tape measurement

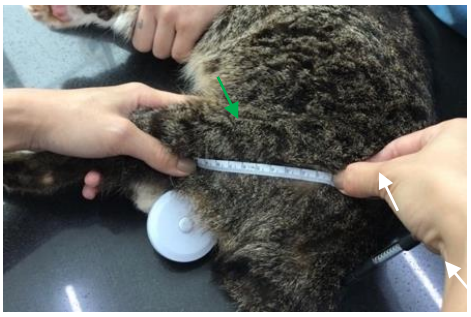


Figure 17 Measuring the length of the thigh from greater trochanter (white arrow) to lateral femoral condyle (green arrow)

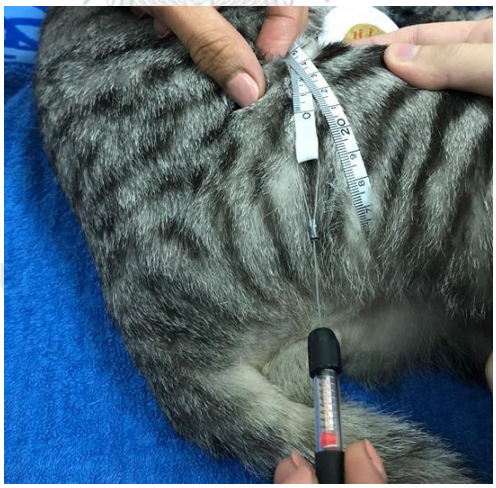


Figure 18 Thigh circumference measurement

3.3.5 ROM measurement

Traditional goniometer (figure 19) was used to measure the ROM of hip and stifle joints (figure 20) when they were flexed and extended. Cat patients were positioned in the recommended testing position and be stilled then palpating the

bony landmarks which were greater trochanter, ilial wing and lateral femoral condyle. Placing goniometer on the fulcrum of the joint and gently flexed the joint until it reached the first point of patience's discomfort then extended it softly to measure ROM of hip joints. To measure stifle joint, cats were restrained in the same position. The goniometer was located on the lateral femoral condyle which one arm was along the femoral shaft; another one was along the tibial shaft (Jaegger et al., 2002).

Each series of measurements were repeated three times and recorded the average ROM. Normal ROM in cat is also showed (table 10).

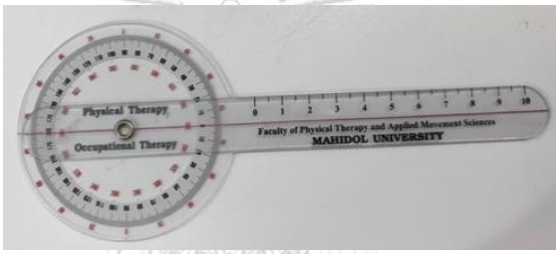


Figure 19 Traditional goniometer

Figure 20 ROM measurement

Table 10 Normal ROM in cats (Newton, 1985)

Joint	**ROM (Degree)**	
	Flexion	**Extension**
Hip	50-60	100-110
Stifle	50-60	90 (hyperextension 10-20)

3.3.6 Jump test and VDO recording

The study was performed in a quiet room, with only the examiner and the cat owner(s). The cat weight on an electronic scale and allow to acclimatise itself with the surrounding for 10-15 minutes. Then, every move of walking-patience was recorded via VDO recording to 3 examiners who unfamiliar with these cat patients' background to evaluate lameness scores. Afterward, cats had to jumped up and down between the ground and material boxes, which 40,80 centimetres in height (the 80 centimetres-height was 2 boxes put together to make specific height of objects) (figure 21) Cats performed jumping at day 0, 14, 28, 42 and 60 of treatment by using foods and laser pointer as deceivers (figure 22). Started from the lower height, 40, if the cat could perform the 40- centimetres height then moved on to the next higher level. After finish jumping, there was the end of the VDO.

Figure 21 Cat on a material box at 40, 80 centimetres height

Figure 22 Laser pointer as a deceiver

3.3.7 Lameness score

Upon physical evaluation, if cats showed subtle or overt lameness, lameness score would be graded followed lameness scoring criteria (table 11) which modified from (Impellizeri et al., 2000)

Table 11 Lameness scoring criteria (Modified from (Impellizeri et al., 2000))

Lameness score	**Walking**	**Running**
0	Without lameness	Without lameness
1	Subtle lameness	Without lameness
2	Obvious lameness	Without lameness
3	Difficult in walking	Lameness can be detected
4	Non-weight bearing	Lameness can be detected
5	Non-weight bearing	Non-weight bearing

3.3.8 Pain score evaluation

By using three experience veterinarians, who were unfamiliar with these cat patients' background, to evaluate the pain from the 3-minutes long videos. The video was recorded displays starting from closed observation until handled by the owners, and the average was calculated. The evaluation performs on the date of 0, 14, 28, 42 and 60 of the experiment.

3.3.8.1 Feline Composite Measure Pain Scale (CMPS-Feline)

CMPS-Feline (see Appendix 3) has been approved for cats and consolidated evaluation of the patient's facial expression, decreasing the misclassification of painful and nonpainful cats. The development of pain assessment system for use in feline patients is the utmost importance. Further work in this area is still needed (Shipley et al., 2018).

3.3.8.2 Colorado State University Feline Acute Pain Scale (CSU-FAPS)

This user-friendly system is one of the most common uses of pain score assessment in clinical field, CSU-FAPS (Appendix 4) were introduced in our study in order to recognise pain

3.3.8.3 Feline Musculoskeletal Pain Index (FMPI)

Owners assigned to fill a questionnaire called FMPI, courtesy of North Carolina State University. aimed at detecting chronic pain and behavioural changes in cats (see Appendix 5).

3.4 Statistical analysis

All statistics were analysed using Prism 7 program. Paired T-test, Wilcoxon signed rank test, the *one-way* analysis of variance (ANOVA), and Friedmann test were used in this study (table 12).

Table 12 Statistical analysis used in this study

Statistical test	Clinical assessment
Paired T-test	ROM measurement, Thigh circumference measurement
Wilcoxon signed rank test	radiographic score, subluxation score, FMPI
The *one-way* analysis of variance (ANOVA)	blood profile, urinalysis, blood pressure measurement, body temperature
Friedmann test	lameness score, CSU-FAPS, CMPS-feline, Jump test
Unpaired T-test	To compare between group
Multiple comparisons	Blood creatinine, Jump test

CHAPTER IV

RESULTS

4.1 Animals

Twenty-six CKD combined with OA cats including 20 Domestic shorthair (DSH), 4 Scottish fold, 1 Exotic shorthair and 1 American shorthair. Cats' age varied between 1-13 years with 5.69 ±2.80 years on average were included in our present study. Cats were divided into 2 groups; treatment and control groups (table 13). Treatment group and control group found average age at 5.5 ±3.31 years and 5.9 ±2.02. Body condition scores (BCS) were ranging 1-5 which 1 was very underweight, 5 was very overweight. Mean BCS reported from treatment group was 3.18 ±0.67. In control group, the average BCS was 3.29 ±1.05. Body temperature, measured by a rectal thermometer, of animals had no significantly change during our study (see appendix 6). Only 9 cats (34.6%) found lameness upon physical examinations.

Table 13 Patients' signalment in each group.

Groups	Number of animals	Mean age (year) ±SD	Sex (n)		Mean BCS ±SD
			Male	Female	
Treatment	14	5.5 ±3.31	8	6	3.18 ±0.67
Control	12	5.9 ±2.02	4	8	3.29 ±1.05

4.2 Clinical assessment on OA

4.2.1 Radiographic findings

As a dominant sign, most of animals (100%) had lesion at caudal acetabulum and subluxation of both hip joints. There was no change in subluxation score of each cat and no significant difference in radiographic score between and within groups;

two cats in treatment group found improvement of radiographic scores at day 60 (table 14).

Table 14 Radiographic score of cats' patients.

Groups	Mean ±SD (day 0)	Mean ±SD (day 60)
Treatment	1.9 ±0.8756	1.8 ±0.9189
Control	1.625 ±0.744	1.75 ±0.7071

4.2.1.1 Subluxation scores

Hip subluxation was one of the dominant signs found in every patient with the highest score was 5. Scores from both groups had no change throughout the study (table 15). The variation of subluxation scores was also reported (table 16).

Table 15 Mean subluxation score

Groups	Mean ±SD (day 0)	Mean ±SD (day 60)
Treatment	3.167 ±1.115	3.167 ±1.115
Control	3.2 ±0.919	3.2 ±0.919

Table 16 Number of animals on radiographic findings of subluxation score.

Grading	Number of animals	
	Treatment	Control
Grade 1	0	1
Grade 2	5	3
Grade 3	2	3
Grade 4	7	3
Grade 5	0	2

4.2.2 Thigh circumference measurement

Thigh circumference measurement of thighs was recorded from 19 patients due to their temperaments. There were no statistically change between and within both treatment and control groups on day 0 and 60 of the study (table 17).

Table 17 Mean thigh circumference

Groups	**Mean (cm) ±SD (day 0)**	**Mean (cm) ±SD (day 60)**
Treatment	15.9 ±4.533	16.3 ±4.244
Control	16 ±3.873	16.44 ±4.503

4.2.3 ROM measurement

Using traditional goniometer, ROM was measured only when cats were allowed. Only 17 patients were examined and found no statistical difference between groups whether hip or stifle joints on day 0 and 60 (table 18).

Table 18 Mean ROM of hip and stifle joints

(number reported in extension-flexion)

Groups	**Mean ±SD (day 0)**		**Mean ±SD (day 60)**	
	Hip joint	**Stifle joint**	**Hip joint**	**Stifle joint**
Treatment	77.22 ±20.78	79.38 ±15.91	77.78 ±22.24	80.63 ±15.68
Control	90 ±15.63	86.11 ±13.64	91 ±15.78	85.56 ±14.02

4.2.4 Lameness score

After acclimatised themselves with the surrounding for 10-15 minutes, all cats were evaluated the lameness scores while walking at pre-treatment (day 0) and continue every 14 days (appendix 14). Signs of lameness were shown in only 9 patients; 34.6% (5 in treatment group and 4 in control group).

4.2.5 CMPS-Feline

After lameness signs were recorded, CMPS-Feline was evaluated. Mean scores were recorded on day 0, 14, 28, 42, and 60. In each group and between group found no significant difference (appendix 15).

4.2.6 CSU-FAPS

Mean scores of CSU-FAPS were recorded on day 0, 14, 28, 42, and 60. In each group and between group found no significant difference (appendix 16).

4.2.7 FMPI

In this study, we used the first 17 questions to allow assess activity, pain intensity and overall quality of life of our patients. If owners selected 'don't know', or 'does not apply', these were considered missing data points. After that, we calculated the FMPI score of the cats who had the problems with a modified full score to equivalent to the other. The maximum score was 68, which mean that the cats were suffering from the highest pain and impairment. At day 0, the variation of scores was recorded from 2-40 and 0-39 in treatment and control groups. Mean scores on day 0 of the study were 16.54 ±13.43 and 13.42 ±14.13 in treatment and control groups, respectively. At day 60, FMPI means scores were decreased significantly ($p=0.0029$) in treatment group, but no statistically changed in control group (table 19, figure 25). Up to 77% were found impairment in question 4 followed by question 3,5 at 65.38% and question 14 at 57.69% (figure 23,24)

For question 18,19, at day 60, treatment group (85.71%) and control group, the owners (41.67%) marked pain level as less severe as day 0. 14.29% in treatment and 58.33% in control group marked no change. However, no worse pain was detected during this study.

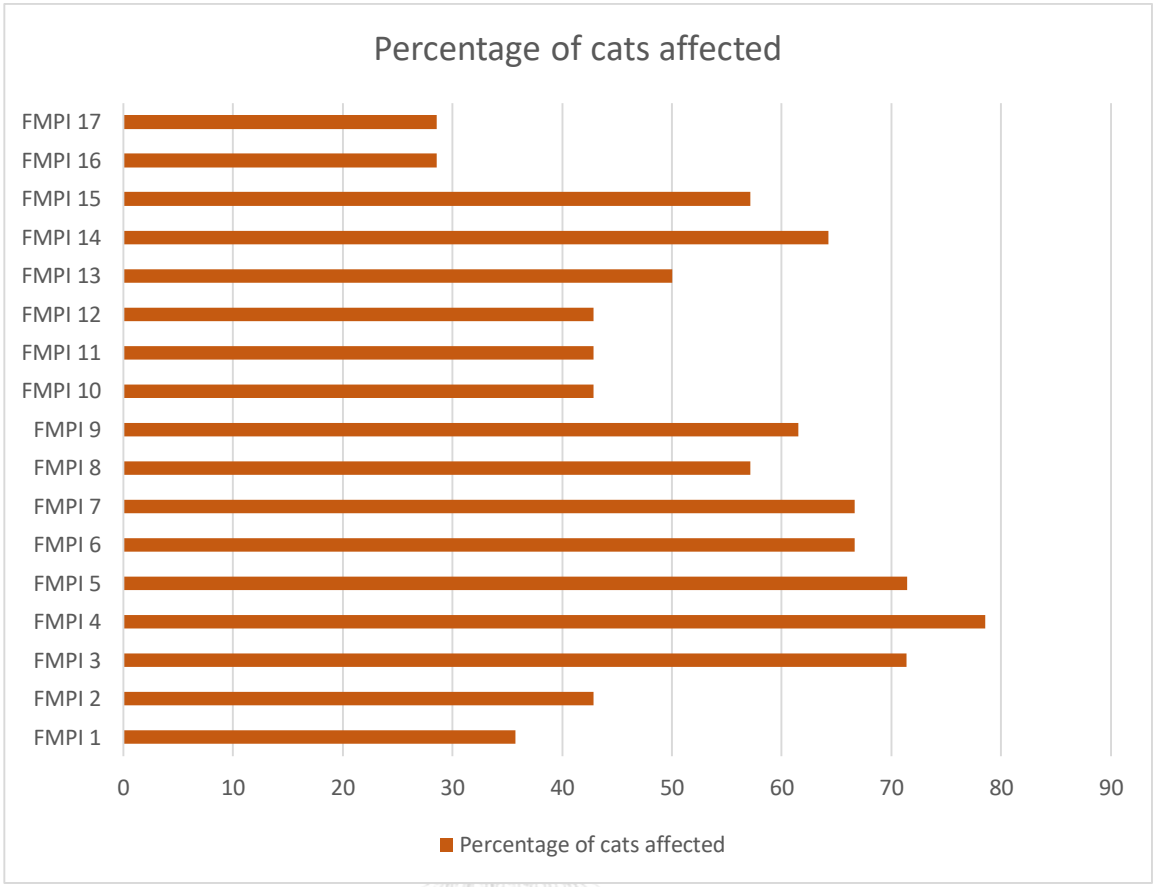


Figure 23 Activity deterioration reported in percentage of cats affected (treatment group).

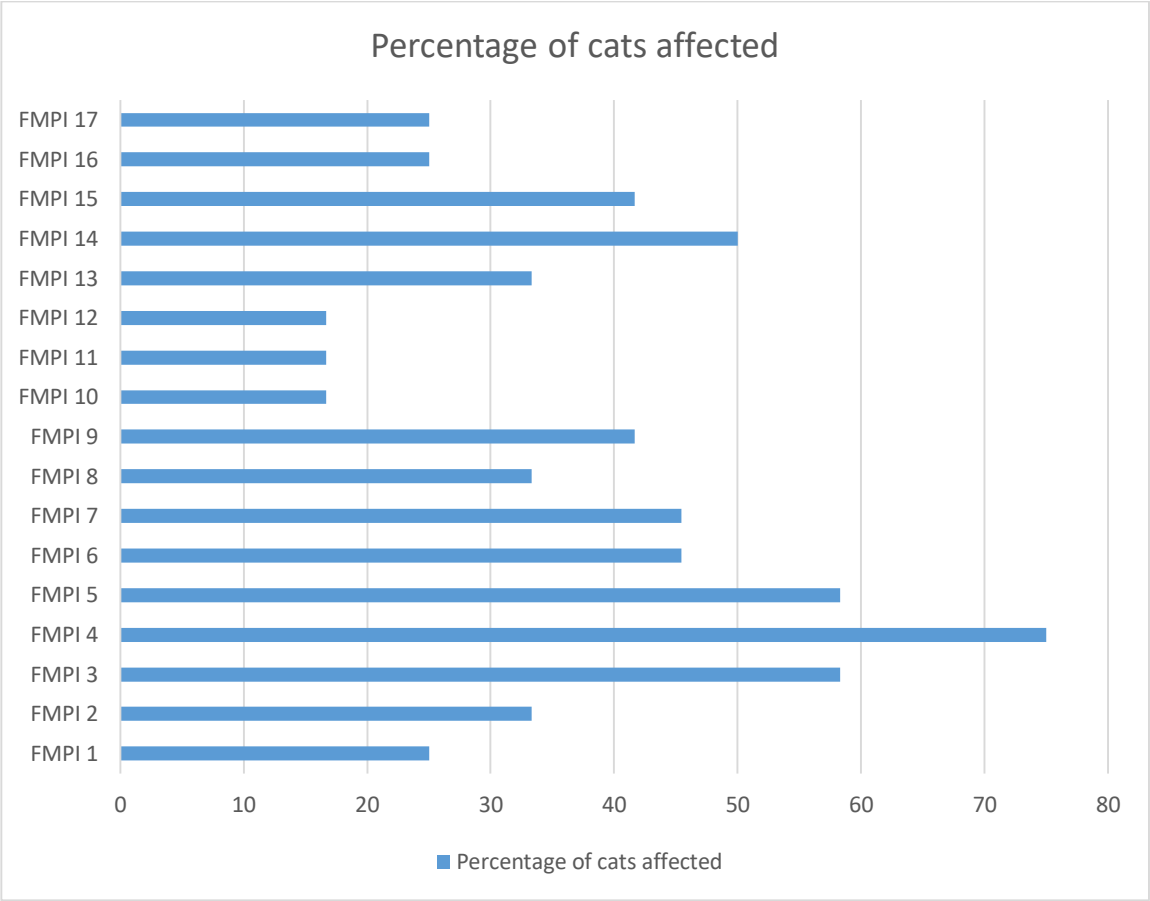


Figure 24 Activity deterioration reported in percentage of cats affected (control group)

Table 19 Variation of FMPI scores

Groups	Variation		Mean ±SD	
	Day 0	Day 60	Day 0	Day 60
Treatment	2-40	0-24	16.54 ±13.43	7.077 ±6.331**
Control	0-39	0-30	13.42 ±14.13	11.92 ±11.16

(*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001)

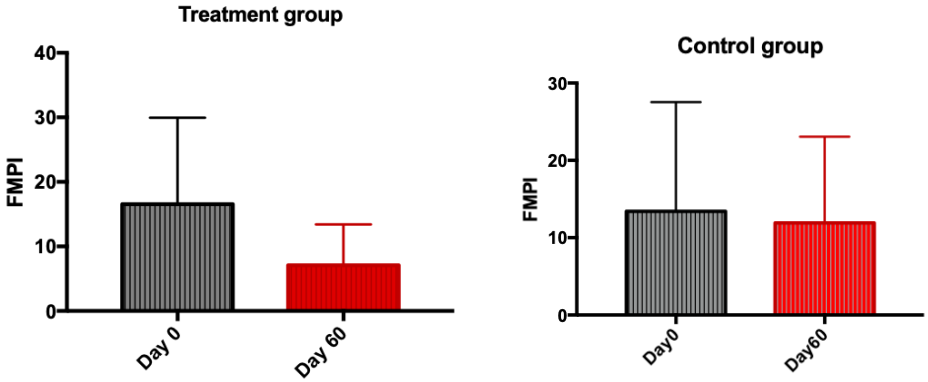


Figure 25 FMPI mean score

4.2.8 Jump test

All cats were allowed to jump down from material boxes at 40 and 80 centimetres in height. Both levels from treatment group, the scores found significantly increased at p=0.012 and <0.0001, respectively and no significant change in the control group (figure 26)

After using Dunnett's multiple comparisons test for jump test at 40 centimetres height, we found statistically significant at day 0 compared with day 42 (p=0.012) and day 0 compared with day 60 (p=0.046).

For jump test at 80 centimetres height, using Dunn's multiple comparisons test, we first found statistically significant at day 28 compared with day 0 (p= 0.010) followed by day 42 compared with day 0 (p= 0.005) and day 60 compared with day 0 (p= 0.0004).

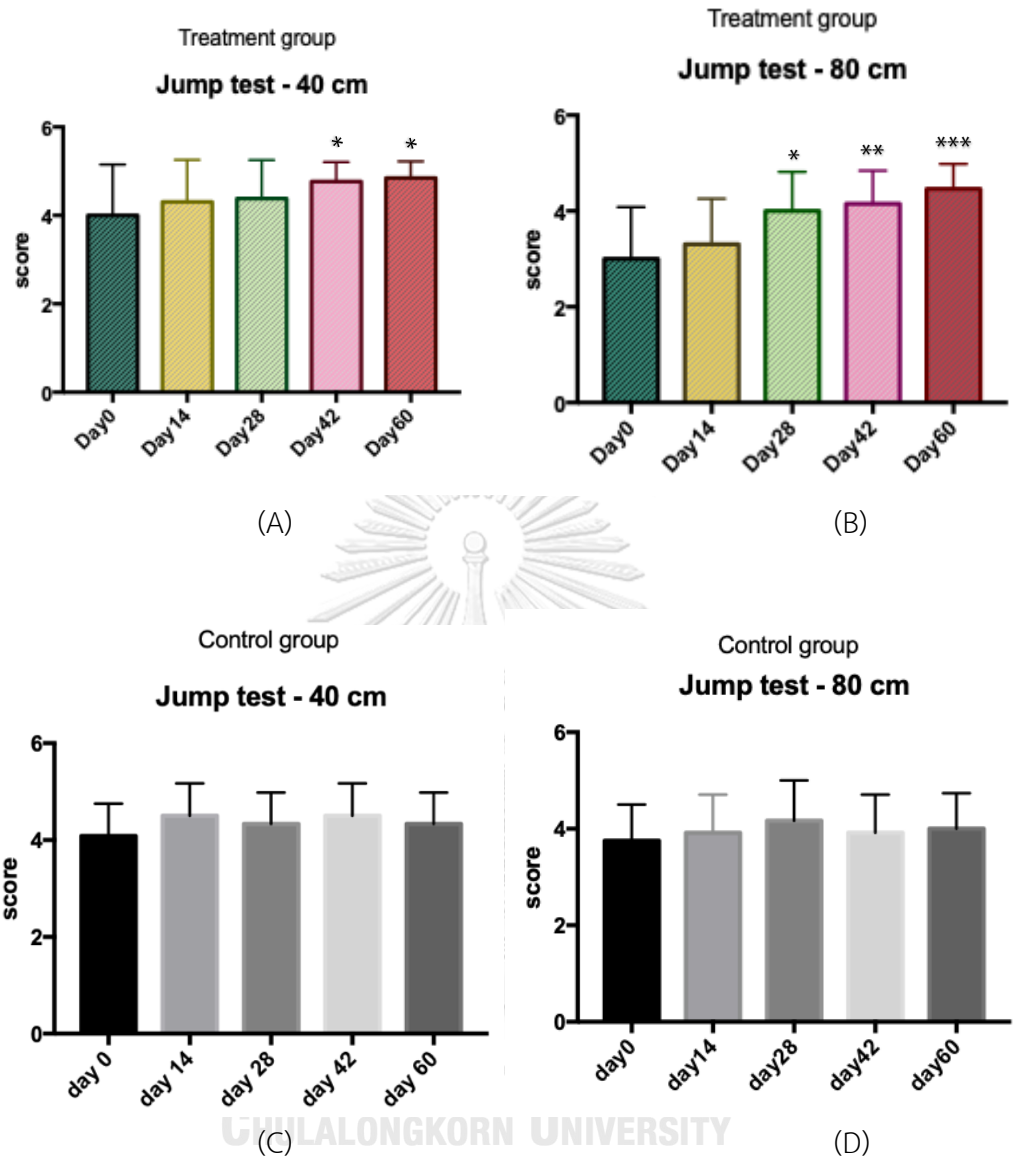


Figure 26 Jump test score variations in improvement from treatment and control group.

(A) described the score variations and improvement from Jump test at 40 centimetres height in treatment group, (B) described the score variations and improvement from Jump test at 80 centimetres height in treatment group, (C) described the score variations and improvement from Jump test at 40 centimetres height in control group, and (D) described the score variations and improvement from Jump test at 80 centimetres height in control group (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001).

4.3 Clinical assessment on CKD

4.3.1 Blood collection

Complete blood count, serum chemistry: ALT, ALP, BUN, Creatinine and TP were evaluated in every cat at day0, 14, 28, 42, 60 of treatment. All blood values revealed no significantly difference ($p>0.05$) between and within group in both control and treatment groups see appendix 7,8

Only blood creatinine level significantly decreased in treatment group ($p=0.036$) between day 0, 42 (p value = 0.049) and day 14, 42 (p value =0.018) (figure 27).

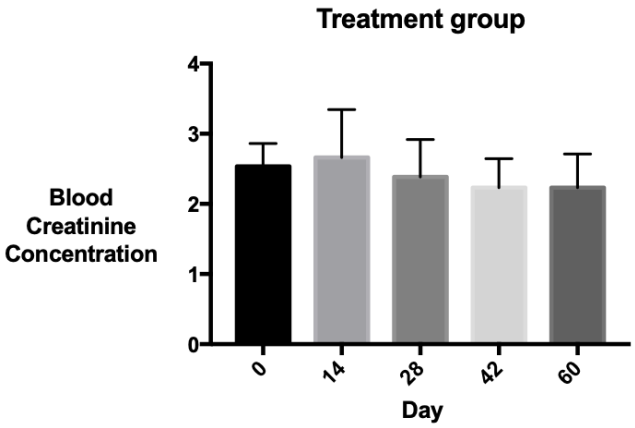


Figure 27 Blood creatinine concentration from treatment group

4.3.2 Urinalysis

Mid-stream voided was collected to perform chemical analysis using a multi-test dipstick and urinalysis in every cat at day 0, 14, 28, 42, 60 of treatment. pH and urine specific gravity measurement were not significantly change between controls and treatment groups (Appendix 9,10,11). Urine sediment under microscope remained inactive in all cats.

4.3.3 Blood pressure measurement

Hypertension was also associated with chronic kidney disease (Bijsmans et al., 2015). In this study, we monitored indirect blood pressure measurement every two weeks. The results showed blood pressure of all cats were in normal range with no statistically difference. (Appendix 12)

CHAPTER V

DISCUSSION

Feline osteoarthritis is common in cats (Freire et al., 2011; Ryan et al., 2013; Lemetayer and Taylor, 2014) and appears to be idiopathic. This disease has a high prevalence with 91% of affected cats had at least 1 site of appendicular OA. OA is involving cats with all ages, and for each year increasing. Imaging findings of OA increases by an estimated 13.6% (Lascelles et al., 2010). Advancing age is still the main risk factor for both increasing prevalence and severity of OA (Buckwalter and Mankin, 1998; Klinck et al., 2012); Ryan et al., 2013).

Obviously, obesity associated with lameness in cats (German et al., 2010; Klinck et al., 2012) but it has not been confirmed as a risk factor for feline OA as it did in many species, including human and dog. It maybe because cat did not have much variation in size even not in the same breed. Obesity has chronic, low-grade systemic inflammation. It raised the systemic concentration of both pro-inflammatory cytokines and acute phase proteins (APPs) (German et al., 2010), and blood cholesterol could influence lipid metabolism in the development of OA (Bennett et al., 2012a). High BCS may affect the severity of OA and even osteoarthritic cats enrolled in this study had regular BCS on average, however, four cats tended to be overweight (BCS4, 4.5) and two were obese cats (BCS 5).

Dogs with osteoarthritis may detect lameness easily such as skipping gaits or partial weight bearing while walking or running, unlike cats, cats tend to hide it as a self-defensive mechanism. Only 34% of cats included in this study expressed a sign of lameness and others with non-lameness sign found no crepitus and pain on palpation. The results revealed that lameness scoring system in cats was not suitable for clinical detection.

Kinetic and kinematic analysis routinely used for normal and pathological gait detection (Chayatup, 2016) as a non-subjective parameter. It could provide reliable and repeatable information of functional abilities in dogs and cats affected by naturally occurring osteoarthritis. However, some problems occurred when using in cats such as a conventional force platform is limited to large quadrupeds, which over 20 kg, so cats required a special-designed device to record ground reaction force. Moreover, handled cat with leash walking, in a straight line with its head in straightforward position at all time, at the same pace without velocity change is very difficult in untrained cats. However, strike action, camera angle and speed can affect the analysis results. In overall, with or without spending time for cat training, the reliability of replicable measures of ground reaction force in cats still remains unknown (Schnabl-Feichter et al., 2017).

Radiographic imaging considered to be an initial disease confirmation (Freire et al., 2011; Lemetayer and Taylor, 2014). Even though the radiographic findings are not always correlated to the symptoms (Bennett and Morton, 2009; Lascelles et al., 2010; Bennett et al., 2012a; Klinck et al., 2012). Radiographic features in feline OA basically found in the hip and elbow joints and appeared to be bilateral. Unlike canine patients, a new bone formation like periarticular mineralisation was seen commonly in these cats (Freire et al., 2011). The hip considered as three degrees of freedom ball and socket joint (Johnson, 2008) which the bone surfaces covered with articular cartilage which smooth viscoelastic tissue designed for bone protection and enables them to distribute loads across the diarthrodial joints (Akkiraju and Nohe, 2015). The thin lining, synovium, covers the surface of the joint. In a healthy hip, the synovium produces a small amount of fluid that lubricates the cartilage and aids in movement. In cats, the shallowed acetabulum is a similar circumstance to humans but differs from dogs, where subluxation of the hip joint, with or without a shallow acetabulum, is an early radiographic finding. In dogs, laxity of the hip joint has been recognised and this is generally accepted to play an essential role in the OA pathogenesis. (Keller et al., 1999; Perry, 2016). The most common radiographic features of feline hip OA is osteophytes which related to our study. However, shallowed acetabulum with remodelling involving the craniodorsal acetabular margin

and remodelling of the femoral neck were also common findings (Freire et al., 2011). The findings such as osteoarthritis-affected joints in cats are usually subtle. Thickening of the tissues surrounding affected joints could be more common (Clarke and Bennett, 2010). In our study, apart of hip subluxation, most radiographic lesions were found at caudal part of the acetabulum. The results of radiographic scoring showed no statistically significant changein control and treatment group. Every cat had same subluxation scores. Meanwhile, two cats in treatment group had radiographic evidence at day 60 with decreasing lesions due to minimising inflammation.

Owner-cooperation is still the vital key for recognition of the feline osteoarthritis. From never being diagnosed, the owners of cats that the age over than seven years (n=8) 100% had a false conventional belief that it was common whether the senior cats had a sedentary lifestyle. With or without owner perception, osteoarthritis is directly related to the pain causing alteration of cats' daily behaviour (Clarke and Bennett, 2006; Kerwin, 2010; Lascelles, 2010; Lascelles et al., 2010; Lascelles and Robertson, 2010; Slingerland et al., 2011; Gruen et al., 2014; Gruen et al., 2017), including changes in a cat's ability or willingness to jump up or down, moving up or down stairs, and are also seen a change in cats' mood and proper elimination (Kerwin, 2010; Slingerland et al., 2011; Gruen et al., 2014). we found jumping deterioration up to 77% of cats, followed by at less interaction with owners (57.69%) and other interest issues such as losing the ability to move fluidity, declined climbing the stairs, and mood swings (table 16,17).

All cat patients in this study had CKD in concurrence so the use of NSAIDs was limited. PCSO-524, a nutraceutical, played a leading role in order to relieve pain and inflammation. Three systems of pain assessment form which we had selected for this study were CMPS-Feline, CSU-FAPS and FMPI. The results were varied in these first two systems because they represented only the acute pain status. Even though both are time-saving, easy to use, and can be used as a guidance for analgesia provision but some cats may not display overt pain behaviour, especially in the presence of other animals and human or in any stressful situations. Therefore, these pain score systems may not reflect the real chronic pain situation in cat’s everyday

life, which directly related to the quality of life of the affected cats. The FMPI, was known for evaluating chronic pain, was an effective test parameter. It grouped cats into four domains; activity, pain, quality of life and total scores (Benito et al., 2013; Gruen et al., 2014). This pain score system received excellent reliability in all group of questionnaires in healthy and pain-DJD cats) and excellent repeatability for healthy and pain-DJD cats. Fundamentals of the FMPI were able to differentiate between healthy cats and cats with DJD (Benito et al., 2013). In our study, related to the previous report from Klinck et al. in 2012, main abnormal activities in daily life, including jumping up and down, and stair use. From the aspect of owner perception on their cats' pain, we found that owners did not recognise that cats were in pain, so they marked on the FMPI (question18,19) as no pain or less pain then we gave owner client education to make them better understanding about cats' conditions, therefore, they could mark more pain.

Differ from the Canine Brief Pain Inventory (CBPI), which had been validated and reliable in clinical dog patients with OA(Muller et al., 2016). CBPI is visual analogue system (VAS) allows owners to mark the severity of the dog's pain and the degree of pain. The CBPI has two domains; pain severity and interference with daily functions. Both are questionnaire-based assessment, whereas FMPI composes of 4 domains, aims to focus on normal cats' daily activity.

In treatment group, the FMPI gave us a good result with $p < 0.0001$ and no significant differences in the control group. In control group, we found the placebo effect at 41.67% (n=5) correlated with some previous studies in cats (Gruen et al., 2014; Gruen et al., 2017). Placebo effect may result from many causes such as the owner paid more attention to their cats, engaging cats more frequently in interactions and play, thereby increasing their total activity of both and the owners give a rating of their abilities, and the owner perhaps reducing anxiety or improving positive feelings. By the way, this study had limited as we only assess cats at day 0 and day 60, to gain more information and activity progression for future research FMPI should have evaluated every 1-2 week(s).

The jump test from specific high allowed us to see cats' activities development after PCSO-524 and placebo administration. Even the jump test gave

us the excellence outcome from the treatment group, but cats were easily stressed out - stimuli from the environment, places and others - could develop maladaptive behaviours. Therefore, it was possible to alter results from everyday life in some cats. For example, cats lived at home are afraid of jumping - may jump immediately without thinking; in contrast, did not dare to jump despite jumping high in their realm. The best activities assessment should be done at home.

Another non-subjective method we recommended for future study is the use of pedometer for assessing total daily cats' activities in their territory. As it has been reported that this simple and inexpensive device can measure physical activity in dogs with reasonable accuracy (Chan et al., 2005).

Other parameters to evaluate clinical osteoarthritis, including thigh circumference measurement and ROM measurement, were used in our study. Thigh circumference was measured from 73.08% (n=19) of patients due to temperament problem. We hypothesised that PCSO-524 could relieve cats' pain so they would gain more muscles due to more active lifestyles. Thigh circumference measurement from day 60 of the study tended to increase compared with day 0 but not significantly. Perhaps cats had sleek hair and moved so the position of measurement may have some discrepancies even we tried to reduce some errors by using the pen marked to correct position of measurement.

ROM measurement required cooperation from cats as well. In our study, we measured the motion of the hip and the stifle joints, only 65.38% (n=17) of our patients. Many studies claimed that PCSO-524 could enhance joint functions so we hypothesised that ROM should be increased as well. The consequence showed no significant difference, but in the treatment group, the motion angles of both joints tended to increase. Since decreasing range of joint motion was commonly seen in osteoarthritic dogs, but uncommon in cats (Klinck et al., 2012) and our patients had no stiff gaits in general. These may be the reasons why our result was not statistically significant difference. The alternative way to measure by reducing the error from not in cooperation of forced handling was sedation, but it was not practical in the clinic. However, there was a study that showed no significant differences in sedated or non-sedated cat in the ROM measurement. Both methods required cooperation from an

animal that is not tolerant of forced handling such as cat. Due to all the problems, we did not consider these two methods as valid parameters. Gait analysis may be recommended for further study.

All patients were CKD cats, so we had to evaluate blood creatinine and BUN values. Serum creatinine concentration, even it is not optimal biomarker to detect kidney disease in early stages, is considered the most routinely applied test for an initial determination of kidney function and diagnosis of renal diseases(Lopez-Giacoman and Madero, 2015). In our study, the treatment group found that PCSO-524 could decrease blood creatinine significantly, also observed in the previous study by Pusoonthornthum in 2017. After using multiple comparisons, we found significantly changed at day0 compared with 42 and day14 compared with 42, which probably due to the pathophysiology of kidney disease that has mild inflammation at all times. After received PCSO-524, which qualifying anti-inflammatory property caused decreasing inflammation or even with diet control and appropriate fluid therapy, may contribute to the decreasing in blood creatinine levels.

Routine urinalysis (USG measurement, urine trip test, examination of urine sediment) and blood pressure measurement were done every two weeks for this study. Urine strip test was a non-invasive and user-friendly diagnosis tool. Lots of false negatives and false positives such as alkaline urine, Hgb, myoglobin, fever, stress could interfere with the results. The use of Urine strip test is to be discouraged wherever possible as they are inaccurate, time-dependent and temperature-dependent. CKD in the early stages (IRIS stages 1 and 2) most can maintain some concentrating ability to keep their USG above the isosthenuria range (>1.015) (Cannon, 2016). As in our study, cat patients in both groups had USG 1.015 and above.

Systemic hypertension also associated with CKD and had a prevalence reported around 19–40% (Sparkes et al., 2016). Sustained systemic hypertension could promote proteinuria microalbuminuria and progressive CKD. Thus, blood pressure evaluation is a must. And in this study, we found all of the animals had blood pressure in the normal range throughout the study.

For further study, UP/C for proteinuria detection is highly recommended in patient with chronic kidney disease. Objective parameters such as pressure mat, kinetic, and kinematic gait analysis may help assess activities more precise. Other recommendations for chronic pain scoring system are Client specific outcome measures-feline (CSOM), Montreal instrument for cat arthritis testing for use by veterinarian, and Montreal Instrument for Cat Arthritis Testing for use by the caretaker. Re-evaluation should be done every 1-2 week(s).

To conclude, this study had the benefit of rising a strong human-animal bond. Owners, after receiving the information about disease understanding, they pay more attention to their pets and provide best home care management. PCSO-524 had high efficacy on clinical outcome (from both owner and animal side). It can improve mobility and motility of cat patients having osteoarthritis concurrence with chronic kidney disease as shown the excellence outcome from FMPI, aimed at directly detecting chronic pain. It can imply that PCSO-524 could bring out a better quality of life at its best without any unpleasant effect.

APPENDIX

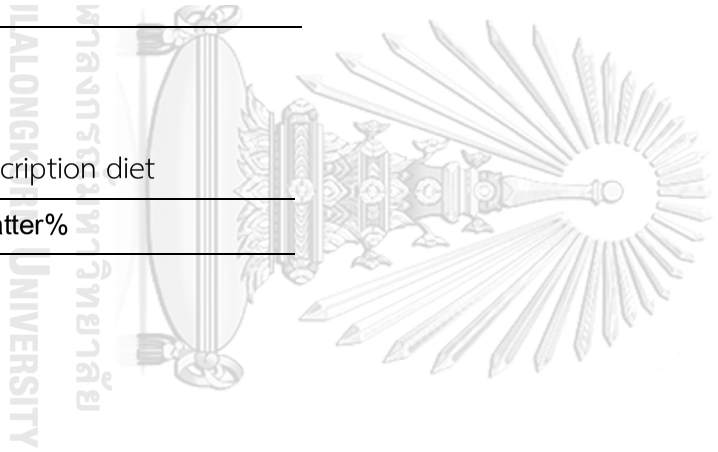
Appendix 1 composition of renal™ prescription diet

Nutrient	Dry matter%
Protein	23%
Crude ash	5.7%
Crude fibre	4.7%
Crude oil fats	17%
Moisture	5.5%
Maize flour, rice, animal fats, wheat gluten, soya protein isolate, vegetable fibres, maize, maize gluten, hydrolysed animal proteins, minerals, chicory pulp, dehydrated poultry protein, fish oil, soya oil, fructo-oligo-saccharides, psyllium husks and seeds, marigold extract (source of lutein)	

Additives	
Vitamin A	20800 IU
Vitamin D3	800 IU
E1 (Iron)	48 mg

E2 (Iodine)	4.8 mg
E4 (Copper)	15 mg
E5 (Manganese)	62 mg
E6 (Zinc)	187mg.

Preservatives - Antioxidants.



Appendix 2 composition of k/d™ prescription diet

Nutrient	Dry matter%
Protein	30.1
Fat	23.1
Crude fibre	0.9
Carbohydrate / NFE	40.5
Calcium	0.75
Phosphorus	0.51
Sodium	0.25
Potassium	0.75
Magnesium	0.081

Taurine	0.28
Vitamin C	143 ppm
Vitamin E	823 IU/kg
Total Omega-3 FA	0.85

Appendix 3 CMPS-Feline

Glasgow Feline Composite Measure Pain Scale: CMPS - Feline

Choose the most appropriate expression from each section and total the scores to calculate the pain score for the cat. If more than one expression applies choose the higher score

LOOK AT THE CAT IN ITS CAGE:

Is it?

Question 1

Silent / purring / meowing	0
Crying/growling / groaning	1

Question 2

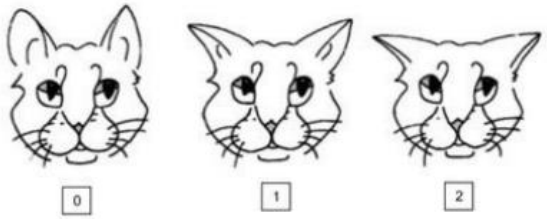
Relaxed	0
Licking lips	1
Restless/cowering at back of cage	2
Tense/crouched	3
Rigid/hunched	4

Question 3

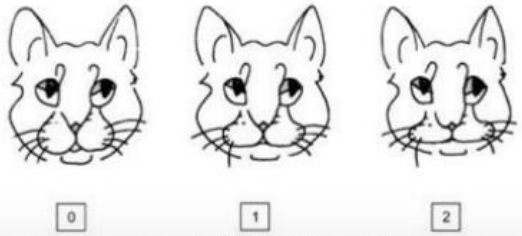
Ignoring any wound or painful area	0
Attention to wound	1

Question 4

a) Look at the following caricatures. Circle the drawing which best depicts the cat's ear position?



b) Look at the shape of the muzzle in the following caricatures. Circle the drawing which appears most like that of the cat?



APPROACH THE CAGE, CALL THE CAT BY NAME & STROKE ALONG ITS BACK FROM HEAD TO TAIL

Question 5

Does it?

Respond to stroking	0

Is it?

Unresponsive	1
Aggressive	2

IF IT HAS A WOUND OR PAINFUL AREA, APPLY GENTLE PRESSURE 5 CM AROUND THE SITE. IN THE ABSENCE OF ANY PAINFUL AREA APPLY SIMILAR PRESSURE AROUND THE HIND LEG ABOVE THE KNEE

Question 6

Does it?

Do nothing	0
Swish tail/flatten ears	1
Cry/hiss	2
Growl	3
Bite/lash out	4

Question 7

General impression

Is the cat?

Happy and content	0
Disinterested/quiet	1
Anxious/fearful	2
Dull	3
Depressed/grumpy	4

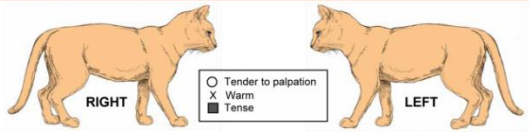
Pain Score ... /20

Appendix 4 CSU-Feline

Colorado State University

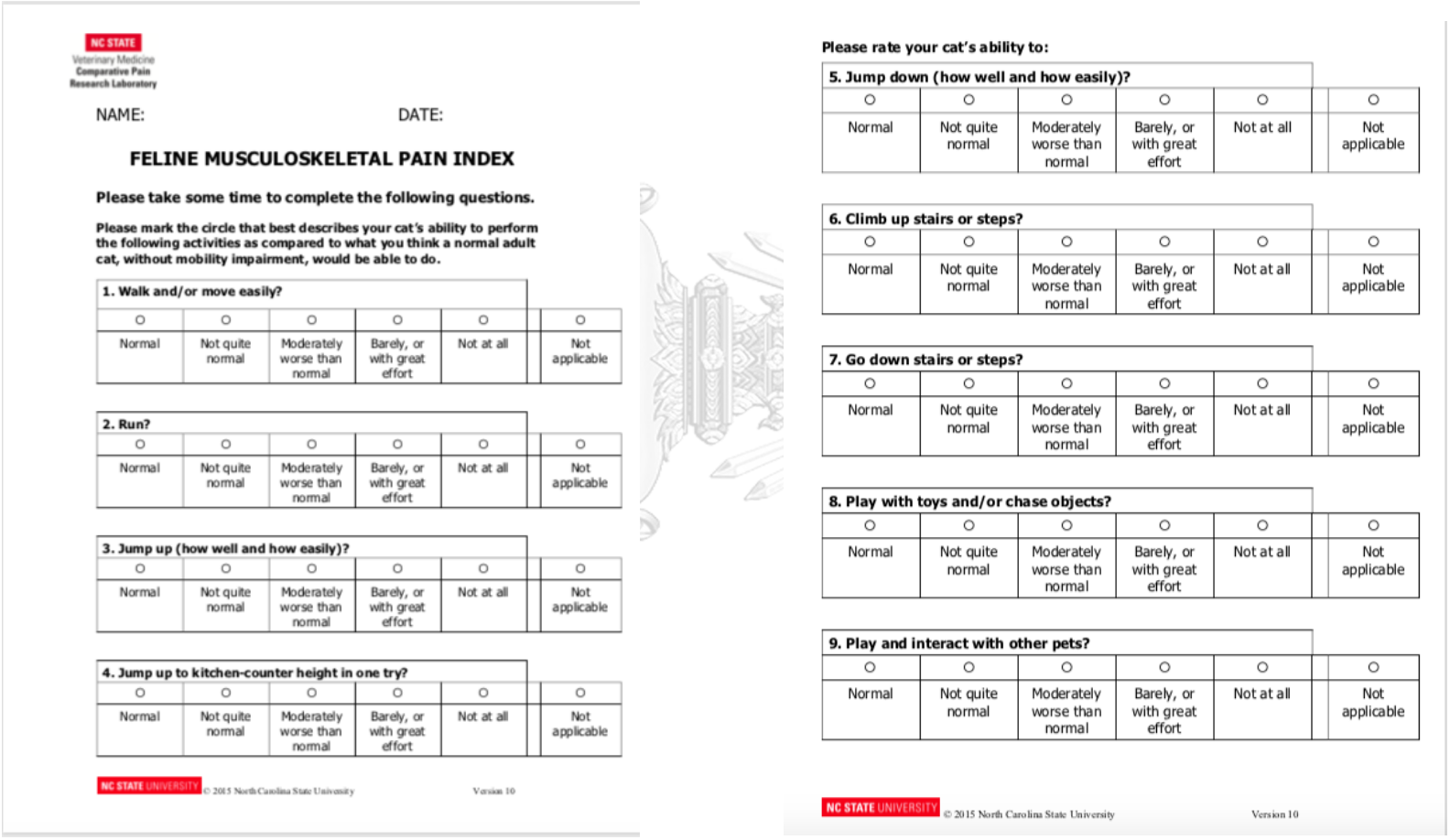
Colorado State University
Veterinary Medical Center
Feline Acute Pain Scale

Pain Score	Example	Psychological & Behavioral	Response to Palpation	Body Tension
No Score		❑ **Animal is sleeping and cannot be evaluated**		
0		❑ **Content and quiet** when unattended ❑ **Comfortable** when resting ❑ Interested in or **curious** about surroundings	❑ **Not bothered** by palpation of wound or surgery site, or to palpation elsewhere	Minimal
1		❑ **Signs are often subtle and not easily detected in the hospital setting**; more likely to be detected by the owner(s) at home ❑ Earliest signs at home may be **withdrawal from surroundings or change in normal routine** ❑ In the hospital, may be content or **slightly unsettled** ❑ **Less interested** in surroundings but will look around to see what is going on	❑ May or may not react to palpation of wound or surgery site	Mild
2		❑ Decreased responsiveness, **seeks solitude** ❑ **Quiet**, loss of brightness in eyes ❑ **Lays curled up or sits tucked up** (all four feet under body, shoulders hunched, head held slightly lower than shoulders, tail curled tightly around body) with eyes partially or mostly closed ❑ **Hair coat appears rough** or fluffed up ❑ May intensively groom an area that is painful or irritating ❑ Decreased appetite, **not interested in food**	❑ **Responds aggressively or tries to escape** if painful area is palpated or approached ❑ Tolerates attention, may even perk up when petted as long as painful area is avoided	Mild to Moderate **Reassess analgesic plan**
3		❑ Constantly **yowling, growling, or hissing** when unattended ❑ May bite or chew at wound, but **unlikely to move** if left alone	❑ **Growls or hisses at non-painful palpation** (may be experiencing allodynia, wind-up, or fearful that pain could be made worse) ❑ **Reacts aggressively** to palpation, **adamantly pulls away** to avoid any contact	Moderate **Reassess analgesic plan**
4		❑ Prostrate ❑ Potentially **unresponsive** to or unaware of surroundings, difficult to distract from pain ❑ Receptive to care (even mean or wild cats will be more tolerant of contact)	❑ **May not respond** to palpation ❑ **May be rigid to avoid painful movement**	Moderate to Severe **May be rigid to avoid painful movement** **Reassess analgesic plan**



Comments _____

Appendix 5 FMPI



NC STATE
Veterinary Medicine
Comparative Pain
Research Laboratory

NAME: DATE:

FELINE MUSCULOSKELETAL PAIN INDEX

Please take some time to complete the following questions.

Please mark the circle that best describes your cat's ability to perform the following activities as compared to what you think a normal adult cat, without mobility impairment, would be able to do.

1. Walk and/or move easily?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

2. Run?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

3. Jump up (how well and how easily)?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

4. Jump up to kitchen-counter height in one try?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

NC STATE UNIVERSITY Version 10

Please rate your cat's ability to:

5. Jump down (how well and how easily)?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

6. Climb up stairs or steps?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

7. Go down stairs or steps?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

8. Play with toys and/or chase objects?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

9. Play and interact with other pets?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

NC STATE UNIVERSITY Version 10

Please rate your cat's ability to:

10. Get up from a resting position?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

11. Lie and/or sit down?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

12. Stretch?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

13. Groom himself or herself?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

14. Interact with you and family members?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

 Version 10

Please rate your cat's ability to:

15. Tolerate being touched and/or held?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

16. Eat?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

17. Use the litter box (get in and out, squat, cover waste?

○	○	○	○	○	○
Normal	Not quite normal	Moderately worse than normal	Barely, or with great effort	Not at all	Not applicable

 Version 10

Appendix 6 Mean of body temperature of both groups

Groups	Normal range (° F)	Mean ±SD				
		Day 0	Day 14	Day 28	Day 42	Day 60
Treatment	99.5 -102.5	101.7 ±0.648	101.7 ±0.722	101.6 ±0.665	101.6 ±0.658	101.6 ±0.635
Control	99.5 -102.5	101.6 ±0.477	101.6 ±0.52	101.5 ±0.648	101.7 ±0.451	101.6 ±0.566

Appendix 7 Mean of haematology and blood chemistry between day0 and day60 of treatment group.

Parameters	**Normal range**	**Mean ±SD**				
		Day 0	**Day 14**	**Day 28**	**Day 42**	**Day 60**
RBC ($x10^6$) per µl	4.95-10.53	7.929 ±1.516	7.819 ±1.616	7.484 ±1.615	7.357 ±1.683	7.357 ±1.683
Hemoglobin (g/dl)	8.5-14.4	11.52 ±1.971	11.38 ±1.79	11.62 ±2.136	11.49 ±2.566	11.17 ±2.627
Hematocrit (%)	25.8-41.8	33.2 ±3.605	34.07 ±3.379	33.13 ±3.2	32.88 ±3.141	32.35 ±2.572
Platelet (x 10^3) per µl	160-660	232.6 ±73.71	234.3 ±81.65	236.3 ±90.84	229.9 ±89.35	226.3 ±81.83
WBC per µl	3.8-19	14.86 ±2.934	14.93 ±2.778	14.51 ±2.587	14.77 ±3.146	14.01 ±3.146

Neutrophils (%)	34-84	71.62 ±7.243	70.88 ±8.84	72.92 ±11.74	70.94 ±8.751	69.92 ±8.614
Eosinophils (%)	0-12	3.253 ±3.003	3.1 ±2.761	3.138 ±2.803	3.107 ±2.71	2.908 ±2.525
Basophils (%)	0-1	0.042 ±0.051	0.05 ±0.052	0.05 ±0.052	0.042 ±0.051	0.026 ±0.045
Lymphocytes (%)	7-60	17.52 ±7.874	17.45 ±8.645	17.46 ±8.417	17.82 ±8.711	17.32 ±9.202
Monocytes (%)	0-5	2.608 ±1.308	2.708 ±1.491	2.667 ±1.438	2.483 ±1.315	2.683 ±1.587
Alanine aminotransferase (ALT)	13-75	57.5 ±20.77	55.58 ±18.81	54.17 ±17.62	53.08 ±19.34	55.58 ±17.85
Alkaline phosphatase (ALP)	3-61	41.92 ±23.73	44.08 ±28.47	41.33 ±25.74	42 ±23.58	42.08 ±22.69
Total protein (TP) g%	6.1-8.8	6.83 ±0.611	6.76 ±0.674	6.67 ±0.749	6.67 ±0.749	6.63 ±0.806
Blood urea nitrogen (BUN) mg%	10-30	53.42 ±17.88	52.74 ±21.32	53.09 ±15.44	49.18 ±19.23	51.15 ±18.16
Creatinine mg%	0.8-2.0	2.531 ±0.328	2.662 ±0.684	2.385 ±0.534	2.231 ±0.415*	2.231 ±0.482

(*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001)

Appendix 8 Mean of haematology and blood chemistry between day0 and day60 of control group.

Parameters	Normal range	Mean ±SD				
		Day 0	Day 14	Day 28	Day 42	Day 60
RBC ($x10^6$) per µl	4.95-10.53	7.252 ±2.009	6.465 ±1.75	6.61 ±1.985	6.899 ±1.784	6.748 ±2.2
Hemoglobin (g/dl)	8.5-14.4	11.92 ±3.566	11.02 ±1.744	11.16 ±2.361	11.85 ±2.351	11.85 ±1.702
Hematocrit (%)	25.8-41.8	33.22 ±7.661	29.68 ±6.827	30.42 ±8.593	31.46 ±7.502	31.67 ±6.927
Platelet ($x 10^3$) per µl	160-660	220.6 ±79.88	215.8 ±72.91	224.5 ±68.26	211.1 ±59.83	216.3 ±86.45
WBC per µl	3.8-19	12.23 ±3.796	11.94 ±3.283	11.53 ±2.352	12.41 ±3.072	11.88 ±2.628
Neutrophils (%)	34-84	67.81 ±8.7748	66.88 ±9.058	66.84 ±7.188	63.68 ±11.08	65.16 ±9.468
Eosinophils (%)	0-12	2.25 ±1.59	2.49 ±1.501	2.43 ±1.359	1.94 ±1.344	2.15 ±1.581
Basophils (%)	0-1	0.05 ±0.053	0.01 ±0.031	0.03 ±0.048	0.03 ±0.048	0.03 ±0.048
Lymphocytes (%)	7-60	14.9 ±6.604	14.44 ±6.304	17.22 ±8.042	16.7 ±8.776	17.97 ±9.512
Monocytes (%)	0-5	2.11 ±1.166	1.9 ±0.585	2.15 ±1.049	2.7 ±0.969	2.36 ±0.72
Alanine aminotransferase (ALT)	13-75	53.7 ±16.87	56.7 ±16.84	51.7 ±20.2	54.5 ±19.32	53.2 ±17.05

Alkaline phosphatase (ALP)	3-61	30.3 ±13.72	28.4 ±12.6	29.6 ±13.13	27.1 ±11.49	26.5 ±11.88
Total protein (TP) g%	6.1-8.8	7.13 ±0.57	6.83 ±0.685	6.91 ±0.814	7.07 ±0.829	6.91 ±0.608
Blood urea nitrogen (BUN) mg%	10-30	45.55 ±19.34	46.5 ±17.79	46.49 ±20.73	53.93 ±21.12	46.2 ±17.79
Creatinine mg%	0.8-2.0	2.363 ±0.746	2.338 ±0.769	2.625 ±0.927	2.5 ±0.847	2.65 ±0.835

Appendix 9 urine dipstick result from treatment group

	Mean ±SD				
	Day 0	**Day 14**	**Day 28**	**Day 42**	**Day 60**
pH	6.5 ±0.76	6.5 ±0.941	6.429 ±0.851	6.5 ±0.76	6.5 ±0.855
Protein	neg	neg	neg	neg	neg
Glucose	neg	neg	neg	neg	neg
Ketones	neg	neg	neg	neg	neg
Bilirubin	neg	neg	neg	neg	neg
Urobilinogen	neg	neg	neg	neg	neg
Blood	neg	neg	neg	neg	neg
Nitrites	neg	neg	neg	neg	neg

Appendix 10 urine dipstick result from control group

	Mean ±SD				
	Day 0	Day 14	Day 28	Day 42	Day 60
pH	6.5 ±0.522	6.417 ±0.515	6.417 ±0.515	6.417 ±0.515	6.5 ±0.522
Protein	neg	neg	neg	neg	neg
Glucose	neg	neg	neg	neg	neg
Ketones	neg	neg	neg	neg	neg
Bilirubin	neg	neg	neg	neg	neg
Urobilinogen	neg	neg	neg	neg	neg
Blood	neg	neg	neg	neg	neg
Nitrites	neg	neg	neg	neg	neg

Appendix 11 Mean of USG of both groups

Groups	Normal range	Mean ±SD				
		Day 0	Day 14	Day 28	Day 42	Day 60
Treatment	1.012-1.035	1.016 ±0.005	1.016 ±0.005	1.016 ±0.005	1.015 ±0.004	1.015 ±0.003
Control	1.012-1.035	1.018 ±0.006	1.018 ±0.006	1.018 ±0.005	1.018 ±0.005	1.018 ±0.006

Appendix 12 Mean of blood pressure of both groups

Groups	Normal range	Mean ±SD				
		Day 0	Day 14	Day 28	Day 42	Day 60
Treatment	<140	135 ±9.608	132.5 ±10.14	133.2 ±10.3	133.2 ±9.116	131.1 ±10.22
Control	<140	135.7 ±8.516	136.1 ±10.77	135.4 ±10.65	135 ±10.92	133.2 ±11.54

Appendix 13 Mean of jump test of both group

Groups	Mean ±SD (day0)		Mean ±SD (day14)		Mean ±SD (day28)		Mean ±SD (day42)		Mean ±SD (day60)	
	40 cm	80 cm	40 cm	80 cm	40 cm	80 cm	40 cm	80 cm	40 cm	80 cm
Treatment	4 ±1.155	3 ±1.08	4.308 ±0.947	3.308 ±0.948	4.385 ±0.87	4* ±0.817	4.769* ±0.439	4.077** ±0.76	4.846* ±0.376	4.231*** ±0.725
Control	4.083 ±0.067	3.75 ±0.754	4.5 ±0.674	3.917 ±0.793	4.333 ±0.651	4.167 ±0.835	4.5 ±0.674	3.917 ±0.794	4.333 ±0.651	4 ±0.739

(*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001)

Appendix 14 Mean of lameness score of both groups.

Groups	Mean ±SD				
	Day 0	Day 14	Day 28	Day 42	Day 60
Treatment	0.5 ±0.65	0.429 ±0.646	0.357 ±0.633	0.357 ±0.497	0.214 ±0.579
Control	0.667 ±0.888	0.333 ±0.651	0.25 ±0.622	0.25 ±0.452	0.417 ±0.793

Appendix 15 Mean of CMPS-Feline of both groups.

Groups	Mean ±SD				
	Day 0	Day 14	Day 28	Day 42	Day 60
Treatment	3.667 ±3.473	3.833 ±3.738	3.25 ±2.927	2.833 ±2.623	2.917 ±2.151
Control	3.667 ±2.708	3.583 ±2.353	3.167 ±2.29	3.333 ±2.309	2.917 ±2.466

Appendix 16 Mean of CSU-FAPS of both groups.

Groups	Mean ±SD				
	Day 0	Day 14	Day 28	Day 42	Day 60
Treatment	0.4615 ±0.66	0.385 ±0.65	0.308 ±0.48	0.308 ±0.48	0.4615 ±0.66
Control	0.333 ±0.492	0.1667 ±0.389	0.25 ±0.452	0.333 ±0.492	0.333 ±0.492

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