ORIGINAL ARTICLE

New Era in Diagnosis and Treatment of Canine Parvovirus

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ABSTRACT

Canine parvovirus (also referred to as CPV, CPV2, or parvo) is a contagious virus mainly affecting dogs. CPV is highly contagious and is spread from dog to dog by direct or indirect contact with their feces. Vaccines can prevent this infection, but mortality can reach 91% in untreated cases. Treatment often involves veterinary hospitalization. Canine parvovirus may infect other mammals including foxes, wolves, cats, and skunks. Felines are susceptible to panleukopenia, a different strain of parvovirus. Parvovirus CPV2 is a relatively new disease that appeared in the late 1970s. It was first recognized in 1978 and spread worldwide in one to two years.[15] The virus is very similar to feline panleukopenia. In this research we want to find the most effective and new regimens in treatment of canine parvovirus.

Keywords: Canine parvovirus, CPV,

INTRODUCTION

There are two types of canine parvovirus called canine minute virus (CPV1) and CPV2. CPV2 causes the most serious disease and affects domesticated dogs and wild canids. There are variants of CPV2 called CPV-2a and CPV-2b, identified in 1979 and 1984 respectively.[17] Most of canine parvovirus infection are believed to be caused by these two strains, which have replaced the original strain, and the present day virus is different from the one originally discovered, although they are indistinguishable by most routine tests.

Dogs that develop the disease show signs of the illness within three to seven days. The signs may include lethargy, vomiting, fever, and diarrhea (usually bloody). Generally, the first sign of CPV is lethargy. Secondary signs are loss of weight and appetite or diarrhea followed by vomiting. Diarrhea and vomiting result in dehydration that upsets the electrolyte balance and this may affect the dog critically. Secondary infections occur as a result of the weakened immune system. Because the normal intestinal lining is also compromised, blood and protein leak into the intestines, leading to anemia and loss of protein, and endotoxins escape into the bloodstream, causing endotoxemia. Dogs have a distinctive odor in the later stages of the infection. The white blood cell level falls, further weakening the dog. Any or all of these factors can lead to shock and death. Younger animals have worse survival rates.[3]

Diagnosis is made through detection of CPV2 in the feces by either an ELISA or a hemagglutination test, or by electron microscopy. PCR has become available to diagnose CPV2, and can be used later in the disease when potentially less virus is being shed in the feces that may not be detectable by ELISA[4].

Survival rate depends on how quickly CPV is diagnosed, the age of the dog, and how aggressive the treatment is. There is no approved treatment, and the current standard of care is supportive care, involving extensive hospitalization, due to severe dehydration and potential damage to the intestines and bone marrow. A CPV test should be given as early as possible if CPV is suspected in order to begin early treatment and increase survival rate if the disease is found.

Supportive care ideally also consists of crystalloid IV fluids and/or colloids (e.g., Hetastarch), antinausea injections (antiemetics) such as maropitant, metoclopramide, dolasetron, ondansetron and prochlorperazine, and broad-spectrum antibiotic injections such as cefazolin/ enrofloxacin, ampicillin/enrofloxacin, metronidazole, timentin, or enrofloxacin[6]. IV fluids are administered and antinausea and antibiotic injections are given subcutaneously, intramuscularly, or intravenously. The fluids are typically a mix of a sterile, balanced electrolyte solution, with an appropriate amount of B-complex vitamins, dextrose, and potassium chloride. Analgesic medications can be used to counteract the intestinal discomfort caused by frequent bouts of diarrhea; however, the use of opioid analgesics can result in secondary ileus and decreased motility.

In addition to fluids given to achieve adequate rehydration, each time the puppy vomits or has diarrhea in a significant quantity, an equal amount of fluid is administered intravenously. The fluid requirements of a patient are determined by the animal's body weight, weight changes over time, degree of dehydration at presentation, and surface area.

A blood plasma transfusion from a donor dog that has already survived CPV is sometimes used to provide passive immunity to the sick dog. Some veterinarians keep these dogs on site, or have frozen serum available. There have been no controlled studies regarding this treatment[6]. Additionally, fresh frozen plasma and human albumin transfusions can help replace the extreme protein losses seen in severe cases and help assure adequate tissue healing. However, this is controversial with the availability of safer colloids such as Hetastarch, as it will also increase the colloid osmotic pressure without the ill effect of predisposing that canine patient to future transfusion reaction.nce the dog can keep fluids down, the IV fluids are gradually discontinued, and very bland food slowly introduced. Oral antibiotics are administered for a number of days depending on the white blood cell count and the patient's ability to fight off secondary infection. A puppy with minimal symptoms can recover in two or three days if the IV fluids are begun as soon as symptoms are noticed and the CPV test confirms the diagnosis. If more severe, depending on treatment, puppies can remain ill from five

days up to two weeks. However, even with hospitalization, there is no guarantee that the dog will be cured and survive.

Treatments in Development: Kindred Biosciences is developing a monoclonal antibody for parvovirus. The company announced in August of 2019 that they had 100% efficacy in the treatment and prophylaxis of parvovirus in a pilot efficacy study, and announced in September of 2020 that they had 100% efficacy in the prophylaxis of parvovirus in a pivotal efficacy study[7,8].

Unconventional treatments: There have been anecdotal reports of oseltamivir (Tamiflu) reducing disease severity and hospitalization time in canine parvovirus infection. The drug may limit the ability of the virus to invade the crypt cells of the small intestine and decrease gastrointestinal bacteria colonization and toxin production. However, due to the viral DNA replication pattern of parvovirus and the mechanism of action of oseltamivir, this medication has not shown to improve survival rates or shorten hospitalization stay.[9] Lastly, recombinant feline interferon omega (rFeIFN-ω), produced in silkworm larvae using a baculovirus vector, has been demonstrated by multiple studies to be an effective treatment. However, this therapy is not currently approved in the United States[10-13].

An unpublished 2012 study from Colorado State University showed good results with an intensive at-home treatment using maropitant (Cerenia) and Convenia (a long acting antibiotic injection), two drugs released by Zoetis (formerly Pfizer). This treatment was based on outpatient care, and would cost $200 to $300, a fraction of the $1,500 to $3,000 that inpatient care cost. However, the more-effective care is intravenous (IV) fluid therapy. In the CSU study, survival rate for the new treatment group was 85%, compared to the 90% survival for the conventional inpatient treatment.[14] Note that the outpatient dogs received initial intravenous fluid resuscitation, and had aggressive subcutaneous fluid therapy and daily monitoring by a veterinarian. The dogs have to be taken to the vet every 12 hours for successful treatment and recovery of the dog.

Two forms of disease are present:intestinal and cardiac: Intestinal form, Dogs become infected through oral contact with CPV2 in feces, infected soil, or fomites that carry the virus. Following ingestion, the virus replicates in the lymphoid tissue in the throat, and then spreads to the bloodstream. From there, the virus attacks rapidly dividing cells, notably those in the lymph nodes, intestinal crypts, and the bone marrow.

Cardiac form, this form is less common and affects puppies infected in the uterus or shortly after birth until about 8 weeks of age[3]. The virus attacks the heart muscle and the puppy often dies suddenly or after a brief period of breathing difficulty due to pulmonary edema

Review of literatures:

Romane Adieb Awad, **Brit Martens** and **Safwat Ali Hassan** has shown a treatment regimen:

Treatment trail: All of the diseased dogs (n=360) received the following treatment:

Fluid therapy: Each individual diseased puppy of the 360 examined dogs checked clinically and received the estimated amount of fluids therapy mixture according to the degree and type of the dehydration with daily re-adjustment for first 5 successive days of treatment[12-14]

Supportive therapy: According to severity of anorexia and body weight of each diseased puppy the amount of balanced formula of amino acids, electrolytes and water soluble vitamins calculated, then administered intravenously with fluid therapy for the first 4 successive days[14-16]

Stomach protection agents: Against hyperacidity like H_2 antagonist or proton pump inhibitors, dose according to body weight of each individual puppy and administered once daily intravenously with fluid therapy for 4 successive 4 days[17,18]

Vitamin K: Injection form (10mg/vial) once daily intravenously with fluid therapy for first 3 successive days of treatment for each diseased puppy[19]

Anti emetic: Metoclopramide hydrochloride in form of injection 10 mg/2 mL vials i.v. or sub/cut by rate of 0.2 mL kg^{-1} b.wt., for 5 days[3,20]

Antibacterial drug: Ampicillin 10% solution and enrofloxacin 5% solution injections, subcutaneously with dose as recommended (1 mL/10 kg b.wt.) by producing companies for 7 days[3,15,16]

A group of 120 dogs from the above mentioned dogs received purified specific antibodies (neutralizing antibodies) against FPV (Feliserin PLUS®) for injection intramuscularly or subcutaneously at a rate recommended by producing company (4-8 mL) according to breed and size of the dogs and severity of CPV infection (acute and sub-acute) daily repeat until recovery for at least 3 successive days was obtained from IDT, Biologika GmbH, Am Pharmapark, D-O6861 Dessau-Roβlau, Germany, according to Gerlach et al[21].

Another group of 120 dogs received lyophilized inactivated Parapox ovis virus strain D1701, reconstituted with its supplied diluents, 1 mL dose for 1 puppy, administered subcutaneously at day 0, 2 and 4 of acute occurrence of canine Parvovirus enteritis as a source for generation of 230 IFN units as indicated by producing company obtained from Zoetis Belgium SA, Rue Laid Burniat 1, 1348 Louvain-la-Neuve-Belgium under commercial product name zylexis®, according to[22-24].

This study was attempted to establish a new strategy for CPV therapy in diseased puppies. The results of this study exhibited that the use of Feline specific neutralizing anti-bodies showed promising results against CPV infection in comparison to the old classical treatment and could be applied for CPV infection in diseased dogs.

It is knowing that Canine parvo enteritis resulted in about 90% mortality among infected dogs of different ages, sex and breeds if not treated[1,3]. In majority of cases, death occurs due to dehydration, electrolytes imbalance, septicemia, severe colitis and damage of colon which is a vital organ for fluid and food absorption[1,3].

This study creates the successful treatment for Canine Parvovirus infection that can be effective for treating infected dogs and reducing case fatality among diseased dogs significantly. This study will help the researchers to uncover the critical areas of failure of treatment trials that many researchers were not able to explore. Thus, a new CPV effective treatment regimen may be arrived at. These results recommend the use of specific

neutralizing anti-bodies against FPV than the use of inactivated parapox ovis strain D1701 in treatment of Canine Parvovirus infection in dogs

Mathios E Mylonakis, Iris Kalli and Timoleon S Rallis showed another treatment regimen as below: In the majority of cases, inpatient treatment is warranted; surprisingly, in a recent study, the proportion of dogs that recovered after treatment in the hospital (78.3%) did not differ from that of dogs recovered after at-home treatment (63.2%)[17].

Treatment for PVE is largely supportive and symptomatic. The principal components of treatment include 1) fluid therapy, 2) antibiotic treatment, 3) antiemetic treatment, and 4) nutritional support. An array of other treatment measures including, though not limited to, antiviral treatments and pain management have been assessed in the past or are currently under investigation regarding their potential utility in PVE.

Fluid therapy: Maintenance of hydration and oncotic support as well as correction of acid–base and electrolyte disturbances are of utmost importance in PVE. Since subcutaneous fluid absorption is impaired in dehydrated animals, venous access is the cornerstone of fluid treatment. In case of a peripheral vein catheterization, catheter should be replaced in 72 hours to minimize the chances of bacterial colonization.6 Provided that the dog can tolerate the procedure, aseptic jugular vein catheterization by a multilumen catheter may be a better venous access option compared to a peripheral vein access in PVE because 1) optimization of fluid therapy can be assisted by central venous pressure measurement, 2) multiple drug and fluid types can be administered, 3) serial blood sampling is facilitated, 4) the catheter may remain in place for the entire period of hospitalization, and 5) contamination of the catheter site from vomiting or diarrhea can be easier to avoid compared to a peripheral vein catheter[27]. Based on the evidence that PVE may be associated with a hypercoagulable state, jugular catheterization may raise the possibility of thrombosis[28]. We have never seen clinically relevant thrombosis associated with jugular catheterization in PVE. If placement of an intravenous catheter is difficult, an intraosseous catheter is a very satisfactory alternative, until access to a vein is established[29].

Puppies admitted with severe hypovolemia need reestablishment of their circulating volume in 1–2 hours. As a rule, a balanced isotonic crystalloid solution (e.g., Lactated Ringers) is the fluid of choice for initial restoration of intravascular volume and rehydration, with a rate titrated to improve perfusion parameters, including capillary refill time, mucosal color, pulse character, and mean arterial pressure or lactate concentrations. Typically, the canine shock dose (80–90 mL/kg) is split in consecutive boluses of 15–20 mL/kg given over 15 minutes until improvement of the perfusion status is achieved. In general, if the administration of 50% of the calculated shock volume of isotonic crystalloids has failed to achieve sufficient improvement, adding a colloid should be considered. In dogs admitted without evidence of hypovolemic shock, hydration may be restored over 12–24 hours. The daily fluid allowances should incorporate the maintenance requirements (40–60 mL/kg), the current fluid deficits (body weight [kg] × % dehydration = volume [L] to correct), and the ongoing losses (might be subjectively estimated to 250 mL)[30,31].

Parvoviral enteritis may be associated with huge protein losses[31]. Therefore, colloidal support should be provided when peripheral edema (subcutaneous, conjunctival, pleural, or abdominal effusions), hypoalbuminemia (<2 g/dL), or hypoproteinemia (<4 g/dL) occurs[27,31]. Synthetic colloids (e.g., 6% hetastarch) appear to be more cost-effective options in the clinical setting, as they provide better oncotic support (allowing for a 40%–60% reduction of the daily crystalloids volume) and are more affordable compared to natural colloids[27]. Although synthetic colloids may reportedly adversely affect von Willebrand's factor, factor VIII, platelet function, and fibrin polymerization, clinically relevant bleeding tendency has not been documented in animals receiving daily maintenance rate not exceeding 20mL/kg72.72 Fresh plasma has been suggested in the past because of its purported additional benefits, including coagulation factors and antiviral antibodies[23]. However, plasma has limited availability, may be prohibitively expensive, and has relatively low oncotic pressure, and large volumes (22.5 mL/kg) are required to achieve a mild increase (0.5 g/dL) in the serum albumin concentrations[27,33]. Human or canine albumin solutions may be used as alternatives to fresh plasma for oncotic support; however, their efficacy in PVE has yet to be evaluated. Whole blood (20 mL/kg, within 4 hours) or packed red blood cells is the preferred choice if severe anemia develops in the course of PVE.

Hypokalemia is a frequent issue in PVE[18], which may result in weakness, ileus, and cardiac compromise. Typically, maintenance fluids are supplemented with ≥20mEq/L of potassium chloride for sustaining normokalemia or restoring hypokalemia. The rate of potassium administration should not exceed 0.5mEq/kg/h, and daily measurement of serum level is warranted for better monitoring[24]. Hypoglycemia may be a severe complication of PVE, especially in toy breeds[18]. Therefore, glucose measurement should be performed at least once or twice daily, and supplementation of the maintenance fluids with 2.5%–5% dextrose may be warranted if a declining serum glucose concentration is documented.

Antibiotic treatment: Parenteral administration of wide-spectrum bactericidal antibiotics is warranted in dogs with severe PVE due to the high risk of septicemia associated with the disruption of the mucosal barrier and the concurrent profound neutropenia[24,25,27,35]. Ampicillin and cefoxitin as single-agent treatments or in combination with enrofloxacin (Table) are rational empirical choices offering protection against Gram-positive, Gram-negative, and anaerobic organisms[27,36]. Enrofloxacin may cause cartilage damage in young growing dogs; however, this is a rare occurrence if standard doses are used and the duration of treatment does not exceed 5 days[36]. Aminoglycosides may also be considered in well-hydrated animals.

Antiemetic treatment: Metoclopramide, a dopaminergic antagonist that blocks the chemoreceptor trigger zone and exerts a prokinetic effect in the upper intestinal tract, may be given as a bolus or as a constant-rate infusion in dogs with severe vomiting (Table). The serotonin receptor antagonists ondasetron or dolasetron may be used

successfully in cases of intractable vomiting[27]. The recent advent of maropitant, an antagonist of neurokinin1 receptors, has improved substantially the efficacy of antiemetic treatment in dogs.

Table :Doses of most commonly used drugs in canine parvoviral enteritis

Drug	Dose and interval	Route
Ampicillin	20–40 mg/kg/8 hours	IV
Cefoxitin	20–30 mg/kg/8 hours	IV
Enrofloxacin	5–10 mg/kg/24 hours	IV
Metoclopramide	0.2–0.4 mg/kg/6–8 hours	IV, IM, SC
	1–2 mg/kg/24 hours	CRI
Ondasetron	0.1–0.15 mg/kg/24 hours	IV
Dolasetron	0.5 mg/kg/24 hours	IV
Maropitant	1 mg/kg/24 hours	SC
Butorphanol	0.1–0.2 mg/kg/4–6 hours	IV

Abbreviations: IV, intravenously; IM, intramuscularly; SC, subcutaneously; CRI, cc

Nutritional support: The nil per os feeding strategy in PVE has recently been challenged. Enteral feeding is associated with improved mucosal integrity, faster repair, and as a result, reduced possibilities for bacterial translocation[27,29]. This was accentuated in a relatively recent study, in which early enteral nutrition via nasoesophageal catheter starting 12 hours postadmission was associated with earlier clinical improvement, significant weight gain, and possibly improved gut barrier function compared to dogs subject to the traditional food withholding until cessation of vomiting for 12 hours. Parenteral nutrition is rarely needed in PVE because of the acute course of the disease.

Antiviral treatments: Use of convalescent serum from dogs that have recovered from CPV infection as a means of providing passive immunization has been reported anecdotally[27]. In a recent study, the administration of a single 12 mL dose of CPV-immune plasma as adjunctive treatment for canine PVE after the appearance of clinical signs did not improve any assessed parameter, including time to hematologic recovery, viral load, severity of clinical findings, and duration of hospitalization[33]. However, a beneficial effect may still be possible to achieve if a larger volume of plasma is given prior to the occurrence of the clinical signs[23].

Recombinant feline interferon-ω (rFeIFN-ω) has been promising in previous studies. In a study of 94 dogs with naturally occurring PVE, severity of clinical signs and mortality reduced significantly in those treated with rFeIFN-ω (2.5 mU/kg, intravenously, daily for 3 days) as opposed to placebo-treated dogs.34 In another experimental study, rFeIFN-ω (2.5 mU/kg, intravenously, daily for 3 days) was also similarly effective.35 Currently, the limited commercial availability and the particularly high cost prevent rFeIFN-ω from being regularly included in the clinical setting.

Oseltamivir, a neuraminidase inhibitor, has attracted attention for the treatment of PVE. In a previous study, the use of oseltamivir (2 mg/kg, per os, for 5 days) improved body weight and hematological parameters in dogs with PVE compared to placebo-treated dogs; however, no tangible benefit was documented in terms of survival or duration of hospitalization[36]. In addition, in a recent study in our hospital, oseltamivir at the same dose scheme was ineffective in decreasing morbidity and mortality in dogs with PVE.37 The lack of any clinically relevant benefit, along with the concern that widespread use of the drug in dogs may favor the development of oseltamivir resistance in humans with influenza infections, does not justify the routine inclusion of this drug in the treatment of PVE.

Pain management: Abdominal pain occurs frequently in PVE as a result of severe enteritis, and less commonly due to concurrent intussusception, and may adversely affect appetite.18 Therefore, analgesic treatment may be warranted. In this respect, butorphanol or buprenorphine (Table) may be useful.

Prevention of canine PVE: Modified live vaccines (MLVs) are currently used worldwide affording prolonged (7 years or longer) immunity that would confer protection against both disease and infection.[26] Effective immunization is essential for the protection of the individual pet and the decrease of the population of susceptible animals in a region The initial puppy vaccination series starts normally at 6–8 weeks of age, and then every 2–4 weeks until 16 weeks of age or older.33 In the shelter environment, a more stringent vaccination schedule may be implemented. Vaccinations for CPV (along with other core vaccines) may start immediately on admission, as early as 4 weeks of age and be repeated at 2- to 3-week intervals until 20 weeks of age if the animal is still in the facility. For dogs older than 16–20 weeks on admission, one dose prior to or immediately on admission and a repeat in 2 weeks is proposed[33].

A dog that successfully recovers from CPV2 generally remains contagious for up to three weeks, but it is possible they may remain contagious for up to six. Ongoing infection risk is primarily from fecal contamination of the environment due to the virus's ability to survive many months in the environment

CONCLUSION

Canine parvoviral enteritis is a leading cause of morbidity and mortality in dogs younger than 6 months of age, despite the availability of safe and highly efficacious MLVs. Although the diagnosis of the disease is usually straightforward (compatible clinical and hematological abnormalities in a suboptimally vaccinated puppy, with or without a positive fecal viral antigen test), treatment and prevention strategies are ever evolving in an attempt to decrease the incidence of this life-threatening disease. Future studies should try to optimize the clinical management of the affected dogs by 1) improving the monitoring tools during hospitalization (e.g., establishment of more robust noninvasive markers of the disease severity and prognosis), 2) establishing the best fluid therapy strategy (eg, to substantiate the beneficial role of and refine the most effective colloid solutions), and 3) suggesting more cost-effective antiemetic and antiviral treatments. On the other hand, further research may be warranted in elucidating to which extend the apparent vaccination failures in the clinical setting are vaccine-associated (e.g., vaccines with reduced immunogenicity against the new

field variants) or vaccination policy-associated (eg, level of herd immunity in an area, schedule of primary vaccination series, booster timing).

In addition as romane adieb awad et al ,showed: the use of feline specific neutralizing anti-bodies against fpv was proven to be more efficient in treatment of canine parvovirus infection in dogs with survival rate of 81.7% in comparison to the use of lyophilized inactivated parapox ovis virus strain d1701 as a source for production of ifn with survival rate of 16.6%. while the use of fluid therapy and supportive treatment in the third group gave a recovery rate of 8.3% in diseased dogs.

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