UNIVERSITI PUTRA MALAYSIA

FELINE CONGESTIVE HEART FAILURE: MORTALITY RATE AND SURVIVABILITY AND DETERMINATION OF CLINICAL EFFICACY OF PIMOBENDAN AS ALTERNATIVE THERAPY

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FELINE CONGESTIVE HEART FAILURE:

MORTALITY RATE AND SURVIVABILITY AND DETERMINATION OF CLINICAL EFFICACY OF PIMOBENDAN AS ALTERNATIVE THERAPY

JESSIE BAY JI XI

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It is hereby certified that we have read this project paper entitled "Feline Congestive Heart Failure: Mortality rate and Survivability and Determination of Clinical Efficacy of Pimobendan as Alternative Therapy", by Jessie Bay Ji Xi and in our opinion it is satisfactory in terms of scope, quality, and presentation as partial fulfillment of the requirement for the course VPD 5908 – Project

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Abstrak

Abstrak daripada kertas projek yang dikemukakan kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripada keperluan kursus VPD 5908 -Projek

Kegagalan Jantung Kongestif Feline: Kadar Kematian dan Ketahanan dan Penentuan Keberkesanan Klinikal Pimobendan sebagai Terapi Alternatif

Oleh

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2018

Penyelia: Dr. Khor Kuan Hua

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Kes penyakit jantung kucing semakin meningkat. Pesakit-pesakit ini sering datang dengan simptom simptom kegagalan jantung kongestif, tromboembolisme aorta tisu dan kematian secara tiba-tiba. Matlamat kajian adalah untuk menentukan; 1) menentukan kadar kematian dan survivabiliti kucing yang didiagnosis dengan penyakit jantung kongestif dan, 2) untuk mengaitkan perkembangan klinikal padakucing yang didiagnosis dengan penyakit jantung kongestif yang dirawat dengan pimobendan. Maklumat mengenai pesakit kucing di Hospital Veterinar Universiti, Universiti Putra Malaysia yang didiagnosis dengan penyakit jantung dikumpulkan dan pemilik kucing dihubungi untuk mendapat maklumat susulan mengenai keadaan pesakit jantung kucing . Klasifikasi Persatuan Perubatan *New York* yang telah

diubahsuai digunakan untuk mengklasifikasikan pesakit jantung kucing. Kadar mortaliti dan survivalbiliti ditentukan menggunakan penganggar Kaplan-Meier. Kucing yang tidak menunjukkan perkembangan selepas rawatan dengan kombinasi inhibitor-ACE direkrut dan dirawat dengan pimobendan selama dua bulan. Perkembangan kucing akan berdasarkan pemerhatian tanda-tanda klinikal, pengukuran serum troponin konsentrasi jantung, pemantauan tekanan darah, radiografi, dan ekocardiografi. Data yang diperoleh akan dianalisis menggunakan ujian T-pair dan One-way ANOVA untuk menentukan keberkesanan pimobendan sebelum dan selepas rawatan dalam terapi sepanjang 2 bulan. Kadar kematian yang ditentukan ialah 26.7% dan tidak ada faedah kelangsungan hidup bagi kucing dengan pemilik yang ikut regim yang disyorkan ($p > 0.05$). Rawatan Pimobendan bermanfaat untuk kucing yang didiagnosis dengan dilated kardiomyopati dan restrictive kardiomyopati. Kegunaan pimobendan dalam kucing menghidapi penyakit jantung hypertrophy kardiomyopati perlu dipantau dengan teliti.

Kata kunci: biomarker jantung, kardiomiopati, Kaplann-Meier, radiografi

ABSTRACT

An abstract of the project paper presented to the Faculty of Veterinary Medicine in partial fulfillment of the course VPD 5908- Project.

Feline Congestive Heart Failure: Mortality rate and Survivability and Determination of Clinical Efficacy of Pimobendan as Alternative Therapy

by

Jessie Bay Ji Xi

Supervisor: Dr. Khor Kuan Hua

Co- supervisor: Prof Dr. Rasedee Abdullah

Abstract

The occurrences of heart disease in cats had increased with the availability of echocardiography. These patients are often presented with congestive heart failure, feline aortic thromboembolism and sudden death. In this study, the objectives were; 1) to determine the mortality rate and survivability of cats diagnosed with congestive heart failure and, 2) to correlate the clinical progressions and outcomes of cats diagnosed with congestive heart failure that were treated with pimobendan. Information on cats presented at the University Veterinary Hospital, Universiti Putra Malaysia that were diagnosed with cardiac diseases were collected and the cat owners were contacted for follow-ups on the cats' heart condition. The modified New York Medical Associate classification was used to stage the cats' heart condition. The mortality rate and survivability was determined using the Kaplan-Meier estimator. Cats that showed no improvement after treatment with diuretics-ACE inhibitor

combination were recruited and treated with pimobendan for two months. The clinical efficacy of the drug was monitored based on observation of clinical signs, measurement of serum cardiac troponin concentrations, blood pressure monitoring, radiography, and echocardiography. Data obtained was analysed using paired *T*-test and One-way ANOVA to determine the effect of pimobendan pre- and post-treatment during the 2 months therapy. As a conclusion, the mortality rate determined was 26.7% and the there was no survival benefit for the cats with compliant owners ($p > 0.05$) despite the class of the feline cardiac patients grouped into. Pimobendan treatment was beneficial for cats diagnosed with dilated cardiomyopathy and restrictive cardiomyopathy. Administration of pimobendan in cats with hypertrophy cardiomyopathy has to be monitored closely.

Keywords: Congestive heart failure, cardiac biomarkers, cardiomyopathy

Chapter 1

Introduction

Cardiac failure is a complex condition as a consequence of cardiac diseases resulted from structural and/or functional impairment of ventricular filling or ejection of blood (Yancy *et al.*, 2013). Clinical signs of congestive heart failure (CHF) are characterised by a combination findings of respiratory signs (i.e. tachypnoea/ dyspnoea) obtained from clinical history, abnormal findings of the cardiorespiratory examination and radiography (i.e. pulmonary edema, pleural effusion and ascites) finding. To determine the cause of CHF, echocardiography remains the most important diagnostic tool that provides the definitive diagnosis of the heart disease (Ferasin, 2015).

Hypertrophic cardiomyopathy (HCM) and hypertrophic obstructive cardiomyopathy (HOCM) are the most common underlying cause of CHF in cats (Paige *et al.*, 2009). HCM are characterised by ventricular hypertrophy, diastolic dysfunction, elevation of left ventricular end diastolic pressure and left atrial pressure (Reina-Doreste *et al.*, 2014). Cats with HCM with and concurrent left ventricular outflow tract obstruction (LVOT) are classified as HOCM. HOCM cats normally have either cranial motion of the mitral valve during systole, assymetrical septal hypertrophy, or a combination of both (Reina-Doreste *et al.*, 2014). Therefore, CHF in cats diagnosed with HCM or HOCM occurred when the end-diastolic pressures and the left atrial pressure was elevated causing an increased of the pulmonary venous

pressure. This eventually leads to the formation of pulmonary edema, pleural, pericardial and abdominal effusion (Côté, 2017).

Cardiovascular biomarkers (Connolly *et al*., 2009; Borgeat *et al.*, 2015) are widely used in veterinary practices to determine the severity of the cardiac disease conditions in cats. Measurements of cardiac troponin I (cTnI) and N-terminal pro-B type natriuretic peptide (NTproBNP) are commonly used in conjunction with other diagnostic assessments, such as radiography and echocardiography (Ferasin and DeFrancesco, 2015). Besides its utility for diagnosis, these cardiac biomarkers had been routinely used in human medicine to monitor disease progression during long-term medication.

Clinical management of feline cardiac patients includes a combination of diuretics, angiotensin-converting enzyme (ACE) inhibitors, and anti-thrombotics drugs. Up till today, there is not one drugs that has been shown to be able to control CHF well (Hunt, 2005), but studies have reported that treatment would improve quality of life in cats diagnosed with heart disease.

Recently, a positive inotropic drug has been introduced as off-label used. MacGregor (2011) suggested pimobendan to be used as a treatment of heart disease in cats. In 2007, pimobendan obtained approval of use by FDA in United States (Atkins et al., 2009). Since then, pimobendan has been frequently used in the treatment of canine CHF secondary to dilated cardiomyopathy (DCM) or myxomatous mitral valvular disease (MMVD) (Boswood, 2010). With the beneficial efficacy seen in dogs,

it was believed that pimobendan may provide similar beneficial effects to feline heart patients with no systolic dysfunction (Gordan *et. al*., 2012). It was also expected that treatment using pimobendan may prolong survival time while reducing incidence of CHF in cats.

In this study, there were two objectives investigated. Study 1; determined the mortality rate and survivability of cats diagnosed with CHF, and Study 2; determined the effect of pimobendan on blood cardiovascular biomarkers, cTnI and NTproBNP, in cats diagnosed with heart disease with concurrent congestive heart failure during a 2-month treatment period. Both of the study was written in two different chapters, namely Chapter 3 and Chapter 4 of this thesis.

References

Abbott, J., & MacLean, H. (2006). Two-Dimensional Echocardiographic Assessment of the Feline Left Atrium. Journal Of Veterinary Internal Medicine, 20(1), 111. doi: 10.1892/0891-6640(2006)20[111:teaotf]2.0.co;2

Available at: https://www.fda.gov/ohrms/dockets/98fr/2007-141-273-fois001.pdf. Accessed August 8, 2017.

Adams, J., Bodor, G., Davila-Roman, V., Delmez, J., Apple, F., Ladenson, J., & Jaffe, A. (1993). Cardiac troponin I. A marker with high specificity for cardiac injury. Circulation, 88(1), 101-106. doi: 10.1161/01.cir.88.1.101

Atkins, C., Bonagura, J., Ettinger, S., Fox, P., Gordon, S.&Haggstrom, J. et al. (2009). Guidelines for the Diagnosis and Treatment of Canine Chronic Valvular Heart Disease. *Journal of Veterinary Internal Medicine*, *23*(6), 1142-1150. http://dx.doi.org/10.1111/j.1939-1676.2009.0392.x

Berendsen M and Knol BW (2002). Treatment compliance. Tijdschr Diergeneeskd 2002; 127: 548–51.

Boon JA (1998) The echocardiographic examination. In:Manual of Veterinary Echocardiography. Baltimore: Williams and Wilkins, pp. 35–150

Borgeat, K., Connolly, D. and Luis Fuentes, V. (2015). Cardiac biomarkers in cats. *Journal of Veterinary Cardiology*, 17, ppS74-S86.

Boswood, A. (2010). Current Use of Pimobendan in Canine Patients with Heart Disease. *Veterinary Clinics of North America: Small Animal Practice*, *40*(4), 571-580. http://dx.doi.org/10.1016/j.cvsm.2010.04.003

Chapman, C. (1996). Therapeutic compliance. Australian Veterinary Journal, 74(6), 442-442. doi: 10.1111/j.1751-0813.1996.tb07565.x

Connolly, D., Cannata, J., Boswood, A., Archer, J., Groves, E., & Neiger, R. (2003). Cardiac troponin I in cats with hypertrophic cardiomyopathy. Journal Of Feline Medicine And Surgery, 5(4), 209-216. doi: 10.1016/s1098-612x(03)00007-x

Connolly, D., Guitian, J., Boswood, A., & Neiger, R. (2005). Serum troponin I levels in hyperthyroid cats before and after treatment with radioactive iodine. *Journal Of Feline Medicine And Surgery*, *7*(5), 289-300. doi: 10.1016/j.jfms.2005.01.002

Connolly, D., Brodbelt, D., Copeland, H., Collins, S. &Fuentes, V. (2009). Assessment of the diagnostic accuracy of circulating cardiac troponin I concentration to distinguish between cats with cardiac and non-cardiac causes of respiratory distress. *Journal of Veterinary Cardiology*, *11*(2), 71-78. http://dx.doi.org/10.1016/j.jvc.2009.09.002

Côté, E. (2017). Feline Congestive Heart Failure. *Veterinary Clinics Of North America: Small Animal Practice*, *47*(5), 1055-1064. doi: 10.1016/j.cvsm.2017.04.008

Ferasin, L., Sturgess, C., Cannon, M., Caney, S., Gruffydd-Jones, T., & Wotton, P. (2003). Feline idiopathic cardiomyopathy: A retrospective study of 106 cats (1994–2001). Journal Of Feline Medicine And Surgery, 5(3), 151-159. doi: 10.1016/s1098-612x(02)00133-x

Ferasin, L. (2009). Feline Myocardial Disease. Classi- fication, Pathophysiology and Clinical Presentation. J. Fel. Med. Surg., 11: 3-13.

Ferasin, L.& DeFrancesco, T. (2015). Management of acute heart failure in cats. *Journal of Veterinary Cardiology*, *17*, S173-S189. http://dx.doi.org/10.1016/j.jvc.2015.09.007

Fox, P., Oyama, M., Reynolds, C., Rush, J., DeFrancesco, T.& Keene, B. et al. (2009). Utility of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) to distinguish between congestive heart failure and non-cardiac causes of acute dyspnea in cats. *Journal of Veterinary Cardiology*, *11*, S51-S61. http://dx.doi.org/10.1016/j.jvc.2008.12.001

Fuentes, V. (2012). Arterial Thromboembolism. *Journal Of Feline Medicine And Surgery*, *14*(7), 459-470. http://dx.doi.org/10.1177/1098612x12451547

Gordon, S., Saunders, A., Roland, R., Winter, R., Drourr, L. &Achen, S. et al. (2012). Effect of oral administration of pimobendan in cats with heart failure. *Journal of The American Veterinary Medical Association*, *241*(1), 89-94. http://dx.doi.org/10.2460/javma.241.1.89

Goutal, C., Keir, I., Kenney, S., Rush, J., & Freeman, L. (2010). Evaluation of acute congestive heart failure in dogs and cats: 145 cases (2007-2008). Journal Of Veterinary Emergency And Critical Care, 20(3), 330-337. doi: 10.1111/j.1476-4431.2010.00524.x

Hemdon, W., Kittleson, M., Sanderson, K., Drobatz, K., Clifford, C., & Gelzer, A. et al. (2002). Cardiac Troponin I in Feline Hypertrophic Cardiomyopathy. Journal Of Veterinary Internal Medicine, 16(5), 558-564. doi: 10.1111/j.1939-1676.2002.tb02387.x

Huang, X., Dorhout Mees, E., Vos, P., Hamza, S., & Braam, B. (2016). Everything we always wanted to know about furosemide but were afraid to

ask. American Journal Of Physiology-Renal Physiology, 310(10), F958-F971. doi: 10.1152/ajprenal.00476.2015

Hunt SA (2005). ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: A Report of the American college of Cardiology/American Heart Assocation Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Journal of the American College of Cardiology. 2005; 46: 1116 -1143

Januzzi, J., Camargo, C., Anwaruddin, S., Baggish, A., Chen, A., & Krauser, D. et al. (2005). The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study. The American Journal Of Cardiology, 95(8), 948-954. doi: 10.1016/j.amjcard.2004.12.032

Khor, K., Campbell, F., Rathbone, M., Greer, R., & Mills, P. (2012). Acceptability and compliance of atenolol tablet, compounded paste and compounded suspension prescribed to healthy cats. Journal Of Feline Medicine And Surgery, 14(2), 99-106. doi: 10.1177/1098612x11431521

Januzzi, J., Chen-Tournoux, A., & Moe, G. (2008). Amino-Terminal Pro–B-Type Natriuretic Peptide Testing for the Diagnosis or Exclusion of Heart Failure in Patients with Acute Symptoms. The American Journal Of Cardiology, 101(3), S29-S38. doi: 10.1016/j.amjcard.2007.11.017

Lefebvre, H., Brown, S., Chetboul, V., King, J., Pouchelon, J., & Toutain, P. (2007). Angiotensin-Converting Enzyme Inhibitors in Veterinary Medicine. Current Pharmaceutical Design, 13(13), 1347-1361. doi: 10.2174/138161207780618830

Litster, A., & Buchanan, J. (2000). Vertebral scale system to measure heart size in radiographs of cats. Journal Of The American Veterinary Medical Association, 216(2), 210-214. doi: 10.2460/javma.2000.216.210

Liu SK. Acquired cardiac lesions leading to congestive heart failure in the cat. Am J VetRes 1970;31(11):2071-88

MacGregor, J., Rush, J., Laste, N., Malakoff, R., Cunningham, S.&Aronow, N. et al. (2011). Use of pimobendan in 170 cats (2006–2010). *Journal of Veterinary Cardiology*, *13*(4), 251-260. http://dx.doi.org/10.1016/j.jvc.2011.08.001

Maisel, A., Krishnawswamy, P., & Nowak, R. (2002). Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. ACC Current Journal Review, 11(6), 55. doi: 10.1016/s1062-1458(02)00937-6

Paige, C., Abbott, J., Elvinger, F., & Pyle, R. (2009). Prevalence of cardiomyopathy in apparently healthy cats. Journal Of The American Veterinary Medical Association, 234(11), 1398-1403. doi: 10.2460/javma.234.11.1398

Payne, J., Brodbelt, D., & Luis Fuentes, V. (2015). Cardiomyopathy prevalence in 780 apparently healthy cats in rehoming centres (the CatScan study). Journal Of Veterinary Cardiology, 17, S244-S257. doi: 10.1016/j.jvc.2015.03.008

Pion PD, Kittleson MD, Rogers QR, Morris JG (1987) Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. Science 237, 764–768.

Reichlin, T., Schindler, C., Drexler, B., Twerenbold, R., Reiter, M., & Zellweger, C. et al. (2012). One-Hour Rule-out and Rule-in of Acute Myocardial Infarction Using High-Sensitivity Cardiac Troponin T. Archives Of Internal Medicine, 172(16), 1211. doi: 10.1001/archinternmed.2012.3698

Reina-Doreste, Y., Stern, J., Keene, B., Tou, S., Atkins, C., & DeFrancesco, T. et al. (2014). Case-control study of the effects of pimobendan on survival time in cats with hypertrophic cardiomyopathy and congestive heart failure. Journal Of The American Veterinary Medical Association, 245(5), 534-539. doi: 10.2460/javma.245.5.534

Serres, F., Pouchelon, J., Poujol, L., Lefebvre, H., Trumel, C., & Daste, T. et al. (2009). Plasma N-terminal pro-B-type natriuretic peptide concentration helps to predict survival in dogs with symptomatic degenerative mitral valve disease regardless of and in combination with the initial clinical status at admission. Journal Of Veterinary Cardiology, 11(2), 103-121. doi: 10.1016/j.jvc.2009.07.001

Singletary, G., Rush, J., Fox, P., Stepien, R., & Oyama, M. (2012). Effect of NT-pro-BNP Assay on Accuracy and Confidence of General Practitioners in Diagnosing Heart Failure or Respiratory Disease in Cats with Respiratory Signs. Journal Of Veterinary Internal Medicine, 26(3), 542-546. doi: 10.1111/j.1939-1676.2012.00916.x

Smith SA, Tobias AH. Feline arterial thromboembolism: an update. Veterinary Clinics: Small Animal Practice. 2004 Sep 1;34(5):1245-71

Spratt, D., Mellanby, R., Drury, N., & Archer, J. (2005). Cardiac troponin I: evaluation of a biomarker for the diagnosis of heart disease in the dog. Journal Of Small Animal Practice, 46(3), 139-145. doi: 10.1111/j.1748-5827.2005.tb00304.x

Uppe, P., Jeyaraja, K., & Sumathi, D. (2013). Dilated cardiomyopathy in cats - A case report. Veterinary World, 6(4), 226. doi: 10.5455/vetworld.2013.226-227

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/ AHA guideline for the management of heart failure. A report of the American college of cardiology foundation/ American heart association task force on practice guidelines. Circulation 2013;128:e240ee327.

Yancy, C., Jessup, M., Bozkurt, B., Butler, J., Casey, D., & Colvin, M. et al. (2017). 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation, 136(6), e137-e161. doi: 10.1161/cir.0000000000000509