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Master's Thesis of Veterinary Medicine

Efficacy and Outcome of Tissue Plasminogen Activator and Rivaroxaban in Feline Arterial Thromboembolism

고양이 동맥혈전색전증에 적용한 Tissue Plasminogen Activator와 Rivaroxaban의 효과와 치료결과

February 2023

Department of Veterinary Medicine

Graduate School

Seoul National University

Major in Veterinary Clinical Sciences

Seonghoon Kim

Efficacy and Outcome of Tissue Plasminogen Activator and Rivaroxaban in Feline Arterial Thromboembolism

Supervised by Professor Inhyung LEE

Submitting a master's thesis of
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Major in Veterinary Clinical Sciences
Department of Veterinary Medicine
Graduate School
Seoul National University

Seonghoon Kim

Confirming the master's thesis written by
Seonghoon Kim
December 2022

Chair of Committee _____(Seal)

Vice Chair of Committee _____(Seal)

Member of Committee _____(Seal)

Efficacy and Outcome of Tissue Plasminogen Activator and Rivaroxaban in Feline Arterial Thromboembolism

Abstract

Thrombolytic therapy is beneficial for reestablishing arterial blood flow, but its use is restricted because of its side effects, including hemorrhagic complications and reperfusion injuries. This study aimed to report the outcomes of acute feline arterial thromboembolism (ATE) treated with tissue plasminogen activator (tPA) and the factor Xa inhibitor, rivaroxaban (RVX). This retrospective observational study recruited 16 cats with feline ATE treated between July 2017 and July 2021 from a referral animal hospital in South Korea. Seven and nine cats were treated with dual (tPA + RVX) therapy and only RVX therapy, respectively. Medical records were reviewed for evidence of adverse events—hemorrhagic complications, hyperkalemia, and reperfusion injury—and clinical conditions at admission. The primary outcome was survival to discharge, and the principal safety outcome was major bleeding.

The day to complete ATE resolution, which was confirmed via vascular ultrasound, was 7.3 ± 4.5 days in the dual therapy group. In all 16 cats, three cats and four cats in the dual therapy group and RVX group, respectively, experienced bleeding complications. The median survival

time for all cats was 29 days (range 1–1574 days), 386 days (range 42–1574 days) in dual therapy group, and 5 days (range 1–344 days) in RVX group. The recurrence rate of ATE while on therapy was 6.2%, in which this cat did not receive consistent medication, and the time to recurrence was 379 days.

In conclusion, dual therapy with tPA and rivaroxaban resulted in increased survival rates than conservative therapy for acute feline ATE.

Keyword: cat, rivaroxaban, thromboembolism, thrombolytic therapy, tissue plasminogen activator

Student Number: 2016-21774

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Introduction

Acute feline arterial thromboembolism (ATE) is characterized by coldness, pain, paralysis, pulseless limb, and ischemic necrosis of the affected limb(s) (Borgeat *et al.* 2014; Fox *et al.* 1999; Luis *et al.* 2012; Smith *et al.* 2003). Most cats with ATE have underlying hypertrophic cardiomyopathy (HCM), pulmonary neoplasia, hyperthyroidism, or other diseases (Borgeat *et al.* 2014; Laste *et al.* 1995; Smith *et al.* 2003; Stokol *et al.* 2008). The prevalence of HCM in cats is 15%, and ATE occurs in 12–17% of cats with HCM (Atkins *et al.* 1992; Ferasin *et al.* 2003; Paige *et al.* 2009; Payne *et al.* 2015; Rush *et al.* 2002). The prognosis for feline ATE is poor, with euthanasia mounting up to 90% (Borgeat *et al.* 2014; Schoeman *et al.* 1999).

Analgesia and thromboprophylaxis are currently the common treatments for ATE. However, the prognosis with reported survival rates was 27%–45% (Fox *et al.* 1999; Laste *et al.* 1995; Schoeman *et al.* 1999; Smith *et al.* 2003; Welch *et al.* 2010). The therapeutic goals of ATE include treating any predisposing conditions, preventing further thrombus formation, promoting collateral circulation, and in some cases, dissolving existing thrombi (Little *et al.* 2012; Rush *et al.* 2002). Feline ATE is treated either by conservative therapy such as antithrombotics and supportive care (Laste *et al.* 1995; Rush *et al.* 2002; Schoeman *et al.* 1999; Smith *et al.* 2003; Smith *et al.* 2004) or thrombolytic agents such as tissue plasminogen activator

(tPA), streptokinase, and urokinase (Guillaumin *et al.* 2019; Koyama *et al.* 2010; Moore *et al.* 2000; Pion *et al.* 1989; Ramsey *et al.* 1996; Whelan *et al.* 2005; Welch *et al.* 2010). Compared to other thrombolytic agents, tPA specifically dissolves cross-linked fibrin rather than circulating fibrinogen, making it more effective against specific thrombi (Little *et al.* 2012; Welch *et al.* 2010). Therefore, tPA could be associated with a lower risk of bleeding and may be used explicitly for thrombi (Deitcher *et al.* 2002; Dunn *et al.* 2011). Moreover, its use has a reported survival rate of 27% to 50%; however, its use also lead to severe complications, including life-threatening hyperkalemia, resulting from minor hemorrhage (50%), reperfusion injury (33%), or lack of efficacy (failure to resolve the thrombus). Additionally, no beneficial effects on survival have been observed compared with conservative therapy (Bonagura *et al.* 2013; Hogan *et al.* 2017; Killingsworth *et al.* 1986; Pion *et al.* 1988; Pion *et al.* 1988; Welch *et al.* 2010).

The ideal therapeutic approach clinically is reperfusion of arterial blood flow to the infarcted arterial bed using thrombolytic therapy immediately within the golden hour after the embolic event (Hogan *et al.* 2017; Pion *et al.* 1987). Therefore, reperfusion therapy with thrombolytic agents should be commenced immediately in patients who are more likely to benefit clinically, such as patients with ATE of the bilateral pelvic limbs (Hogan *et al.* 2017; Moore *et al.* 2000; Pion *et al.* 1989). Furthermore,

thrombolytic therapy must be considered because reestablishing arterial flow is critical for survival in the clinical setting (Hogan *et al.* 2017).

In cases of ATE events, the current American College of Veterinary Internal Medicine consensus guidelines for feline cardiomyopathy recommend administering an antiplatelet agent, such as clopidogrel, and factor Xa inhibitor, such as rivaroxaban (RVX) (Luis *et al.* 2020). RVX is orally administered and has well-tolerated, predictable, and safe pharmacokinetics and anticoagulant properties in cats (Blais *et al.* 2019; Dixon-Jimenez *et al.* 2016; Myers *et al.* 2015). Treatment using RVX and clopidogrel showed improved clinical management of cats, with a low risk of bleeding and survival rate of up to 50% a year after an initial ATE event (Lo *et al.* 2022). Several clinical trials of thrombolytic agents failed to demonstrate significant survival improvements in cats with ATE compared to conventional standard-of-care therapy despite consistent evidence of its thrombolytic effects (Welch *et al.* 2010). Although tPA may increase the risk of death during the first 24 h of treatment, the increased risk may be offset by its clinical benefits, including decreased thrombus volume and time required for recanalization of the occluded artery.

Therefore, this retrospective study aimed to compare two clinical treatment approaches (administration of RVX with and without tPA) for cats with ATE and determine which provides better long-term patient outcomes.

Materials and Methods

The medical record databases of a referral animal hospital in South Korea were searched for client-owned cats that received concomitant clopidogrel (Pravic, Sinilpharm, Seoul, Korea) and RVX (Xarelto, Bayer AG, Germany) therapy with (dual therapy group) or without tPA (Actilyse, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany) (RVX group) between July 2017 and July 2021. The inclusion criterion was a confirmed ATE episode. Diagnosis was made from the physical observation of any affected limbs using the following five criteria: paleness, coldness, pain, lack of pulse, and lack of motor function (Guillaumin *et al.* 2019). Additional criteria used to confirm diagnosis included any of the following: lack of Doppler flow with vascular ultrasound (Logiq E9 ultrasound system, GE Healthcare, Wauwatosa, WI, USA) on the affected limb(s), and a difference in glucose or lactate level between the affected and non-affected limb(s) (Klainbart *et al.* 2014). This study included only patients with ATE confirmed using vascular ultrasound to achieve a more homogeneous and clinically relevant patient population. Only the first episode was documented if the same patient had multiple ATE episodes. The main exclusion criteria were the absence of treatment attempts other than analgesia and euthanasia immediately after admission. In this study, 39 cats were admitted to the hospital with ATE during the study period. Among

these, 11 cats were euthanized (1 in dual therapy group and 8 in RVX group), and 12 cats were lost to follow-up. Cats whose owners could not be reached were considered lost to follow-up. Therefore, 16 cats were included to compare the difference in treatment effect between the dual therapy group (n = 7) and RVX group (n = 9) in ATE. Adequate measures were taken to minimize the animals' pain or discomfort.

Medical records were reviewed for evidence of the incidence of adverse events and clinical outcomes (24 hours alive and 7 days alive and dead). Antithrombotic therapy-related adverse events included evidence of spontaneous bleeding diatheses such as epistaxis, hematemesis, or hematuria. Only serious adverse events reported by the owner or resulting in a veterinary visit were evaluated. Medical records were also evaluated for signalment, cardiovascular disease diagnosis, and medication regimen.

Total 1 mg/kg of tPA administered during 3 h intravenously. 10% tPA 1 mg/kg dose over 1 min intravenously as a loading dose, 50% tPA over 1 h, and 40% tPA over 2 h. TPA therapy was administered with the owner's approval if less than 6 h had elapsed since symptoms onset; but the treatment choice was based on the owner's discretion, if the period was longer than 6 h. The time from ATE onset to admission was determined based on the history, such as when the cat last appeared normal or when the owner started hearing vocalizations indicating pain from the cat. Owners and referring veterinarians of the cats whose outcome could not be

determined from the medical record database were contacted via telephone to determine current survival status, medication regimen, adverse events or dates, and suspected cause of death. Survival was calculated as the days between the start of treatment and clinical outcome for each group. Survival outcome was which cats still alive at the end of study date, October 2021.

Statistical Methods

Kaplan–Meier curves were used to estimate survival function and time to event, with cats still alive censored at the end of the study. All statistical analyses, including Kaplan–Meier curves, were performed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL). Statistical differences in measured values at the initial stage, such as rectal temperature, blood lactate (Nova StatStrip Xpress Lactate Meter, Nova Biomedical, Waltham, Massachusetts, USA), blood glucose (Accu-Chek® Active Blood Glucose Meter, Roche Diagnostics GmbH, Mannheim, Germany), serum potassium (ABL9 blood gas analyzer, Radiometer Medical ApS, Copenhagen, Denmark), serum creatinine (Catalyst Dx Chemistry Analyzer, IDEXX Laboratories, Westbrook, Maine, USA), pH (ABL9 blood gas analyzer, Radiometer Medical ApS, Copenhagen, Denmark), platelet (ProCyte Dx hematology analyzer, IDEXX Laboratories, Westbrook, Maine, USA), packed cell volume (ProCyte Dx hematology analyzer, IDEXX Laboratories, Westbrook, Maine, USA), and prothrombin time (PT) (CG02NV Blood Coagulation Analyzer, A&T Corporation, Oshu, Japan) levels were analyzed between the groups. The data was presented as median (range) or mean ± standard deviation. The normality of the data distribution was assessed using the Kolmogorov–Smirnov test before performing the statistical tests. The normality results in the groups were

above 0.05 (all $p \geq 0.16$). Therefore, the measured value differences between the two groups were analyzed using an independent *t*-test. Statistical significance was set at $p < 0.05$.

Results

1. Study population and characteristics

Table 1 presents the baseline characteristics of the study population, including sex, weight, age, and clinical presentation. The median age of cats was 7.5 years (1–14). Eleven cats (68.7%) were castrated males. This study included 15 cats affected in both pelvic limbs and one cat with single-limb involvement (left forelimb only). Thoracic radiographs revealed that four of the 16 cats (25%) in the RVX therapy group had concurrent congestive heart failure (CHF) with ATE. Two cats were diagnosed with unclassified cardiomyopathy; 13 were diagnosed with HCM, in which one had HCM due to hyperthyroidism; one was diagnosed with transient myocardial thickening. Seven cats in the dual therapy group received 10% tPA 1 mg/kg dose over 1 min intravenously as a loading dose, 50% tPA over 1 h, and 40% tPA over 2 h. Nine cats were initially prescribed with RVX and clopidogrel without tPA administration due to more than 6 h of delayed hospital admission, concurrent cardiogenic pulmonary edema, and owners' concern about potential side effects. The dual therapy group received emergency tPA treatment, RVX (1.53 ± 0.67 mg/kg/day orally), and clopidogrel (18.75 mg/cat/day orally). Seven cats required medication adjustments during the study, which included an increase in RVX (n = 3), decrease in RVX (n = 3), and medication discontinuation due to disease improvement (n = 1). Additional cardiac medications administered concurrently during this study

included pimobendan (n = 7), furosemide (n = 2), benazepril (n = 2), enalapril (n = 1), spironolactone (n = 3), diltiazem (n = 1), and atenolol (n = 5). All cats in both groups received supportive care, including treatment for cardiac disease and pain medications if applicable (many with multimodal analgesia), in which the attending clinician determined the doses. In the dual therapy group, the median time from suspected ATE onset to admission was 3 h (range 1–5 h). In the RVX group, the median time from suspected ATE onset to RVX therapy admission was 4 h (range 1–14 h). The cats in the dual therapy group were admitted to the hospital significantly sooner after the onset of symptoms than those in the RVX group.

Table 2 presents the blood lactate, blood glucose, serum potassium, serum creatinine, pH, platelets, packed cell volume, and PT levels at admission. The median rectal temperature in the dual therapy group and RVX group before treatment was 37.57 ± 0.87 ℃ and 36.47 ± 1.85 ℃, respectively (p = 0.243). In the dual therapy group, the differences in blood lactate and glucose levels between the affected and non-affected limbs were 4.53 ± 2.92 mmol/L and 65.83 ± 40.74 mg/dL, respectively. In the RVX group, the differences in blood lactate and glucose levels between the affected and non-affected limbs were 6.89 ± 4.66 mmol/L and 135.4 ± 52.96 mg/dL, respectively. A comparison of blood lactate levels between the dual therapy group and RVX group revealed no significant differences (p = 0.269); however, blood glucose levels differed significantly (p = 0.036). No

cats had hemorrhage before treatment. The baseline PT in cats receiving only RVX was 11.09 ± 4.53. At 3 h post-administration of RVX, the value had increased to 18.96 ± 6.87. In the dual therapy group, the baseline PT was 10.53 ± 3.30, and its value 3 h after tPA administration had increased to 20.87 ± 11.77 (p = 0.014 for the RVX group and p = 0.049 for the dual therapy group).

2. Adverse events

Table 3 shows the adverse events and clinical outcomes of the 16 cats analyzed in this study. During the study, 3 cats (42%) in the dual therapy group and 4 (44%) in the RVX group experienced antithrombotic therapy-related bleeding disorders. Four of the 7 cats experienced adverse events that were attributable to tPA administration. Four cats had metabolic acidosis (pH < 7.337), and 4 cats were azotemic (creatinine ≥ 1.6 mg/dL) after tPA administration. No cats were hyperkalemic (> 4.9 mEq/L) after tPA administration. Hemorrhagic complications, including pigmenturia (n = 6), hematochezia (n = 2), and epistaxis (n = 1) were recorded (Three cases of pigmenturia, one case of hematochezia, and one case of epistaxis in the dual therapy group; and three cases of pigmenturia and one case of hematochezia in the RVX group).

3. Clinical outcomes

Within 3 h of treatment, one cat in the dual therapy group with no motor function before tPA administration showed improved motor function and complete ATE resolution, which was confirmed using a vascular ultrasound. After the 24-h study period, 15 of the 16 cats were alive. Moreover, 10 of the 15 cats that survived the 24-h study period survived until the 7-day study period. The average number of days to complete ATE resolution confirmed using a vascular ultrasound was 7.3 ± 4.5. However, despite complete ATE resolution, the cats did not show significant improvement in motor function in the affected limbs. Two cats in the RVX group died due to treatment failure, with worsening pelvic limb signs at 14 days in 1 cat and 16 days in another. In the dual therapy group, one cat died 42 days after therapy due to CHF, and another died 386 days later due to chronic kidney disease. One cat (6.2%) in the dual therapy group had a recurrent ATE event after medication discontinuation due to disease improvement, and its time to recurrence was 379 days. During the study, CHF was newly diagnosed after initiating therapy in one cat in the RVX group. The median survival time for all cats was 29 days (interquartile range [IQR] = 3–384) (Figure 1). The median survival time in the dual therapy group was 386 days (IQR = 60–544) and 5 days (IQR = 2–15) in the RVX group (Figure 2). The chi-square value of the log-rank test in the two groups was 10.372 ($p = 0.001$).

Table 1. Demographic characteristics of the study population (n = 16)

Characteristics	
Male	11/16 (68.7%)
Weight (kg)	4.85 (2.44–9.5)
Age (years)	7.5 (1–14)
CHF at presentation	4/16 (25%)
HCM or remodeled HCM	15/16 (93.75%)
Initial rivaroxaban dose (mg/kg/day)	1.53 ± 0.67
Initial clopidogrel dose (mg/kg/day)	18.75

Data are presented as median (range), proportion (%) or mean ± standard deviation
Abbreviations: CHF, congestive heart failure; HCM, hypertrophic cardiomyopathy

Table 2. Measured levels of cats receiving rivaroxaban with tPA (dual therapy group) and without tPA (RVX group).

Group	Cat	Rectal temperature (°C)	Limb Lac.			Limb BG			PT			HCT 0h	PLT 0h	K 0h	pH 0h	Cre 0h
			Fore	Hind	|Diff.|	Fore	Hind	|Diff.|	Initial	3h post (Riva)	*P*-value					
Dual therapy	1	37.3	3.2	5.6	2.4	109.0	73.0	36.0	9.5	34.10		39.2	288.0	3.8	-	2.1
	2	36.6	3.7	6.1	2.4	137.0	58.0	79.0	18.0	37.0		41.4	370.0	4.6	7.28	1.1
	3	38.2	2.7	7.6	4.9	125.0	73.0	52.0	9.7	-		31.0	104.0	3.6	7.32	1.2
	4	37.5	1.7	5.2	3.5	191.0	-	-	8.9	15.0	0.049*	-	-	2.9	7.45	3.3
	5	38.6	2.2	5.5	3.3	126.0	116.0	10.0	9.1	17.7		40.3	211.0	3.7	7.35	1.9
	6	36.4	3.1	13.9	10.8	151.0	32.0	119.0	9.2	8.9		47.2	185.0	3.2	-	0.9
	7	38.4	6.9	2.5	4.4	90.0	189.0	99.0	9.3	12.5		37.3	147.0	4.0	7.31	1.6
Mean ± SD		37.57 ±0.87	3.36 ±1.70	6.63 ±3.55	4.53 ±2.92	132.71 ±32.25	90.17 ±55.57	65.83 ±40.74	10.53 ±3.30	20.87 ±11.77		39.40 ±5.30	217.50 ±97.14	3.69 ±0.55	7.34 ±0.07	1.73 ±0.82
RVX	1	38.9	1.6	3.9	2.3	264.0	-	-	8.8	11.4		44.5	120.0	3.5	7.34	1.6
	2	38.6	1.2	17.2	16.0	235.0	70.0	165.0	-	20.0		-	-	-	-	0.8
	3	36.1	4.7	9.2	4.5	323.0	114.0	209.0	8.7	22.1		45.5	219.0	-	-	1.5
	4	37.4	3.8	13.0	9.2	210.0	-	-	10.2	14.6		36.9	128.0	3.1	-	1.6
	5	36.6	2.8	8.9	6.1	186.0	81.0	105.0	10.5	11.0	0.014*	-	-	3.2	7.13	3.7
	6	37.3	6.1	13.1	7.0	-	51.0	-	22.1	29.2		43.7	276.0	1.3	7.29	1.6
	7	35.7	16.8	15.6	1.2	-	-	-	10.7	27.2		-	-	3.8	7.26	0.8
	8	34.3	4	12.8	8.8	281.0	156.0	125.0	8.8	16.2		33.0	75.0	3.8	7.36	1.0
	9	33.3	4.0	-	-	83.0	10.0	73.0	8.9	-		37.9	182.0	4.7	7.26	2.5
Mean ± SD		36.47 ±1.85	5.00 ±4.67	11.71 ±4.23	6.89 ±4.66	226.00 ±77.74	80.33 ±50.54	135.4 ±52.96	11.09 ±4.53	18.96 ±6.87		40.25 ±5.04	166.67 ±73.49	3.77 ±0.57	7.27 ±0.08	1.68 ±0.92
p-value		0.243	0.368	0.049*	0.269	0.035*	0.748	0.036*	0.772	0.897		0.873	0.337	0.797	0.201	0.669

Abbreviations: tPA, tissue plasminogen activator; RVX, rivaroxaban; Lac, blood lactate; BG, blood glucose; PT, prothrombin time; HCT, hematocrit; PLT, platelet count; K, serum potassium; Cre, serum creatine

Table 3. Adverse events and the clinical outcome between the dual therapy group and RVX group.

		Adverse effects						
Group	Cat	Hyperkalemia > 4.9 mmol/L	Anemia	Azotemia creatinine > 1.6 mg/dL	Acidosis pH < 7.337	24-h survival	7 days survival	Outcome
Dual therapy	1	No	Yes	Yes	Yes	Yes	Yes	Alive
	2	No	Yes	Yes	No	Yes	Yes	Alive
	3	No	No	No	Yes	Yes	Yes	Alive
	4	No	No	Yes	No	Yes	Yes	Alive
	5	No	No	Yes	Yes	Yes	Yes	Alive
	6	No	-	No	-	Yes	Yes	Alive
	7	No	No	No	Yes	Yes	Yes	Alive
Rivaroxaban	1	No	-	No	-	Yes	Yes	Alive
	2	Yes	-	-	-	Yes	No	Died
	3	-	No	Yes	No	Yes	Yes	Died
	4	-	-	-	-	Yes	No	Died
	5	No	No	Yes	Yes	Yes	No	Died
	6	No	No	Yes	Yes	Yes	Yes	Died
	7	No	No	Yes	Yes	Yes	No	Died
	8	No	Yes	No	No	Yes	No	Died
	9	No	No	Yes	Yes	No	No	Died

Figure 1. Kaplan–Meier curves for all cats receiving concomitant clopidogrel and rivaroxaban (RVX) therapy with tissue plasminogen activator (tPA) (dual therapy group) and without tPA (RVX group). The median survival time for all cats was 29 days (IQR = 3–384).

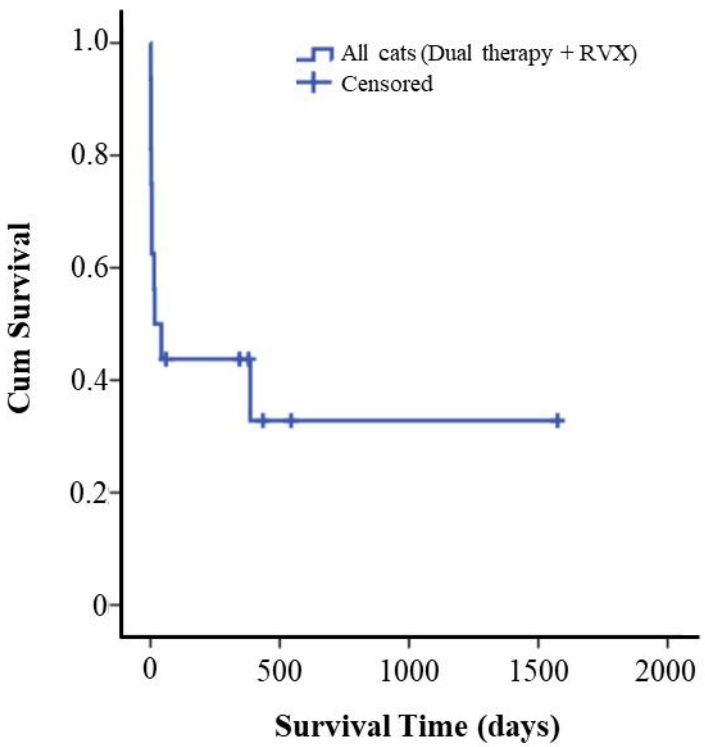
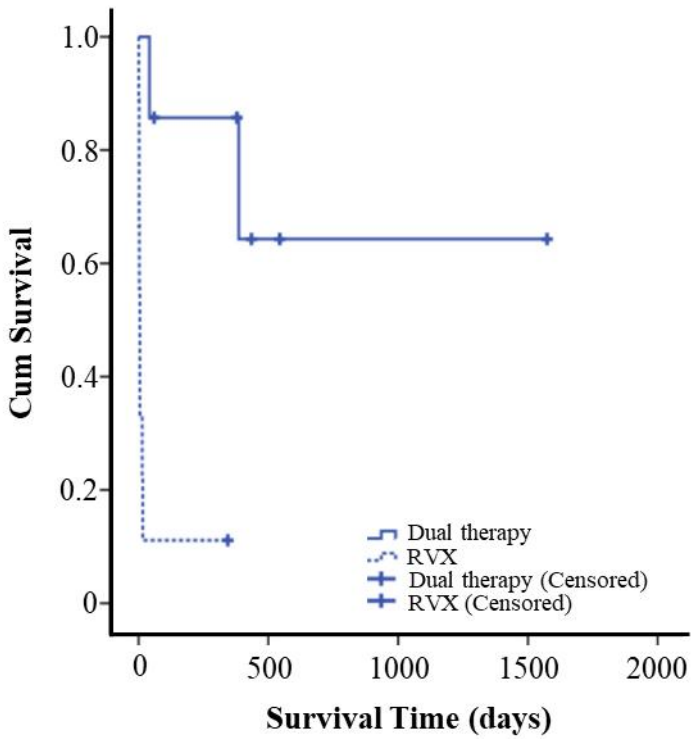


Figure 2. Kaplan–Meier curves for the dual therapy group (solid blue line) and rivaroxaban (RVX) group (solid green line). The median survival time in the dual therapy group was 386 days (IQR = 60–544) compared to 5 days (IQR = 2–15) in the RVX group.



Discussion

Some of the previously reported survival rates of cats treated with tPA following ATE were 56.2% (Guillaumin *et al.* 2019), 27% (Welch *et al.* 2010), and 50% (Pion *et al.* 1988). In a study by Guillaumin et al. (Guillaumin *et al.* 2019), the median follow-up time was 148 days (range 61–1366 days). In a study of 11 cats treated with tPA, Welch et al. (Welch *et al.* 2010) reported that 27% of cats were discharged from the hospital. At the end of the study, one of the surviving cats lived for more than 1.5 years after being discharged from the hospital. The other two cats survived for 110 and 210 days, respectively, after hospital discharge. A study has reported that 50% of cats treated with RVX lived for more than 1 year after their first ATE event (Lo *et al.* 2022). At the end of the study, 33% of cats with ATE were still alive. In this study, the 7-day survival rates were 100% and 33.3% after dual and RVX therapy, respectively. Furthermore, the median survival time for the dual therapy group and RVX therapy group was 386 days and 5 days, respectively.

Previous studies on thrombolytic therapy failed to demonstrate markedly improved survival in cats with ATE compared to conservative therapy, despite consistent evidence of a thrombolytic effect. Moreover, the high rate of adverse effects limits the use of tPA (Guillaumin *et al.* 2019; Welch *et al.* 2010). Therefore, rather than focusing on complete ATE resolution within hours, the focus was on reducing ATE size via

thrombolytic effects by reducing the time required for the recanalization of the occluded artery, which may provide additional clinical benefits. Moreover, when high doses of tPA are administered, a systemic thrombolytic state can occur (Hogan *et al.* 2017). With a lower dose, complications from systemic fibrinolytic effects, including reperfusion injury and hemorrhage, can theoretically be reduced. Therefore, lower doses of tPA than normal were administered for systemic dosing, and infusion time was increased to potentially reduce the systemic risk of bleeding in this study.

The five cats (71.4%) in the dual therapy group, in which complete reperfusion with tPA administration failed, may have benefited from additional thrombotic therapy, such as RVX and clopidogrel, which promotes collateral blood flow, resulting in faster clinical improvement. Blood flow through this collateral network significantly influences clinical signs and overall survival. Therefore, if therapeutic thrombolysis fails or is not attempted, perfusion to the pelvic limbs can be increased by increasing flow through the collateral network (Hogan *et al.* 2017). A study by Lo et al. (Lo *et al.* 2022) demonstrated the beneficial effect of RVX and clopidogrel in ATE.

In this study, few clinically significant adverse events, common in dual and RVX therapy in cats with ATE, were observed, and the survival to discharge was higher than that reported in previous studies (Guillaumin et al.

2019; Pion *et al.* 1988; Welch *et al.* 2010). Three (42%) of the 7 cats experienced minor bleeding as an adverse event while receiving dual therapy with tPA and RVX at a referral animal hospital for over 4 years. However, the hemorrhagic complications observed in cats with ATE treated with dual therapy (42%) were not different from the complications experienced by a reference group treated with RVX therapy (44%). Additionally, none of the cats required a blood transfusion or hospitalization.

In post-ATE cats, the main goal of patient management is to prevent recurrence, as up to 47% of cats experience subsequent thromboembolic events (Borgeat *et al.* 2014). A recent study revealed that post-ATE cats receiving RVX and clopidogrel lived longer and had fewer ATE recurrences than cats receiving other anticoagulant therapies (Atkins *et al.* 1992; Borgeat *et al.* 2014; Lo *et al.* 2022; Rush *et al.* 2002; Smith *et al.* 2003). In this study, the median survival time following both therapies in post-ATE cats was 29 days (IQR = 3–384) for all cats, 386 days (IQR = 60–544) in the dual therapy group, and 5 days (IQR = 2–15) in the RVX group. Lo et al. (Lo *et al.* 2022) reported a median survival time of 502 days in post-ATE cats. The 1-year survival rate after the initial presentation of ATE was 85.7% and 11.1% for the dual therapy group and RVX therapy group, respectively. Other studies have reported 1-year survival rates of cats after the initial presentation of ATE as 50% (Lo *et al.* 2022), 20% (Lunsford *et al.* 2007), and 0% (Atkins *et al.* 1992). Comparing several retrospective studies is

problematic due to differences in study goals, design, and population. However, the recurrence rate of ATE in this study was 6.2%, which is lower than the reported rates from previous studies that evaluated combined RVX and clopidogrel (16.7%) and clopidogrel (49%) (Hogan *et al.* 2017; Lo *et al.* 2022). These findings suggest that clopidogrel and RVX are more effective in preventing ATE recurrence than other antithrombotic medicines.

In this study, cats treated with tPA took 7 days for ATE resolution, which was confirmed via vascular ultrasound. In all cats, ATE volume decreased after tPA treatment. Previous studies have reported pulse restoration or improved limb function; however, “days to resolution” comparisons were not performed if the ATE did not resolve within 24 h (Welch *et al.* 2010).

Regarding the tPA administration time, patients are generally administered with tPA within 6 h because most veterinary emergency clinicians who administer tPA therapy are likely to follow the 6-h guidelines reported in the human literature (Zini *et al.* 2013). The timing of admission was an important deciding factor in determining whether to administer tPA; however, if concurrent CHF was diagnosed on thoracic radiographs, tPA administration was terminated. Thrombolytic therapy should not be administered in CHF because routine CHF medications cause systemic perfusion deterioration because of volume reduction and vasodilation (Smith *et al.* 2003). However, fluid therapy is an essential therapeutic

approach for the adverse effect of tPA administration (Hogan *et al.* 2017). Therefore, the benefit-to-risk ratio for thrombolytic therapy should be determined for each cat before tPA administration. Respiratory or necropsy evidence of CHF has been reported in 40% (Schoeman *et al.* 1999), 44% (Smith *et al.* 2003), 65% (Moore *et al.* 2000), and 65% (Laste *et al.* 1995) of cats with ATE. In this study, 4 cats (n = 4) were diagnosed with CHF, which excluded them from receiving dual therapy, although they were admitted within 6 h.

Nevertheless, this study has several limitations, mainly due to its retrospective design. These include the lack of consistent data obtained from individual cats, reliance on owners' observations, and small study population size. Adverse events which were recorded since the owners reported the event to the clinician or during the veterinary visit were evaluated. Therefore, less serious adverse events may have been overlooked. Moreover, this study had limited data to evaluate the development of reperfusion injury because many clinicians are concerned about reperfusion injury from thrombolysis. The treatment administered or adjusted was exclusively based on the decision of the attending clinician because treatments and medication dosages were not standardized for all cats. Existing comorbidities or concomitant medications, which differed between cats, could have affected the clinical outcomes. Late admission to the hospital and concurrent CHF might have represented a more unstable group

that was less likely to survive within the RVX group, which may have influenced the outcomes. Patients who were euthanized might have been excluded during the initial treatment, resulting in biased survival results. Despite these limitations, this study's results suggest that dual antithrombotic therapy with tPA and RVX is generally well tolerated in cats with ATE, with minor adverse effects such as pigmenturia, hematochezia, and epistaxis. Additionally, this study's findings suggest that lower doses of tPA administered over 3 h with increasing infusion times may result in fewer systemic adverse effects and a better outcome. Therefore, further research is required to validate these findings and develop more concrete treatment guidelines for these cases.

Conclusions

In conclusion, the results of this study demonstrated that using thrombolytics in cats with ATE resulted in better outcomes than a control population treated with RVX. The use of thrombolytics in cats with ATE remains controversial; however, successful treatment with dual therapy may provide increasing survival rates of cats with ATE.

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국 문 초 록

고양이 동맥혈전색전증에 적용한 Tissue Plasminogen Activator와 Rivaroxaban의 효과와 치료결과

지도교수 이 인 형

김 성 훈

서울대학교 대학원
수의학과 임상수의학 전공

고양이 동맥혈전색전증에서 혈전용해치료법은 동맥 혈류의 재관류에 도움을 주어 임상증상을 개선시킨다. 하지만 혈전용해치료법에 따르는 출혈 및 재관류 손상의 생명을 위협하는 부작용으로 인해 사용이 제한되고 있다.

본 연구는 고양이 동맥혈전색전증에서 tissue plasminogen activator (tPA)와 rivaroxaban을 적용하여 치료한 결과를 보고하고자 실시하였다.

본 연구는 2017년 7월부터 2021년 7월까지 이차진료 동물병원에서 고양이 동맥혈전색전증 치료를 받은 16마리의 고양이를 대상으로 실시하였다. 16마리의 고양이 중에서 7마리는 dual 요법(tPA + rivaroxaban)으로 치료하였으며, 9마리는 rivaroxaban 단독요법으로 치료하였다. 진료 기록은 응급 내원 당시의 임상 증상과 치료 중에

발생하는 출혈성 합병증, 고칼륨혈증, 재관류 손상과 같은 부작용을 확인하기 위해 검토되었다. 치료의 주요한 목표는 생존하여 퇴원하는 것이었다.

Dual 요법군에서 혈전용해제 (tPA) 투여 후 혈관 초음파를 통해 확인된 동맥혈전색전의 완전 소실 확인기간(일)은 7.3 ± 4.5 로 확인됐다. Dual 요법군과 rivaroxaban 단독요법군에 속한 고양이 3마리 (42%)와 4마리 (44%)에서 출혈성 합병증이 나타났다. 모든 고양이의 평균 생존 기간의 중앙값은 29일이었으며, Dual 요법군과 rivaroxaban 단독요법군에서 평균 생존 기간의 중앙값은 각각 386일과 5일이었다. 치료 중 동맥혈전색전증의 재발률은 6.2% 이었다. 해당 고양이는 경구약물치료를 중단한 이후 동맥혈전색전증이 재발한 것이었으며, 중단일로부터 재발까지의 기간은 379일이었다.

본 연구 결과를 통해 고양이 동맥혈전색전증에 tPA와 rivaroxaban을 함께 적용한 dual 요법의 치료가 혈전용해제를 사용하지 않는 기존의 치료 요법보다 생존율을 증가시키는 것을 확인했다.

주요어: 고양이, 혈전색전증, 혈전용해치료, rivaroxaban, tissue plasminogen activator

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