TMP UNIVERSAL JOURNAL OF RESEARCH AND REVIEW ARCHIVES

VOLUME 3 | ISSUE 4 | YEAR 2024 | OCT-DEC 2024

RECEIVED DATE	ACCEPTED DATE	PUBLISHED DATE
30/08/2024	20/09/2024	13/10/2024

Article Type: Research Article

Available online: www.tmp.twistingmemoirs.com

ISSN 2583-7214

THE INVESTIGATION AND STUDY OF CRYPTOSPORIDIUM INFECTION IN STRAY DOGS AND EFFICACY OF TREATMENT WITH TRIMETHOPRIM/ SULFADIAZIN AND CLINDAMYCIN IN TABRIZ AND SUBURBS

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ABSTRACT

This study investigated the prevalence of Cryptosporidium in stray dogs in Tabriz city, Iran, and evaluated the efficacy of a combination of Clindamycin and Trimethoperim/ Sulfadiazin for treating Cryptosporidiosis. Faecal samples of 200 stray dogs were examined by Ziehl Neelsen microscopic method and the results showed that 12 (%6) collars showed infection with Cryptosporidium, with 8 collars in female and 4 in male dogs. According to the age of the dogs, 9 dogs under one year (Puppy) and 3 adult dogs over one year old (%1.5) were diagnosed with Cryptosporidium. There was a statistically significant difference in the prevalence of Cryptosporidium between male and female dogs ($p<0.05$). A treatment course of clindamycin (25 mg/kg/day) and trimethoprim/sulfadiazine (15 mg/kg PO bid for 7 days) was administered and 10 dogs (%83.4) were cured, while 2 dogs showed positive cases. The results suggest that a combination of Clindamycin and Trimethoperim/Sulfadiazin is an effective treatment for Cryptosporidiosis in dogs, but further studies are needed to provide precise pharmacological explanations.

Keywords: Cryptosporidium, Dog, Zoonotic diseases, Clindamycin, Trimethoperim/ Sulfadiazin

INTRODUCTION

Dogs have a great role in the epidemiology of zoonotic diseases which are clearly and abundantly related to humans and the surrounding environment. The increase in owning pet and guard dogs has led to more communication between humans and dogs, clearly lead humans to be exposed to zoonotic diseases caused by dogs (Pavlović et al, 2006, 1).

Cryptosporidium is a protozoan from the Apicomplexan 1 branch of the Coccidian order and the Cryptosporidae family. Cryptosporidium is different from other protozoa of this order in terms of location in the host's intestinal cells, power of self-contamination, and resistance to common

disinfectants, and lack of a specific host (R Fayer et al, 2000, 2). Also, unlike most other Apicomplexan parasites, Cryptosporidium lacks an Apicoplast that makes Cryptosporidium unique among the major Apicomplexan pathogens (Abrahamsen et al., Zhu et al., 3, 4).

Usually, Cryptosporidium oocysts isolated from one vertebrate species are not infectious for another animal species. However, Cryptosporidium Parvum is infectious for 79 species of mammals, including humans.(R M Chalmers et al, 2011. 5) Dogs most commonly harbor *Cryptosporidium canis* while other species of the genus *Cryptosporidium* are found in the gastrointestinal tract of cats, humans and other animals. Although a number of Cryptosporidium Parvum strains have been distinguished at the molecular level and it has been reported that they are different from each other in terms of virulence, but no important characteristics that can suggest another classification have been obtained (U Ryan et al, 2014 6).

In Iran, for the first time in 1984, the presence of cryptosporidiosis in a calf was reported by Gharagozlou and based on histopathological examination (7)

While Cryptosporidium infection is prevalent in various animal species, including lambs, goats, and chickens, the impact of cryptosporidiosis in dogs is often underestimated. While initial reports focused on the susceptibility of young calves (8-21 days old) to Cryptosporidium parvum, with older calves demonstrating greater resilience (E brooke et al, 2008 8). In sheep and goats, acute diarrhea and dehydration are observed mainly in lambs and kids of 1 to 3 weeks. Diarrhea with abdominal pain, lethargy, anorexia, pyrexia, dehydration and sometimes death are the most important clinical symptoms of cryptosporidiosis in ruminants (Heidari et al, 2012 9). Evidence suggests that dogs, particularly puppies and immunocompromised ones, are also at risk (Hamnes et al, 2007 Cui Z et al, 2018 10, 11).

The first documented case of cryptosporidiosis in dogs was reported in America in 1983 by Wilson et al., who reported the first clinical case of canine cryptosporidiosis in a 1-week-old puppy suffering from acute diarrhea attributed to Cryptosporidium parvum (12). While infection in dogs can be asymptomatic, young dogs, especially those co-infected with canine distemper virus, may exhibit clinical signs ranging from mild, intermittent diarrhea to severe, chronic diarrhea accompanied by wasting. This highlights the potential for immunosuppression, such as that caused by canine distemper, to exacerbate Cryptosporidium infection in dogs. (GH Turnwald et al, 1988 DB Sisk DB et al, 1984 K Fukushima 1984 13, 14, 15)

Faecal-oral route is the main route of transmission of cryptosporidiosis, by swallowing infectious oocysts. Oocysts are infectious when they are excreted from the infected host, so direct and close contact with the faeces of infected animals or infected humans, contaminated water and food, and contaminated surfaces are the most important ways of infection. Respiratory transmission of oocysts has also been reported. Cryptosporidium oocysts may survive in water for more than 140 days, are highly resistant to common disinfectants, and have survived even after chlorine has been added to the water. Contaminated water including rivers and lakes, well water and pools are the most important source of Cryptosporidium infection.(16, 17 JM Shields et al,2008 18)

Cryptosporidium appears to have adapted to life without an Apicoplast by acquiring alternative metabolic pathways, such as a giant Type I fatty acid synthase for fatty acid biosynthesis (Zhu G 2004, 19). This absence of the Apicoplast in Cryptosporidium has important implications for drug development strategies against this parasite, as many potential drug targets in other Apicomplexans are associated with Apicoplast functions. (Abrahamsen et al., Zhu et al. 3, 4).

The absence of an Apicoplast, presents a unique challenge in developing effective treatments for Cryptosporidium infections. This is exemplified by clindamycin, a drug recognized for its efficacy against the Apicomplexa stage of Toxoplasma (M E Fichera et al. 1997) (20). Despite

Cryptosporidium lacking this particular life cycle stage, our preliminary research indicates a potential therapeutic benefit of clindamycin in cryptosporidiosis in dogs, suggesting an alternative mechanism of action independent of the Apicoplast. This intriguing finding warrants further investigation to discover the precise pharmacological mechanism and therapeutic potential of clindamycin against Cryptosporidium.

Current treatment options for cryptosporidiosis are limited, with trimethoprim/sulfamethoxazole demonstrating efficacy in humans and captive green iguanas (21, 22). Given the established efficacy of clindamycin against toxoplasmosis, another Apicomplexan parasite, and the successful use of both clindamycin and trimethoprim/sulfamethoxazole in treating toxoplasmosis in various animal models (23, 24), we hypothesize that clindamycin may hold promise as a treatment for cryptosporidiosis. Further research is crucial to evaluate the efficacy and safety of clindamycin in managing and treating this parasitic infection in dogs.

Cryptosporidium is one of the important parasitic protozoans that has been able to adapt to today's conditions and exert its pathogenicity on hosts due to its high adaptability and high vital power of its oocyst. During the last few years, many studies have been done in relation to Cryptosporidium in different parts of the world in the field of medicine and veterinary medicine. The results of these studies have demonstrated that the use of microscopic methods to search for Cryptosporidium oocysts in faeces is effective due to the simplicity of the method, cost-effectiveness and reliability. Intestinal protozoa of dogs are among the zoonotic parasites, and determining the level of contamination, especially common protozoa such as Cryptosporidium, is important to minimize the risk of transmission and prevalence. Therefore, this study was carried out in order to study the epidemiological aspects of the parasite in Tabriz and to investigate the efficacy of the combination of Clindamycin and Trimethoperim/ Sulfadiazin, both administered orally, was evaluated for treating Cryptosporidiosis in the infected dogs.

MATERIALS AND METHODS

All protocols and the guidelines for the ethical use of animals were approved and provided by the Islamic Azad University of Tabriz.

In this study, 200 stool samples from stray dogs of different ages and genders (one hundred male and one hundred female) were randomly prepared and tested. This study was conducted from March 2020 to March 2021. It was done in Tabriz city. Faecal samples were placed in special containers contain %10 formalin were transferred to the parasitology laboratory of the Faculty of Veterinary Medicine of IAU of Tabriz, and for the final diagnosis, the preparation and staining procedures were carried out. The samples were examined using an optical microscope and modified Ziehl Neelsen staining method. By observing at least 20 Cryptosporidium oocysts in each field of view with the magnification of 400, it was considered a positive.

In order to investigate the efficacy the of Clindamycin and Trimethoperim/ Sulfadiazin on positive samples, tested positive dogs with using a course of clindamycin (25 mg/kg/day [three-fourths of the total dose was administered in the morning and one-fourth of the total dose at night] PO for 7 days) (TABLET) and Trimethoprim/ Sulfadiazin (15 mg/kg PO bid for 7 days) (SYRUP) were treated. Then, the sampling procedures were done and the samples after the treatment were transferred to the parasitology laboratory and stained under Modified Ziehl Neelsen and the contamination results were recorded then subjected to statistical analysis. The results were reported descriptively. Chi square test was used to compare the results between males and females, and age difference.

Results

In this study, the faecal samples of 200 stray dogs were examined in Tabriz city, and out of these, 12 collars (%6) showed infection with Cryptosporidium, and the number of uninfected cases was 188 collars (% 82).

Table 1: Percentage and number of Cryptosporidium parasite infections in stray dogs in Tabriz city

Total (%100)	Percentage	Non infected dogs	Percentage	Infection dogs
200	82	188	6	12

Table 2: the prevalence of Cryptosporidiosis in 200 stray dog collars in Tabriz city, based on gender

Male		Female		
Percentage	Infected dogs	Percentage	Infected dogs	
2	4	4	8	
---------	100	----------	100	Total

In 200 stray dogs of Tabriz city (100 female and 100 male collars), 8 collars in female and 4 collars in male showed infection with Cryptosporidium parasite (Table 2).

Table 3: The relation between the age of dogs and the prevalence of Cryptosporidium in 200 stray dog collars in Tabriz city

Adult		Puppy (under one year of age)		
% infection	No	% infection	No	
1.5	3	4.5	9	*Cryptosporidium*
----------	140		60	Total

At the age of less than one year (Puppy), the number of positive cases was 9 collars and at the age of more than one year (Adult), 3 collars showed infection with Cryptosporidium parasite (Table 3)

Table 4: Efficacy of the treatment with clindamycin and trimethoprim/sulfadiazine infection

Efficacy Of the treatment (%)	Total Percentage	No	
....	6	12	Cryptosporidiosis
.....	6	12	Number of the treated infected dogs

0	1	2	Unsuccessfully treated
83.4	5	10	Successfully treated

Based on the results, the number of infected dogs was 12 collar. The dogs were treated (clindamycin (25 mg/kg/day [three-fourths of the total dose was administered in the morning and one-fourth of the total dose at night] PO for 7 days) (TABLET) and trimethoprim/ Sulfadiazin (15 mg/kg PO bid for 7 days) (SYRUP). After treatment, 10 dogs (%83.4) were completely cured while 2 dogs showed positive cases. In the case of the 2 positive dog dogs, the drugs used were not effective (Table 4).

When the analysis of the data and the prevalence of infection was done in terms of the gender of the dogs, a statistically significant difference was observed in the prevalence of Cryptosporidium between male and female dogs ($p<0.05$). In this study, according to the age of the dogs, 9 dogs under one year (Puppy) and 3 adult dogs over one year old (%1.5) were diagnosed with Cryptosporidium. When the overall prevalence was analysed according to age, a statistically significant difference was found in the prevalence of Cryptosporidium (under one year old and over one year old) to the extent of ($p<0.05$). Also, there was a significant relation between the reduction of Cryptosporidium prevalence and the use of Clindamycin and trimethoprim/sulfadiazine were observed, as the use of two drugs caused a significant decrease in the number of oocysts ($p<0.05$).

DISCUSSION:

The results of these studies have shown that the use of microscopic methods for Cryptosporidium oocyst search in faeces is an accessible, easy, and reliable method due to the simplicity of the method and no need for expensive materials and equipment.

According to the results of this study in Tabriz city, %6 of the tested stool samples were contaminated with Cryptosporidium. In a study conducted in 2013 in Kerman city on 100 pet dogs, contamination with Cryptosporidium was reported in three cases (M Fouladi, 2012 25). In another study conducted by Mirzaei in Kerman city in 2011 (26) on stray dogs, out of 98 dogs examined, 4 cases were infected with Cryptosporidium and 7 cases were diagnosed with Giardia. In another study in Ilam province, the prevalence of Cryptosporidiosis in stray dogs in was reported to be about %7.14. This study also has relative agreement with our study (%6) (S Kakeshani et al, 2011 27). Another study by B Mosallanejad et al. in 2010 reported the prevalence of cryptosporidiosis in dogs in Ahvaz at %4.3 (B Mosallanejad et al, 2010) (28). In a review of similar studies in other countries, the prevalence of Cryptosporidium infection in pet dogs in Brazil has been reported to be %1.4 (29). In 2014, N Itoh et al reported the prevalence of Cryptosporidium infection in pet dogs in Japan to be %7.2. In a study in South Africa by Samie et al, the prevalence of dogs infected with Cryptosporidium was %44, with %46.2 in stray dogs and %41.7 in pet dogs (30, 31).

Our findings indicate varying degrees of Cryptosporidium contamination in different regions. Comparative studies demonstrate different prevalence rates, with a relatively higher occurrence noted in Tabriz. These disparities could potentially be attributed to a multitude of factors - variations in environmental conditions, sampling methodologies, diagnostic precision, and geographical or climatic differences. Despite these regional variations, it's noteworthy that Cryptosporidium infection appears to be a widespread issue across the world.
The prevalence of Cryptosporidiosis in puppies in this study align with the results of previous similar investigations (32, 33)

Considering the relatively high level of infection in puppies that were tested in this study, it seems that immunosuppression is a risk factor possibly because in immunocompetent animals, IFN-gamma plays a key role in protective immunity against infection. However, immunosuppressed animals lack this protective mechanism, leading to more severe and prolonged infections (V McDonald 2000, 34).

The mechanism of action of trimethoprim/ sulfadiazine against Cryptosporidium involves their roles as antifolates, targeting dihydrofolate reductase (DHFR) in the parasite (Liu et al. 2009 35) Gałęcki et al in 2018, extrapolated that a combined therapy with Spiramycin combined with Metronidazole and Trimethoprim/ Sulfadiazine effectively eliminated the clinical symptoms of cryptosporidiosis in Iguana iguana (22).

The mechanism of clindamycin and macrolide action against on Aphylum Apicomplexa group has been the subject of considerable speculation over the past decades. One study by FICHERA et al 1995(36), investigated the given chemotherapy agents on Toxoplasma gondii and illustrated that the T. gondii, had not been affected in a short term with Clindamycin. They illustrated that the delayed effect of clindamycin and macrolides might be dependent on the establishment of the second parasitophorous vacuoles.

Over 100 compounds have been tested in laboratory animal models, but none is highly effective clinically (37). According to this study, the treatment of cryptosporidiosis with the studied pharmaceuticals in dogs is not always effective.

Although in this study, a combination of Clindamycin and Trimethoperim/ Sulfadiazin effectively eliminated the symptoms and oocysts of Cryptosporidium in %83.3 of the infected dogs, the precise Pharmacological of the mentioned therapy regiment was not the goal of the study. I strongly recommend further studies to establish a precise Pharmacological explanation.

A comprehensive pathological understanding of cryptosporidiosis in dogs is paramount to the development of effective prevention and control strategies. This includes encouraging responsible pet ownership practices, including routine faecal examinations and immediate veterinary care for puppies exhibiting gastrointestinal signs. Moreover, investigations and researches targeted at exploring potential therapeutic options, such as the combination of Clindamycin and Trimethoprim/ Sulfadiazin, are necessary. Such treatment combinations could provide a highly effective and easily accessible medication option.

In addition to medical interventions, environmental factors play a significant role in disease prevention. It is strongly recommended that dogs be provided with a clean environment, cooked food, and safe water. These measures can significantly reduce the risk of Cryptosporidium infection.

Preventing cross-species transmission is also crucial. Individuals who interact with dogs, both stray and pets, should adhere to stringent personal hygiene standards to prevent contamination in livestock and humans.

Further investigations should also consider the development of canine-specific diagnostic tools for early and accurate detection of Cryptosporidium infection. Such advancements will enhance our capability to control this zoonotic disease effectively and mitigate its impacts on animal and human health.

CONCLUSION

This study highlights the critical role of dogs in the epidemiology of Cryptosporidiosis, and underscores the public health implications associated with Cryptosporidium. Our findings indicate a %6 prevalence of Cryptosporidium infection among stray dogs in Tabriz, with a higher incidence observed in younger dogs and females. This significant variation based on gender and age emphasizes the necessity for targeted surveillance and intervention strategies to effectively manage these infections.

The resilience of Cryptosporidium oocysts in various environments complicates efforts to control transmission, as they can survive common disinfectants and persist in the environment. However, the treatment regimen involving Clindamycin and Trimethoprim/ Sulfadiazine demonstrated a remarkable success rate, curing %83.4 of infected dogs. This highlights not only the effectiveness of these drugs but also their critical role in managing cryptosporidiosis within canine populations. The success of this treatment regimen underscores the importance of timely and appropriate pharmacological interventions in controlling zoonotic diseases, ultimately safeguarding both animal and human health.

Overall, our findings emphasize the importance of monitoring and controlling Cryptosporidium infection in stray dogs, given their potential risk to both animal and human health. The effective use of targeted drug therapies is essential for mitigating these risks and preventing further transmission. Continued research is vital to enhance our understanding to develop comprehensive control measures that leverage effective treatments. By prioritizing the development and implementation of robust treatment protocols, we can significantly improve public health outcomes related to zoonotic diseases.

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