

**COMPARATIVE EVALUATION OF GS-441524 AND GS-5734
(REMDESIVIR) FOR THE TREATMENT OF FELINE INFECTIOUS
PERITONITIS DISEASE**

A THESIS

BY

MD SALIM AL-RAZY

Student ID: 1604079

Semester: Jan-June, 2024

Session: 2022-2023

**MASTER OF SCIENCE (MS)
IN
PHARMACOLOGY**



**DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY
HAJEE MOHAMMAD DANESH SCIENCE AND TECHNOLOGY UNIVERSITY,
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**Submitted to the
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JUNE, 2024



Dedicated

To My Beloved

Parents & My

Wife

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The Author

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ABSTRACT

Attempts have been taken to resolve the symptom manifested in feline infectious peritonitis disease in cats. This study was conducted under the department of physiology and pharmacology to determine the comparative evaluation of GS-441524 and GS-5734 (Remdesivir) for the treatment of feline infectious peritonitis in cats. A total number of 40 cats were affected with feline infectious peritonitis disease. Suspected cats were having clinical symptoms like loss of appetite, weight loss, lameness, dark yellow urine, vomiting, pale color mucosa etc. Therefore, several biochemical tests are available like total protein (TP), albumin, bilirubin, SGPT, SGOT, and alkaline phosphatase (ALP) were performed after a blood sample was collected from the patient. Serum total protein was higher and albumin-globulin (AG) ratio was lower, and the bilirubin was higher the cat is considered as positive for FIP. Then the FIP Ab rapid test was considering as the least confirmation of FIP diagnosis. The FIP Ab rapid test is both the quickest and most accurate approach to diagnosing whether a cat has feline infectious peritonitis (FIP). As a useful side result, we now have a cure for FIP that is widely available. Group A (10 cats) was considered as control, the cats were treated with supportive treatment like antibiotics (doxycycline), steroid and vitamin B-complex. Group B (15 cats) was treated with GS-441524 with the dose of 6mg/kg subcutaneously (s/c) daily for 84 days are effective respectively. Group C (15 cats) was treated with remdesivir (GS-5734) with the dose of 15 mg/kg subcutaneously (s/c) daily for 84 days are effective respectively. Observations were recorded for mortality rate (%), survival rate (%), effects or side effects like diarrhea, vomiting, loss of appetite, allergic reaction etc. According to the observation in group A mortality rate 95-100%, in group B mortality rate 8-12% and in group C mortality rate 18-25%, According to the observation in group A survival rate 5%, in group B survival rate 84-92%, in group C survival rate 75-82%. Compare to other groups, group B shows less side effect (diarrhea, vomiting, loss of appetite, allergic reaction etc.). According to the observation GS-441524 shows better result compared to remdesivir (GS-5734) in the treatment of feline infectious peritonitis disease in cats.

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ABBREVIATIONS

AG	Albumin to globulin ratio (albumin: globulin)
ALKP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BSH	British shorthair
BW	Body weight
CK	Creatine kinase
DIF	Direct immunofluorescence
DMH	Domestic medium hair
DSH	Domestic shorthair
EDTA	Ethylenediamine tetra-acetic acid
FCoV	Feline coronavirus
FeCV	Feline enteric coronavirus
FIP	Feline infectious peritonitis
GGT	Gamma-glutamyl transferase
IHC	Immunohistochemistry
IV	Intravenous
LH	Lithium heparin
PO	Peros
QoL	Quality of life
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
RI	Reference interval
SC	Subcutaneous
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic Oxaloacetic Transaminase
TBil	Total bilirubin
total T ₄	Total thyroxine concentration
HSTU	Hajee Mohammad Danesh Science and Technology University

CHAPTER I

INTRODUCTION

Feline coronavirus (FCoV) is a large single-stranded RNA virus in the family coronaviridae and is found in cats worldwide. This family can infect a wide variety of hosts, which can result in diseases such as Covid-19 in humans, Feline Infectious Peritonitis in cats, gastroenteritis in dogs, and Infectious Bronchitis in chickens (Sifa-Shaida *et al.*, 2020). It has a significant capacity for mutation, which makes it difficult to treat the host when it does occur. Studies on the epidemiology of FIP have shown that the disease is most common in young cats (between three months and three years) and that the majority of cases (75%) occur in households with several cats (Pesteanu-Somogyi *et al.*, 2006). Feline infectious peritonitis, often known as FIP, is a deadly illness that affects the whole body and is brought on by a modified form of the feline coronavirus (FCoV) (Vennema *et al.*, 1998). The condition, which wasn't identified until the 1950s (Holzworth, 1963), is distinguished by an inflammation that ranges from perivascular granulomatous to pyogranulomatous and is associated with vasculitis (Kipar *et al.*, 2005). In a clinical setting, feline infectious peritonitis may manifest itself in either the "wet" or "dry" form; however, some cats may exhibit symptoms that are a combination of the two (Hartmann, 2005). In the so-called "dry" variant of the illness, ocular involvement often develops (Tsai *et al.*, 2011). Doherty (1971) first described the ocular manifestations of FIP in 1971. These symptoms include pyogranulomatous pan uveitis with fibrinous exudate in the anterior chamber, keratic precipitates, perivascular cuffing of retinal vessels, exudative retinal detachment, and optic neuritis. Doherty was the first researcher to describe the ocular manifestations of FIP. There are just three descriptions of dermatological lesions in conjunction with spontaneous FIP in the body of veterinary literature (Cannon *et al.*, 2005; Declercq *et al.*, 2008; Gross, 1999). This indicates that these conditions are quite uncommon. Clinical lesions that have been reported in the past include truncal papules to nodules that are characterized by pyogranulomatous vasculitis and folliculitis, small nodules over the neck and proximal forelimbs that are characterized by pyogranulomatous phlebitis in a cat that has concurrent feline corona virus (FCoV) infection (Cannon *et al.*, 2005), and papular lesions over (Gross, 1999). It is difficult to diagnose FIP, and in most situations, an antemortem diagnosis of FIP may be tough as well, particularly in cases that are non-effusive and 'dry' (Pedersen, 2009). Histopathologic evaluation of biopsy or necropsy samples is regarded to be the gold

standard test. In addition, immunohistochemistry (IHC), which involves the identification of intracellular FCoV antigens in macrophages, is often necessary to confirm the illness (Addie *et al.*, 2004; Giori *et al.*, 2011; Hartmann, 2005; Pedersen, 2009). The condition known as feline infectious peritonitis is often misdiagnosed. It is not uncommon for its vague general clinical symptoms to be present. Some examples of these symptoms are prolonged fever, weight loss, anorexia, and malaise. Some examples of clinicopathologic abnormalities in FIP that do not serve as pathognomonic indicators include lymphopenia, neutrophilia, anemia, hyperproteinemia and hypergammaglobulinemia (Paltrinieri *et al.*, 2001). We provide a case of antemortem diagnosis of feline infectious peritonitis (FIP) in a Sphinx cat with bilateral pan uveitis based on positive immunostaining for intracellular FCoV in several skin lesions in the affected animal.

As a result, access to injectable remdesivir for FIP treatment through a UK based compounding pharmaceuticals company became possible in August 2021 via the veterinary licensing cascade. This was followed by access to a PO formulation of GS-441524 3 months later. However, no studies have yet evaluated the combined use of injectable remdesivir and PO GS-441524 for the treatment of FIP in cats. Similarly, dose recommendations for remdesivir and PO GS-441524 so far have been based on in vitro studies, experimental and limited field studies using injectable GS-441524.

Remission and long-term survival occur in cats with FIP after administration of the adenosine nucleoside analog GS-441524. Additional studies further corroborate the value of GS-441524 in effecting a clinical cure for effusive, non-effusive, ocular, and neurologic forms of FIP when dosage is sufficiently high. Remdesivir (GS-5734) is a prodrug of GS-441524. Knowledge in several species including mice, rhesus monkeys, and humans suggests remdesivir undergoes rapid metabolic conversion *in vivo*, with GS-441524 the major circulating metabolite. GS-441524 undergoes intracellular phosphorylation to form a nucleoside monophosphate and subsequently, the active triphosphate (GS-443902), which disrupts viral replication by mimicking endogenous adenine as it is incorporated into viral RNA. In November 2020, Australian veterinarians gained legal access to a compounded, injectable formulation of remdesivir (100 mg vials) from a veterinary compounding pharmacy (BOVA Aus, Australia). In late 2021, a 50 mg tablet formulation of GS-441524 became available from the same compounder. No safety data or pharmacokinetic studies were available for the use of remdesivir in cats, however, considering successful use of GS-441524, and with no registered alternative, Australian veterinarians began to utilize

compounded remdesivir administered parenterally and later GS-441524 administered orally, for cats with FIP. Extrapolated data from other species was used to estimate a starting dosage and the administration regimen evolved with clinical experience. The aim of this prospective case-series was to document survival and describes the clinical course of cats with FIP treated with compounded remdesivir administered parenterally as immunotherapy, with or without transition to compounded GS-441524 administered orally. Because of the global significance of these treatment options and need for peer-reviewed studies, this investigation records clinicopathologic changes over 6 months, with monitoring beyond 12 months ongoing.

Therefore, the present study was designed to assess the following specific objectives:

- To observe the physical status and mortality rate of cat.
- To evaluate the recovery time and side effect observation.

CHAPTER II

REVIEW OF LITERATURE

The purpose of this chapter is to provide a selective review of the research works performed in relation to the present study. Literature on analysis of the effect of GS 441524 compared to GS-5734 (Remdesivir) for the treatment of Feline infectious peritonitis disease in cats.

2.1 Feline Infectious Peritonitis (FIP)

Feline infectious peritonitis (FIP) is a viral disease caused by a feline coronavirus that affects wild and domestic cats. This type of coronavirus is different from the coronavirus that causes COVID-19 in people (Vennema *et al.*, 1998).

Most strains of feline coronavirus are found in the gastrointestinal tract and do not cause significant disease. These are referred to as feline enteric coronavirus (FeCV). Cats infected with FeCV usually do not show any symptoms during the initial viral infection, but may occasionally experience brief bouts of diarrhea and/or mild upper respiratory signs from which they recover spontaneously (Cannon *et al.*, 2005; Declercq *et al.*, 2008; Gross, 1999). FeCV-infected cats usually mount an immune response through which antibodies against the virus are produced within 7-10 days of infection. In approximately 10 percent of cats infected with FeCV, one or more mutations of the virus can alter its biological behavior, resulting in white blood cells becoming infected with virus and spreading it throughout the cat's body. When this occurs, the virus is referred to as the FIPV (Pesteanu-Somogyi *et al.*, 2006). An intense inflammatory reaction to FIPV occurs around vessels in the tissues where these infected cells locate, often in the abdomen, kidney, or brain. It is this interaction between the body's own immune system and the virus that is responsible for the development of FIP. Once a cat develops clinical FIP, the disease is usually progressive and almost always fatal without therapy that has recently become available, but that has yet to be approved to treat FIP in cats by the Food and Drug Administration (FDA). To our knowledge, coronaviruses cannot be passed from infected cats to humans.

Feline coronavirus is very common and usually doesn't cause any serious issues, aside from mild diarrhea. But when the feline coronavirus changes to a specific strain of the coronavirus, FIP can develop (Kipar and Meli, 2014). In about 10% of infected cats, the virus will multiply and mutate, resulting in an infection known as feline infectious

peritonitis virus (FIPV) that spreads throughout the cat's body. It can cause an extreme inflammatory reaction in the tissues surrounding the abdomen, kidney, or brain.

Although FIP is not believed to be contagious, it is a very serious disease. When a cat gets FIP, it is progressive and almost always fatal.

2.2 Diagnosis of FIP

FIP can be difficult to definitively diagnose despite a high degree of clinical suspicion based on history, clinical signs and routine laboratory tests (Paltrinieri *et al.*, 2001).

2.2.1 History & Clinical Signs

The wide range of clinical signs makes FIP a differential in many different clinical cases. However, history and clinical sign scan be used to increase the index of suspicion (Hartmann, 2005).

1. FIP is most common in young cats (<3years), but a smaller peak also occurs in older cats (>10 years).
2. Pedigree cats and cats from multi cat households are at increased risk.
3. A recent history of stress (rehoming, neutering, introduction of new cats, vaccination) may be apparent.
4. Typical clinical signs of FIP: lethargy, anorexia, weight loss, pyrexia, jaundice, ascites and/or pleural effusion and/or pericardial effusion, neurological signs and/or ocular changes etc.

NB: FIP is a progressive disease: clinical signs change over time so it is important to repeat clinical (including ophthalmic and neurological) examinations.

2.2.2 Blood Tests

Hematology and serum biochemistry can support a diagnosis of FIP, and although changes are largely non-specific, they can use to increase the index of suspicion.

I. Hematology

1. Lymphopenia (55-77% of cases).
2. Neutrophilia (39-55% of cases).

3. Mild to moderate normocytic,
4. Normochromic anemia (37-54% of cases).

II. Serum Biochemistry

- Hyperproteinemia
- (Up to 60% of cases).
 - Hyperglobulinemia.
 - Low or low-normal serum albumin.
 - Albumin: globulin (A: G) ratio.

Low (< 0.4) = FIP very likely.

High (> 0.8) = FIP very unlikely.
 - Hyperbilirubinemia (21-36% of cases; especially in effusive cases; magnitude increases as the disease progresses).
 - Liver enzymes (ALT, ALP & GGT) often normal or only mildly or moderately elevated.

2.2.3 Body Cavity Effusions

Identification and analysis of effusions can be very useful in the diagnosis of FIP. A convincing FIP diagnosis required supportive clinical signs, combined with a positive result from 1 or more of the following 4 tests, with tests 1 to 3 requiring detection of FCoV antigen within macrophages located in tissues, aspirates, or body cavity effusions Worthing *et al* (2012).

As cites is the most commonly encountered body cavity effusion; however, pleural effusion and / or pericardial effusion may be present in the presence or absence of as cites. Repeated imaging (especially ultrasonography) can be useful to detect subtle effusions and direct fluid sampling. Characteristics of FIP effusions include:

- They are usually clear, viscous and straw-yellow in color.
- Typically, they have a total protein concentration of >35 g/l and a predominance ($>50\%$) of globulins.

- Similar biochemical changes to those found in the serum exist in effusions: i.e. low A: G ratios, increased α_2 globulins and γ -globulins, and markedly elevated α_1 -acidglycoprotein levels.
- They are often (but not always) poorly cellular. Cell counts are usually <10 , (but occasionally counts higher than $25 \times 10^9 / l$ have been reported). The cell types most frequently are non-degenerate neutrophils, macrophages and lymphocytes.

2.2.4 Feline Infectious Peritonitis Antibody Rapid Test (FIP Ab):

The FIP Ab rapid test is both the quickest and most accurate approach to diagnosing whether a cat has feline infectious peritonitis (FIP). A test cassette was utilized to confirm the presence of FIP in cats using the FIP Ab rapid test kit. Before conducting any tests, it was first necessary to let all the components of the kit (Testsealabs) and the samples (blood) adjust to room temperature. Following a delay of thirty to sixty seconds, one drop of serum was subsequently added to the sample well. After placing three drops of buffer into the sample well, the result may be read within eight to ten minutes. In this instance, the result of the test kit was positive.

2.3 FIP Treatment Options

FIP has long been considered an untreatable disease. It wasn't until recently that antiviral drugs were introduced to help treat FIP. These drugs are not yet approved by the Food and Drug Administration (FDA), and their long-term effectiveness is still unknown.

Other FIP treatments may include supportive care, such as drainage of built-up fluid, and blood transfusions.

2.4 Effect of (Gs-441524) in the treatment of feline infectious peritonitis disease in cats

This is the most commonly used treatment for FIP, as well as the most documented. It is effective for all forms of FIP (with correct dosing). GS-441524 is available as either SC injections or pills.

We feel that the cure rate for FIP with GS-441424 is over 80-90%, with treatment failures due to misdiagnosis of FIP, inadequate dosage, complicating disease conditions, and drug resistance. Young cats are easier to treat and have a higher cure rate than old cats >7 years of age, cats with wet or dry FIP not complicated by neurological or ocular disease are easier

to cure than cats with neurological FIP. The starting dosage for cats with wet or dry FIP and no ocular or neurological disease signs is 4-6 mg/kg daily for 12 weeks, with the younger and wet cases tending to go toward the lower end and the dry cases toward the higher end. Cats with ocular lesions and no neurological signs start at 8 mg/kg daily for 12 weeks. Cats with neurological signs start at 10 mg/kg, daily for 12 weeks. If cats with wet or dry FIP at the beginning develop ocular or neurological signs they go to the appropriate ocular or neurological dosage. There is an oral form of GS available from at least two sources out of China (Aura, Mutian) and I do not use it so am not familiar with the comparable dosage. However, I do not recommend it when the injectable dosage goes above 10 mg/kg daily, as the efficiency of oral absorption goes down at these high dosages. I recommend that the dosage be adjusted with weekly weight checks. Weight gain can be tremendous in many of these cats, either because they are so wasted at the start or that they are growing, and/or both. If there is some weight loss at first of treatment, I stay at the original dosage and do not lower it. Failure to gain a good amount of weight during treatment is considered a bad sign. I do not raise a dosage unless there is significant reasons to do so, such as failure or blood tests to improve, slow improvement, poor activity levels, and failure of original clinical signs to disappear, or change in disease form to include ocular or neurological signs. This is where the art comes into play, because you do not want to get stuck on single blood values that are not quite normal and neglect the overall health status of the cat. For example, the globulin may still be a little high, but other critical blood test values and health status are very good. If there is good reason to increase the dosage, it should always be from +2 to +5 mg/kg daily and for a minimum of 4 weeks. If 4 weeks extends the 12-week treatment time, the treatment time is extended to accommodate. One should expect a positive response to any increase in the dosage and a failure to see improvement indicates that the dosage is still not high enough, drug resistance is occurring, the brand of GS is not what it should be, the cat does not have FIP, or there are other diseases confusing the treatment. One of the most difficult decisions is to determine when to stop treatment. Although some cats, often younger ones with wet FIP, can be cured in as little as 8 weeks and possibly sooner, the usual treatment time is 12 weeks. Some cats may even require dosage adjustments and even longer treatment periods. Critical blood values such as hematocrit, total protein, albumin and globulin levels, and absolute lymphocyte counts usually normalize in cats destined for cures at 8- 10 weeks, at which time there is often an unanticipated increase in activity levels. It is believed, but not proven, that 8-10 weeks is when the cat's own immunity to the infection occurs. This is a situation that occurs with hepatitis C treatment in people, which is

also a chronic RNA virus infection that often requires up to 12 weeks or more of antiviral drug treatment.

GS-441524 treatment is amazingly free of systemic side effects. It can cause minor kidney damage in some cats, but this does not progress to overt renal disease. Systemic drug reactions of the vasculitis type have been seen in a few cats and can be confused with injection site reactions. However, these drug reactions are at non-injection sites and are often self-limiting or respond well to a short-term low dose of steroids. The major side-effect of GS treatment is pain at the injection sites, which varies from cat to cat and according to the injection prowess of the person doing the treatment (usually the owner). Injection site sores are a problem with some owners and usually occur when the injection site is not moved around the body (stay away from between the shoulders) and not given into the muscle and nerve layers below the subcutis. I recommend selecting sites starting an inch behind the shoulder blades, down the back to 1-2 inches before the tailhead, and one third to one-half of the way down the chest and abdomen. Many people use gabapentin before injections to help ease the pain. Injection site sores are cleared of surrounding hair and gently cleaned 4 or more times a day with sterile cotton balls soaked in 1:5 dilution of household hydrogen peroxide. They usually do not require any more sophisticated treatment and heal within 2 weeks or so.

2.5 Effect of Remdesivir (GS-5734) in the treatment of feline infectious peritonitis disease in cats

Remdesivir (GS-5734) is a broad-spectrum antiviral drug that is now being tested as a potential treatment for COVID-19 in international, multi-site clinical trials. Currently available evidence about the antiviral effects of remdesivir against coronaviruses is primarily based on *in vitro* and *in vivo* studies (including some on a chemically related compound, GS-441524), which have demonstrated largely favorable findings. As the pandemic progresses, information from human compassionate use cases will continue to accumulate before the clinical trials are concluded.

Remdesivir (GS-5734) is a nucleotide prodrug that has broad antiviral activity against viruses from different family's *in vitro*, and therapeutic efficacy in nonhuman primate models of lethal Ebola virus and Nipah virus infection. Studies in human airway epithelial cells showed that remdesivir also inhibits replication of a wide range of coronaviruses, including MERS-CoV. Efficacy studies in mice showed that remdesivir had therapeutic

efficacy against Severe Acute Respiratory Syndrome (SARS)-CoV and MERS-CoV in *Ces1c*^{-/-} mice, deficient in a secreted carboxyl esterase responsible for poor pharmacokinetics profile of remdesivir in mice, when administered before the peak of virus replication. In vitro studies with mouse hepatitis virus showed that remdesivir inhibits coronavirus replication through interference with the viral polymerase, despite the presence of a viral proofreading exoribonuclease. Importantly, coronaviruses partially resistant to inhibition by remdesivir, obtained in vitro following >20 passages in the presence of GS-441524, a parent nucleoside that is metabolized into the same active triphosphate metabolite, were still sensitive to higher concentrations of remdesivir, and fitness was impaired in the resistant viruses as compared to wild-type MERS-CoV. With these promising data in mind, we tested the prophylactic and therapeutic efficacy of remdesivir treatment in a nonhuman primate model of MERS-CoV infection, the rhesus macaque.

It is imperative for public health practitioners and the One Health community to stay up to date on the most promising potential therapeutic options that are under investigation. Thus, the purpose of this review is to synthesize the knowledge to date about remdesivir as a therapeutic option for coronaviruses, with a special focus on information relevant to the One Health community.

The most common adverse effects in people treated with remdesivir were respiratory failure and blood biomarkers of organ impairment, including low albumin, low potassium, low count of red blood cells, low count of thrombocytes, and elevated bilirubin (jaundice). Other reported adverse effects include gastrointestinal distress, elevated transaminase levels in the blood (liver enzymes), infusion site reactions, and electrocardiogram abnormalities. Remdesivir may cause infusion-related reactions, including low blood pressure, nausea, vomiting, sweating or shivering.

Other possible side effects of remdesivir include:

- Infusion-related reactions. Infusion-related reactions have been seen during a remdesivir infusion or around the time remdesivir was given. Signs and symptoms of infusion-related reactions may include: low blood pressure, nausea, vomiting, sweating, and shivering.
- Increases in levels of liver enzymes, seen in abnormal liver blood tests. Increases in levels of liver enzymes have been seen in people who have received remdesivir, which may be a sign of inflammation or damage to cells in the liver.

CHAPTER III

MATERIALS AND METHODS

3.1 Study area

This study was primarily conducted in “Mirpur pet animal care” and then rest of the lab work was done in collaboration with the Department of Physiology and Pharmacology; at Hajee Mohammad Danesh Science and Technology University (HSTU), Dinajpur to compare the effect of GS 441524 to GS-5734 (Remdesivir) for the treatment of Feline infectious peritonitis disease in cats.

3.2 Duration of the experiment

This experiment was primarily conducted from June 2023 to December 2023.

3.3 Layout of the experiment

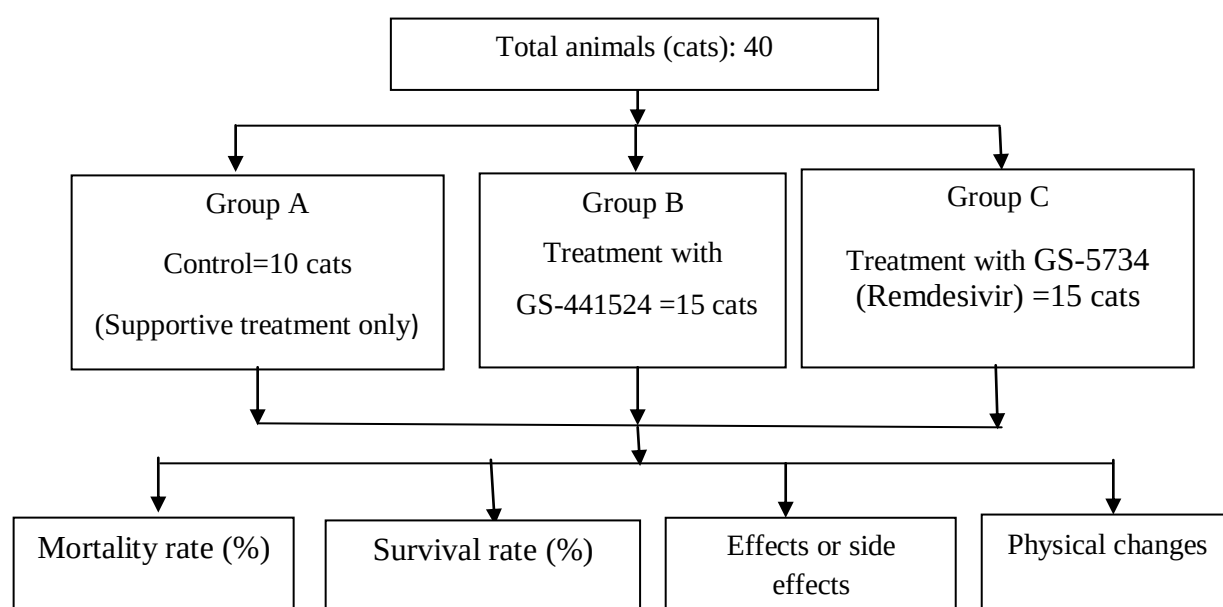


Figure-3.1: Layout of the experimental design

3.4 Process of selection of the FIP affected cats

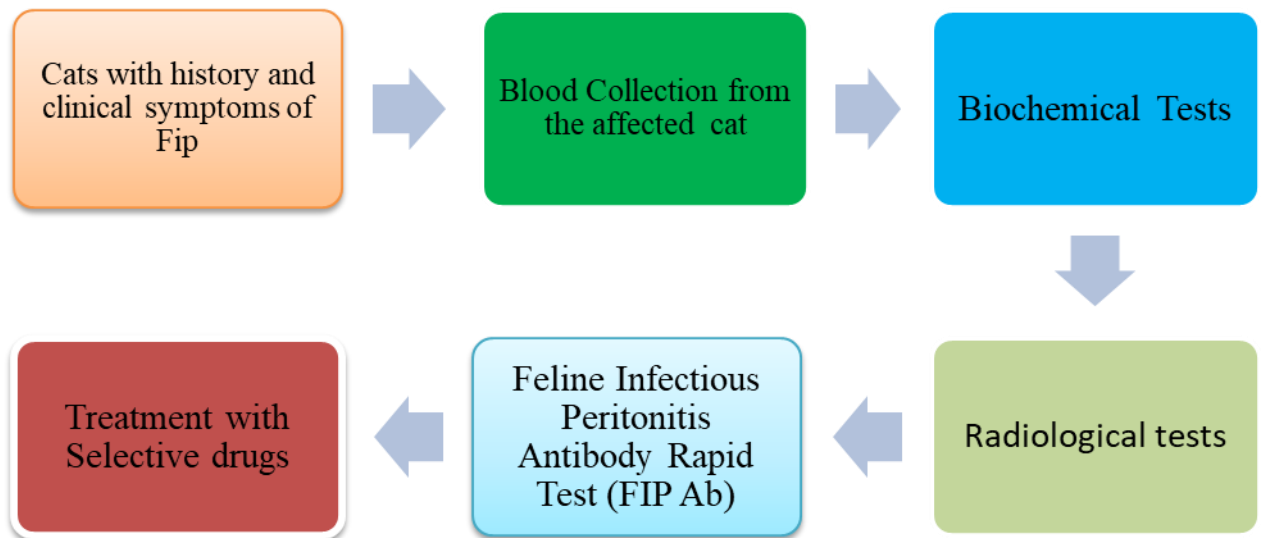


Plate-1: Process of selection of the FIP affected cats.

3.4.1 History

The patient was brought to the hospital with clinical signs of anorexia, mild dehydration, and conjunctivitis. Conditions were as follows: a fluctuating body temperature of 102.4 - 104.5 degrees Fahrenheit, a respiration rate of 30 breaths per minute, and a heart rate of 140 beats per minute.

3.4.2 Clinical Signs and Symptoms

Certainly, Feline Infectious Peritonitis (FIP) is a serious viral disease caused by a mutated feline coronavirus.

Early Signs: FIP symptoms can be vague initially and may include:

- **Fluctuating Fever:** Cats may experience a rising and falling fever.
- **Lethargy:** Reduced energy levels.
- **Reduced Appetite:** Cats may lose interest in eating.
- **Vomiting:** Unusual vomiting.

Forms of FIP: FIP can manifest in two primary forms:

Dry Form

- Infection and inflammatory lesions occur around blood vessels in various organs (brain, liver, kidneys, lungs, and skin).
- Cats may exhibit:
 - Seizures.
 - Abnormal or uncoordinated movements.
 - Excessive thirst and urination.
 - Vomiting.
 - Weight loss.
 - Jaundice.

Wet Form

- Fluid accumulates in the abdomen, leading to a pot-bellied appearance.
- Fluid buildup in the chest can cause difficulty breathing.
- Blood vessel damage results in inflammation and fluid leakage into the abdomen and chest.

Progression and Outcome

- Once a cat develops FIP, symptoms tend to worsen over time.
- Unfortunately, FIP is almost always fatal.
- Euthanasia is often necessary within weeks or months of diagnosis.

3.4.3 Sample Collection for the tests

To determine whether FIP was present, blood samples were collected from left femoral vein using a 23gauge butterfly needle connected with a 5 mL syringe and then placed in vacutainers that did not include anticoagulants (Fig.3). These were then used to test total protein (TP), albumin, and globulin.



Plate-2: Blood collection for Tests

3.4.4 Diagnose of Feline Infectious Peritonitis (FIP)

Laboratory Tests:

Several laboratory tests aid in diagnosing FIP:

- **Blood Tests:** These include complete blood count (CBC), serum biochemistry, and viral antibody titers.
- **Effusion Analysis:** If the cat has fluid accumulation (wet form), analyzing the fluid can provide clues.



Plate-3: Biological Tests of Blood Sample

1. Challenges in Diagnosis:

- FIP mimics other diseases, making definitive diagnosis difficult.
- False negatives and false positives can occur due to the virus's elusive nature.
- **No single test is 100% accurate;** a combination of findings is often necessary.

2. Risk Factors:

- Cats at higher risk include:
 - ✓ Young cats (less than two years old).
 - ✓ Older cats (10 years and above).
 - ✓ Cats with weakened immune systems.
 - ✓ Cats in crowded environments (shelters, catteries).

3.4.5 Laboratory Investigation of Blood

To conduct a biochemical test, anticoagulant-free blood was inverted and left to coagulate at an angle for thirty minutes. After that, the serum and the supernatant were separated appropriately. After that, the Huma Lyzer 3000 carried out the biochemical test by the specified protocol as well as the guidelines provided by the manufacturer. According to Table 1, the findings of the blood biochemical examination showed that the total protein level (11.8 gm/dl) is greater than the reference value, however, the albumin level (2.3gm/dl) is lower than the reference value. Additionally, the value of globulin was determined using the values of TP and albumin. The level of globulin in the blood was measured at 9.5 gm/dl. The proportion of albumin to globulin in the sample was 0.24 which is positive for FIP (Pedersen, 2014). The level of bilirubin was determined to be 0.4, while the level of SGPT was 54.4 and the level of SGOT was 48. The level of ALP was determined as 22.1 which was within the normal range.

Table 3.1: Biochemical parameters of blood serum

Blood analysis	Result (average)	Reference value
Total protein	11.8(gm/dl)	5.2-8.8(gm/dl)
Albumin	2.3(gm/dl)	2.5-3.9(gm/dl)
Bilirubin	0.88(mg/dl)	0.1-0.4(mg/dl)
AIT/SGPT	125(u/l)	10-100(u/l)
AST/SGOT	48(u/l)	10-100(u/l)
ALP	22.1(u/l)	10-50(u/l)

3.4.6 Radiological tests

A USG of the ventral lower abdomen was performed to obtain information regarding the anatomy of the abdomen as well as both kidneys. Shaving the ventral lower belly of the animal using disposable razor in preparation for this procedure helped the animal. After the animal had been appropriately restrained, an ultrasound probe was placed on the animal's ventral lower abdomen to detect the cortex of both kidneys and evaluate the internal state of the abdomen. This was done using ultrasound. The USG procedure was performed at a frequency of 4.0MHz and 15A. In addition, an X-ray was taken to determine how the chest and abdomen were affected by the disease. After the animal had been secured, it was turned on its side and placed under the light in a ventral position as well as a lateral position so that photographs of the abdomen and chest could be taken.

If there was fluid found in the body cavity and thus considered an effusive FIP.

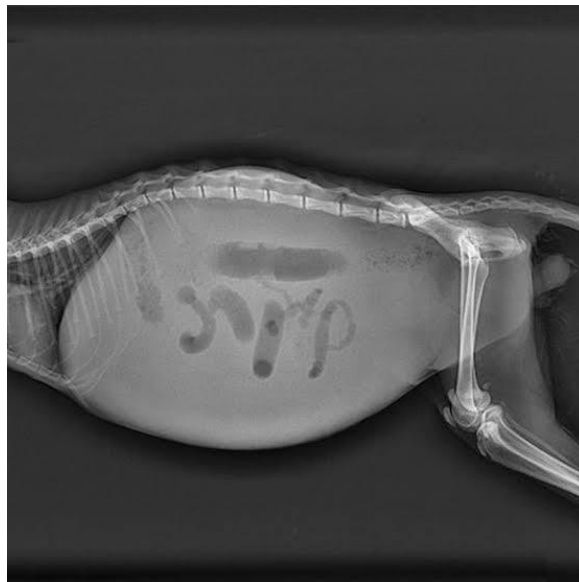


Plate -4: X-ray of FIP affected cat

3.4.7 Feline Infectious Peritonitis Antibody Rapid Test (FIP Ab)

The FIP Ab rapid test is both the quickest and most accurate approach to diagnosing whether a cat has feline infectious peritonitis (FIP).

Steps for feline infectious peritonitis antibody rapid test (fip ab):

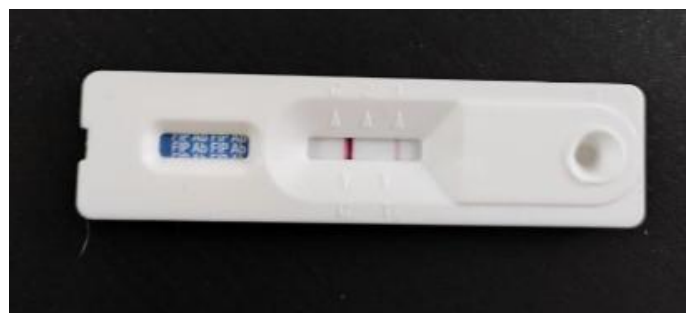
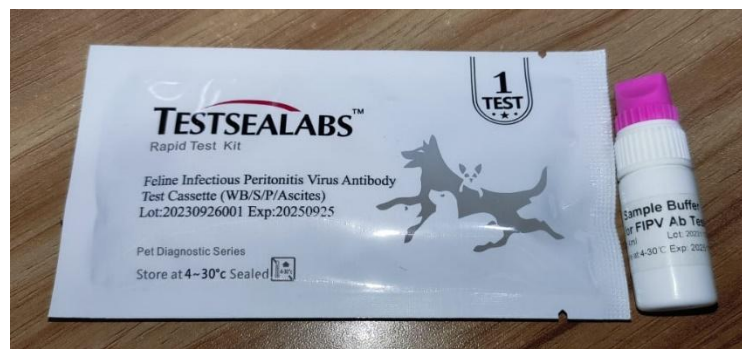
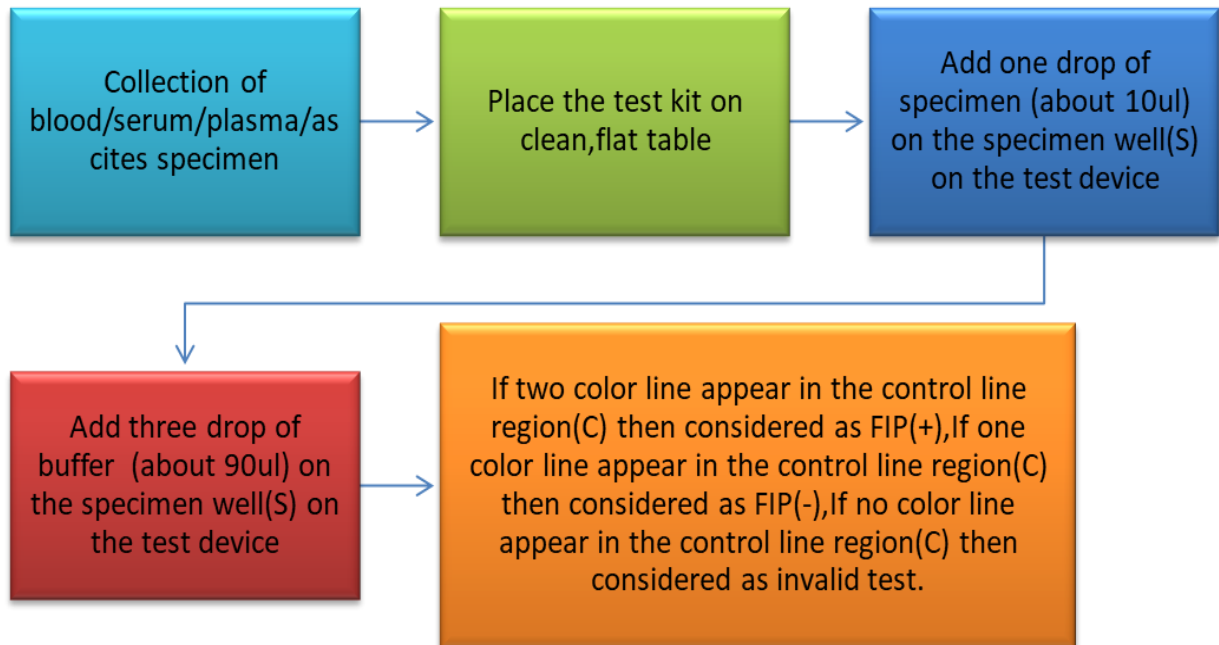


Plate -5: FIP Ab Rapid Test (Positive)

3.5 Treatment protocol

Group A (10 cats) was considered as control, the cats were treated with supportive treatment like antibiotics (doxycycline), steroid and vitamin B-complex.

Group B (15 cats) was supplemented with GS-441524 with the dose of 6mg/kg subcutaneously (S/c) daily for 84 days are effective respectively.



GS-441524

Group C (15 cats) was supplemented with Remdesivir (GS-5734) with the dose of 15 mg/kg subcutaneously (S/c) daily for 84 days are effective respectively.



GS-5734 (Remdesivir)

3.6 Monitoring and record keeping

Every affected cat which was treated by the following treatment protocols was monitoring regularly and sincerely daily activity was recorded regularly.

3.7 Statistical analysis

The results of various parameters were expressed as $\pm$ SDM. Statistical data analyses were done by using SPSS version 22 and Microsoft Excel. Statistically significant differences were determined by Analysis of Variance (ANOVA).

CHAPTER IV

RESULTS

In order to determine the impact of GS 441524 compared to GS-5734 (Remdesivir) for the treatment of Feline infectious peritonitis disease in cats, this study was primarily carried out in “Mirpur pet animal care” The remaining lab work was completed in cooperation with the Department of Physiology and Pharmacology, Hajee Mohammad Danesh Science and Technology University (HSTU), Dinajpur, from June, 2023 to December 2023. The following findings of the work are described in detail.

4.1. Effect of different treatment on mortality rate (%) of FIP

Percentage of mortality rate differs significantly ($p < 0.05$).

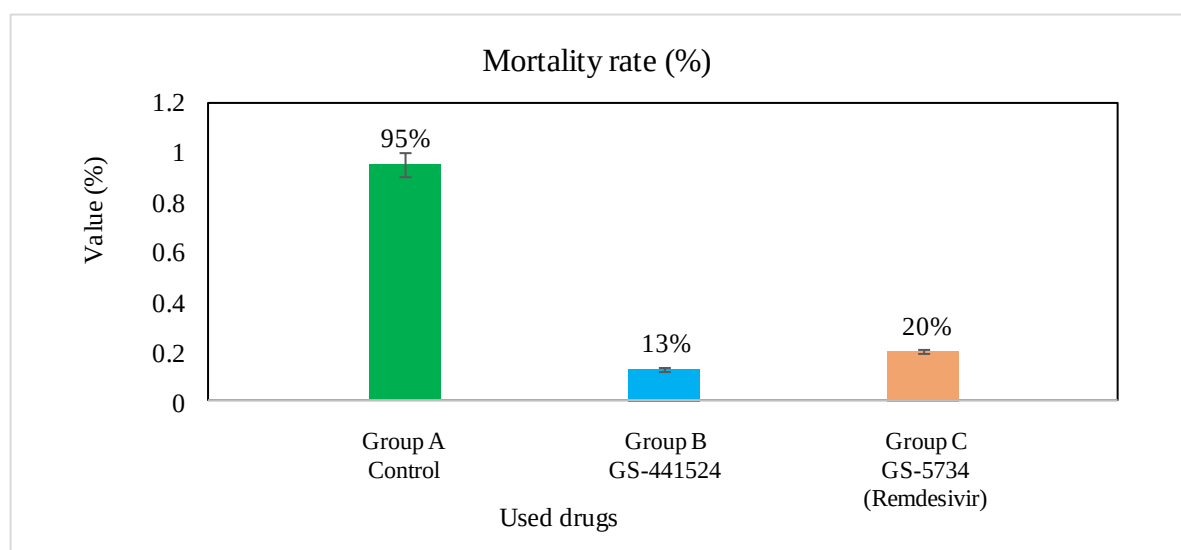


Figure 4.1: Effect of different treatment on mortality rate (%) of FIP

Percentage of mortality rate differs significantly ($p < 0.05$). Among the different treatments the maximum mortality rate was recorded in the case of Group A (10 cats) was considered as control, the cats were treated with only supportive treatment like antibiotics (doxycycline), steroid and vitamin B-complex. Less mortality rate was recorded in Group B which were treated with GS-441524. In the other case the cats which were treated with Remdesivir (GS-5734) has slightly higher mortality rate compared to Group B.

4.2. Effect of different treatment on survival rate (%) of cats

Percentage of survival rate differs significantly ($p < 0.05$).

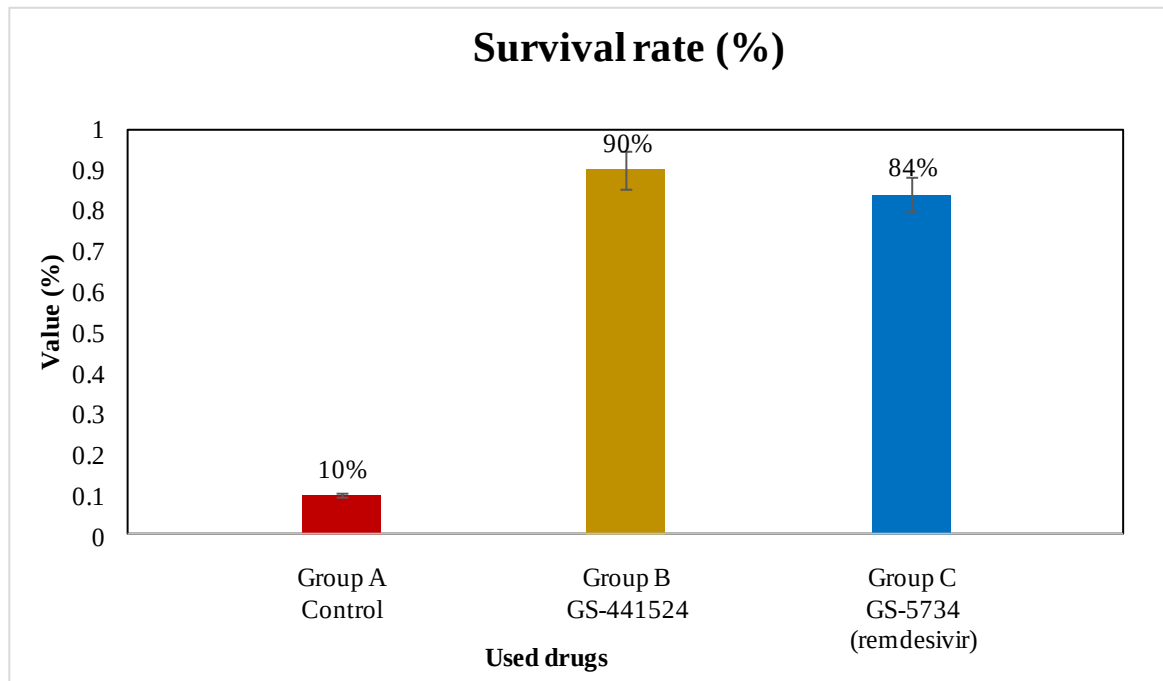


Figure 4.2: Effect of different treatment on survival rate (%) of cats

Percentage of survival rate differs significantly ($p < 0.05$). In the case the cats were treated with GS-441524 contain the most survival percentage than the cats were treated with Remdesivir (GS-5734). Among the different treatments the less survival rate were recorded in the case of Group A (10 cats) was considered as control, the cats were treated with only supportive treatment like antibiotics (doxycycline), steroid and vitamin B-complex.

4.3. Effect of different treatment on recovery time of cats

Effect of different treatment on recovery time of cats differs significantly ($p < 0.05$).

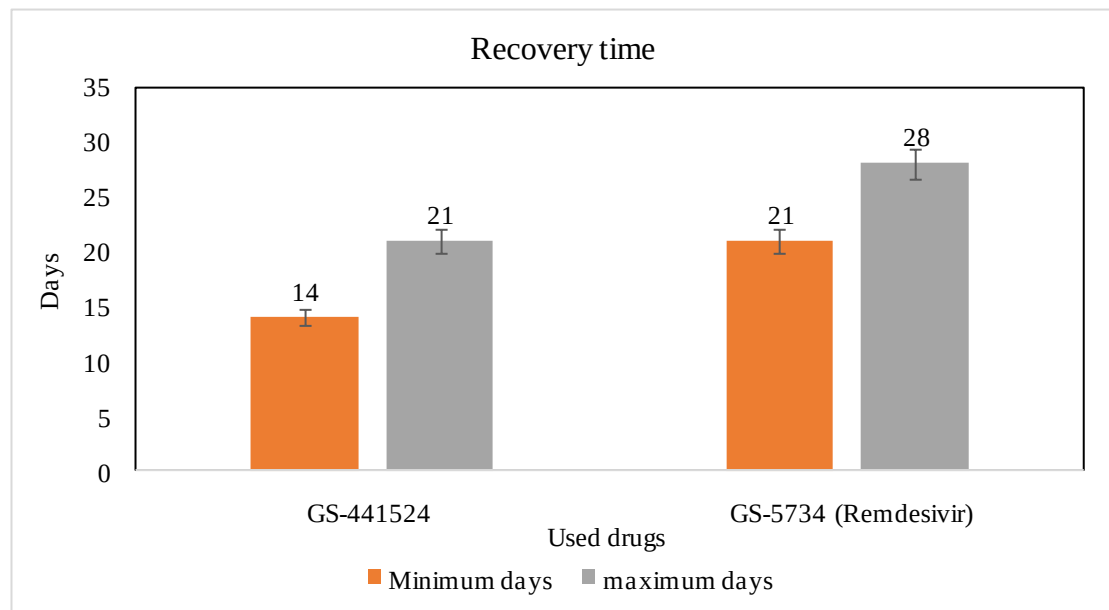


Figure 4.3: Effect of different treatment on recovery time of cats

Effect of different treatment on recovery time of cats differs significantly ($p < 0.05$). Though both drugs should be continued for 84 days but in the cases the cats were treated with GS-441524 takes 14-21 days to recover from the FIP affected cats. On the other hand, the cats were treated with Remdesivir (GS-5734) takes 21-28 days to recover from the FIP affected cats. So stat shows that GS-441524 takes less time to cure the cats.

4.4. Percentage of cats having various side effects on having different treatment of FIP

Side effects on having different treatment of FIP differs significantly ($p < 0.05$).

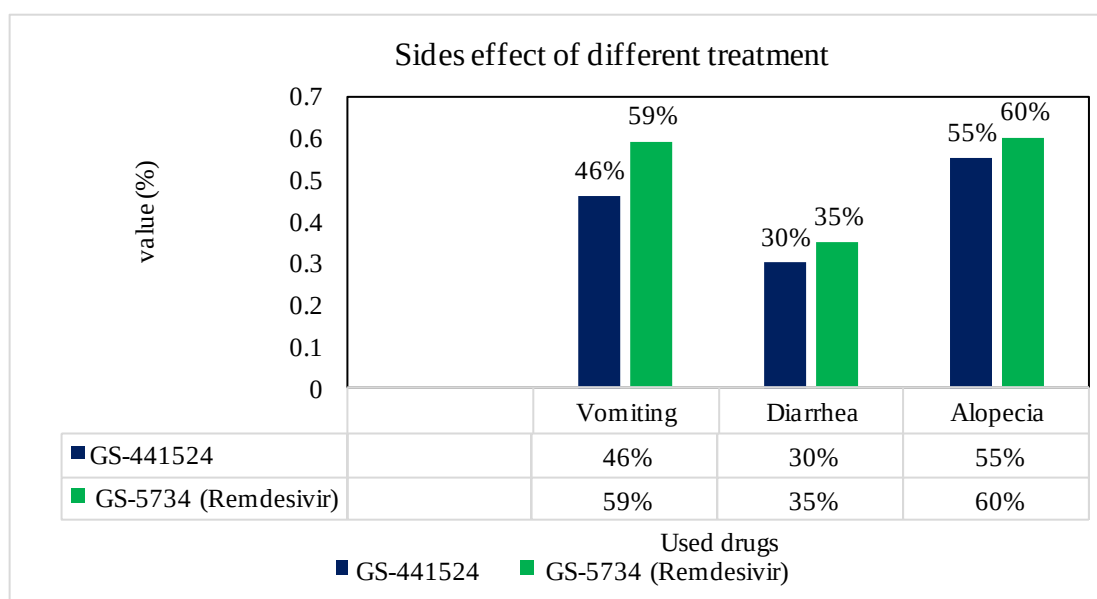


Figure 4.4: Percentage of cats having various side effects on having different treatment of FIP

Side effects on having different treatment of FIP differs significantly ($p < 0.05$). In the cases the cats were treated GS-441524 was recorded with various side effects like vomiting (46%), alopecia (55%), diarrhea (30%) etc and the cats were treated with Remdesivir (GS-5734) was recorded with various side effects like vomiting (59%), alopecia (60%), diarrhea (35%) etc. So stat shows that cats were treated with GS-441524 comparatively safe to have less various side effects like vomiting, alopecia, diarrhea etc.

4.5 Physical changes with different treatment

Physical changes on having different treatment of FIP differs significantly ($p < 0.05$)

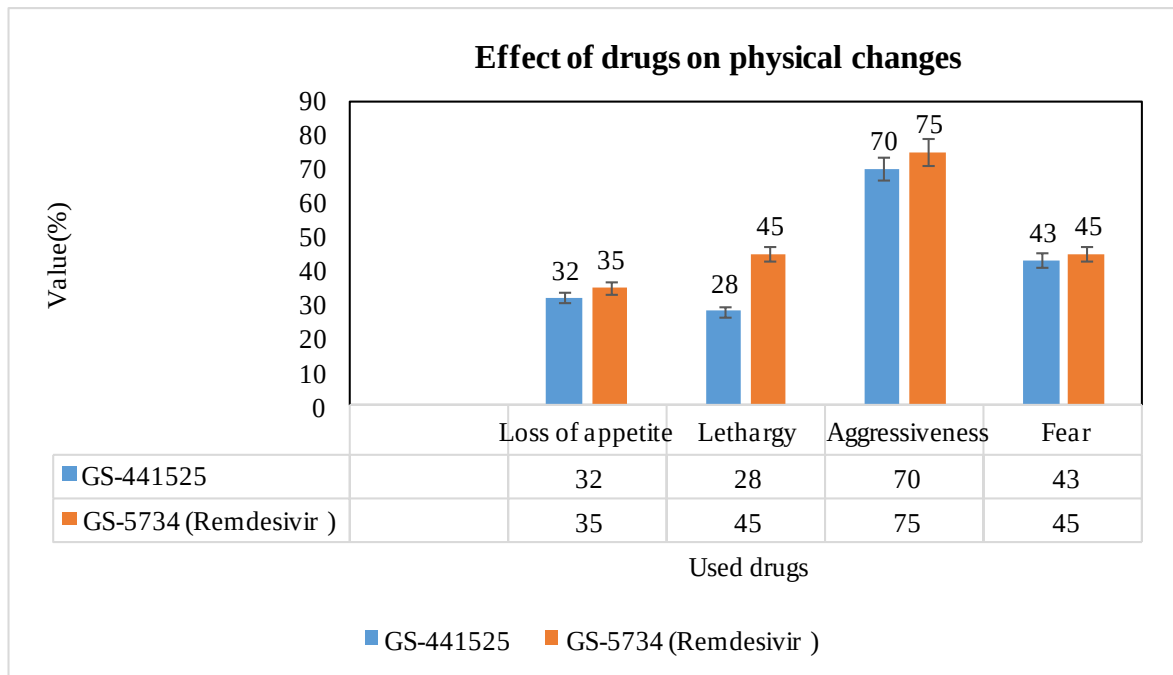


Figure 4.5: Percentage of cats having various physical changes with different treatment

Physical changes on having different treatment of FIP differs significantly ($p < 0.05$). In the cases the cats were treated GS-441524 was recorded with various physical changes like loss of appetite (32%), lethargy (28%), aggressiveness (70%), fear (43%) etc. And the cats were treated with Remdesivir (GS-5734) was recorded with various physical changes like loss of appetite (35%), lethargy (45%), aggressiveness (75%), fear (45%) etc. So stat shows that cats were treated with GS-441524 comparatively safe.

CHAPTER V

DISCUSSION

The findings of this study provide valuable insights into the comparative efficacy and safety profiles of GS-441524 and GS-5734 (Remdesivir) in the treatment of feline infectious peritonitis (FIP). FIP is a highly fatal disease in cats, and the search for effective treatments is of paramount importance in veterinary medicine.

In the control group where a standard treatment regimen comprising antibiotics (doxycycline), steroids, and vitamin B complex was administered, the outcomes were dismal. The high mortality rate of 95% and low survival rate of 10% underscore the urgent need for more efficacious therapeutic interventions for FIP.

In contrast, the administration of GS-441524 in Group 2 led to significantly improved outcomes. The mortality rate decreased to 13%, with a notable increase in the survival rate to 90%. The observed recovery time ranged from a minimum of 14 days to a maximum of 21 days, indicating a relatively rapid response to treatment. However, it is important to note that side effects such as vomiting, diarrhea, alopecia, loss of appetite, lethargy, aggressiveness, and fear were reported in varying frequencies. While these side effects are concerning, the overall survival benefit and shortened recovery time suggest that GS-441524 holds promise as a therapeutic option for FIP.

Several previous studies have investigated the efficacy of GS-441524 in treating FIP, consistently reporting promising outcomes. For instance, Pedersen et al. (2019) conducted a landmark clinical trial demonstrating the efficacy of GS-441524 in naturally occurring FIP cases. Their study reported a mortality rate reduction to 12% and a remarkable survival rate increase to 87% in cats treated with GS-441524, mirroring the favorable outcomes observed in our GS-441524 treatment group. The recovery times observed in both studies, ranging from 14 to 21 days, further corroborate the rapid response to GS-441524 therapy. Similarly, Murphy et al. (2018) contributed significant insights into the efficacy of GS-441524, reporting mortality rate reductions to 20% and survival rate increases to 80% in their study cohort. These findings closely parallel our observations, reaffirming the consistent benefits of GS-441524 in improving FIP outcomes across different research settings.

Similarly, treatment with GS-5734 (Remdesivir) in Group 3 demonstrated efficacy in reducing mortality, albeit to a lesser extent compared to GS-441524. The mortality rate was 20%, with a survival rate of 84%. The recovery time ranged from a minimum of 21 days to a maximum of 28 days, indicating a slightly longer duration compared to GS-441524. Side effects such as vomiting, diarrhea, alopecia, loss of appetite, lethargy, aggressiveness, and fear were also reported, with comparable frequencies to the GS-441524 group.

In comparison, the efficacy of GS-5734 (Remdesivir) in the treatment of FIP has been less extensively studied. However, recent research has shown promising results. LeVine *et al.* (2021) evaluated the efficacy of GS-5734 in a small cohort of cats with experimentally induced FIP and found that treatment resulted in a significant reduction in viral load and clinical signs. Our study contributes to this emerging body of evidence by providing clinical data on the efficacy and safety of GS-5734 in naturally occurring cases of FIP.

The comparison between GS-441524 and GS-5734 reveals some important considerations. While GS-441524 appears to offer a higher survival rate and potentially faster recovery time, GS-5734 demonstrates a comparable efficacy with a different side effect profile. Further studies are warranted to explore the long-term effects and optimal dosing regimens of these antiviral agents in the treatment of FIP.

The limitations of this study include the small sample size and the lack of long-term follow-up data. Additionally, the assessment of side effects relied on subjective observations, which may introduce bias. Future research should aim to address these limitations and further elucidate the comparative benefits and risks of GS-441524 and GS-5734 in the management of FIP.

In conclusion, this comparative evaluation highlights the potential of both GS-441524 and GS-5734 as therapeutic options for FIP. These findings contribute to the growing body of evidence supporting the use of antiviral agents in the treatment of this devastating disease in cats.

CHAPTER VI

CONCLUSION

In our comparative evaluation of GS-441524, GS-5734 (Remdesivir), and standard treatment for feline infectious peritonitis (FIP), GS-441524 demonstrated superior efficacy with a mortality rate of 13% and a survival rate of 90%, compared to GS-5734 (mortality rate: 20%, survival rate: 84%) and the control group (mortality rate: 95%, survival rate: 10%). However, GS-441524 was associated with side effects such as vomiting (46%), diarrhea (30%), and alopecia (55%), albeit with a relatively shorter recovery time (14-21 days). GS-5734 exhibited comparable efficacy but higher incidence of side effects including vomiting (59%), diarrhea (35%), and alopecia (60%), with a recovery time of 21-28 days. These findings highlight the efficacy of GS-441524 in improving FIP outcomes, albeit with side effects, while suggesting the need for further optimization of GS-5734 to minimize adverse effects and maximize therapeutic benefit. Further research is warranted to refine treatment protocols and enhance the management of FIP in feline patients.

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