ORIGINAL ARTICLE

Comparison of Fipronil-Impregnated Bait and Integrated Vector Management (IVM) in the Control of Zoonotic Cutaneous Leishmaniasis in an Endemic Focus of Fars Province, Southern Iran During 2016 to 2017

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Received: 18 October 2017
Revised: 1 November 2017
Accepted: 10 December 2017

Abstract

Background: Fipronil systemic insecticide and integrated vector management (IVM) leading to control and/or reduction of zoonotic cutaneous leishmaniasis (ZCL) cases were evaluated in the studied endemic foci of Fars province, southern Iran, during 2016 to 2017.

Methods: Based on available data on disease circumstances collected from Center for Disease Control (CDC) of Shiraz University of Medical Sciences, incidence of disease, and demographics of the natives, five villages were randomly selected among those with high and medium CL infection in Kharameh area. All villagers were checked by physical examination and the incidence rates of ZCL cases were recorded. IVM interventions were implemented. Indeed, these procedures consisted of fipronil systemic insecticide poison baits, indoor residual spraying (IRS), outdoor spraying of the patients' houses, and the thermal fogging (three times) during peak periods of sand flies' activities.

Results: After interventions, the incidence rates of ZCL decreased by 2.55% in Mehrabad village, in which all IVM methods were implemented. Similarly, the incidence of disease was reduced by 4.89% in Sofla and Moezabad villages, using exclusively fipronil poison baits. Besides, these incidence rates declined by 1.15% in two control villages of Soltan-Shahr and Abshor, where examination of the rodent reservoir hosts was performed.

Conclusion: Fipronil and IVM methods were advantageous in reducing the incidence rates of leishmaniasis, but it seems that the use of fipronil systemic insecticide as a poison bait against reservoir rodent was significantly more effective (P-Value=0.01).

Please cite this article as: Saki E, Soltani A, Djafar Moemenbellah-Fard M, Kalantari M, Dorzaban H, Azizi K. Comparison of Fipronil-Impregnated Bait and Integrated Vector Management (IVM) in the Control of Zoonotic Cutaneous Leishmaniasis in an Endemic Focus of Fars Province, Southern Iran During 2016 to 2017. J Health Sci Surveillance Sys. 2018;6(1):2-7.

Keywords: Zoonotic cutaneous leishmaniasis, Sand fly, Fipronil, IVM, Iran

Introduction

Leishmaniases are caused by the intracellular parasite of Leishmania species. These are transmitted to humans by the bite of sand flies worldwide.[1, 2] In addition, 350 million people are at risk of these diseases, and based on World Health Organization (WHO) reports, an estimated 0.9–1.3 million new cases and 20000–30000

deaths annually occurred in the world.[3] However, recent statistics have revealed that these cases have increased, indeed from 1.5 to 2 million new cases, and 70,000 deaths were recorded every year.[4] The populations subjected to the risk of Cutaneous Leishmaniasis (CL) varied from 14% to 100% in high-risk countries. In fact, CL is an international arthropod-borne disease affecting 88 countries, and about 399 million people were at the risk of this disease.[5] Accordingly, the maximum CL incidence was recorded from Syria (about 22.7 per 10000 people), whereas it was estimated about 2.7 per 10000 people in Iran. Consequently, the cases have tripled during the past two decades in CL high-burden countries.[6] Presently, the main anxiety is the rash of Old World-CL in the North Africa and Middle East which is triggered by the refugee crisis and Syrian civil war, and has affected many people caught in battle regions and/or living in immigrant campsites.[7, 8] In Iran, CL is one of the well-known vector-borne endemic diseases which are frequently transmitted by arthropods after malaria.[9, 10]

Leishmaniases, as one of the greatest neglected tropical infections, are associated with population displacement, poor housing, malnutrition, weak immune response, and lack of funds for disease treatment and control. In fact, the development of this disease is fundamentally related to humans' activities.[4] CL is characterized by active infection of Leishmania parasite and its accompanying lesions, which typically change from the papules and/or nodules to plaques or ulcers. These lesions are usually self-healing in the absence of treatment after distinct periods of time.[3] Leishmaniasis, as a zoonosis with a wide variety of reservoir hosts, occurs in at least three major clinical forms of cutaneous, visceral, and mucocutaneous. In their mammalian host, Leishmania species intracellularly live and reproduce within phagocytic cells. Currently, 18 different Leishmania species are described as pathogenic for humans.[11-13] Remarkably, the permanent aspect of inactive CL is "scarring" in endemic populations. Furthermore, it has locally been shown that equate CL exactly equates with its scar form, known as "aleppo evil" in Syria, "the scar will remain forever" or "little sister" in Saudi Arabia, "trace" in Yemen, and "mountain leprosy" in the Amazon area; this highlights the importance placed on inactive leishmaniasis by those infected.[14] While the Old World-CL is usually not lethal, clinical symptoms can cause disfiguring scars that lead to psychological concerns and social stigma. According to WHO reports, and as a result of global CL and VL, it is estimated that more than 2 million disability adjusted life years (DALYs) are lost. Leishmaniasis, as a major health problem, occurs in 14 out of 22 countries located in the Eastern Mediterranean Region.[15] Nevertheless, because CL is not life limiting, it is not seen as a main concern for policymakers, and currently this is shown by a lack of obligation to patient provision and preventive campaigns such as knowledge of treatment, limited diagnostic capacity, and drug availability in some endemic countries.[16]

Leishmaniasis has remained a part of the major world health problem, and no safe and effective vaccine has been developed for leishmaniases. However, insecticide programs for sand flies and individual protection methods against sand flies bites such as insect repellents, mosquito nets, and insecticide treated clothes seem to be ineffective and inaccessible for risky populations in low and middle income countries.[17, 18] The ambient ecosystem changes as well as the displacement of human populations, and building residual houses near the sand flies and reservoir hosts of leishmaniasis may increase human contact with infected sand flies and may cause changes in the density and variety of reservoirs and vectors of the disease.[19] The rodent burrows are important larval breeding places which prepare a proper temperature and humidity for sand flies in arid zones. Sand flies' larvae feed on the rodents' droppings in the holes; yet, because of the lack of insecticide penetration into the sand flies larval breeding places, which is placed deep in the rodent shells, the direct use of insecticides has not been effective in the control of sand flies in rodent burrows.[20]

Insecticide-treated rodent bait is recently being used as a method to control insect vectors that feed on the reservoir host.[20, 21] Fipronil is a systemic insecticide with high digestive and touching base effects from a novel group of insecticides, named phenyl pyrazoles. The insecticide has an extensive range of effectiveness on various insects, especially on their central nervous system. Furthermore, it can effect the gamma-aminobutyric acid (GABA), glutamate, and mammals lack glutamate receptors in the insects' bodies.[22] Fipronil can remain in the feces of the rodents, and after feeding on these materials by the sand flies larvae, it causes death (100% mortality) of the vector of zoonotic cutaneous leishmaniasis (ZCL) type up to about 1 month after about100 mg/kg insecticide-impregnated baits are eaten by rodents. Similarly, these mortality effects last up to about 21 and 49 days after feeding a fipronil bait by rodents on sand flies larvae and female adults, respectively.[23] Integrated vector management (IVM), if accurately implemented, could be effective in reducing the incidence and load of CL transmission. In these studies, the main aim was to reduce the chance of transmission of CL pathogens, the vectors' infection rate, parasite transmission from the vector to human, and also increase the vectors' mortality after blood loss from rodent reservoirs. Indeed, these procedures consisted of using toxic baits of fipronil systemic insecticide, indoor residual spraying (IRS), outdoor spraying of patients' houses with acute ulcer of leishmaniasis, using the thermal fog during peak

periods of sand flies' activities, and comparison of fipronil systemic insecticide and IVM in the control and/or reduction of ZCL cases in endemic foci of Fars province, southern Iran during 2016 to 2017.

Materials and Methods

Study Area

Fars province (about 122 400 km²) is placed in the south of Iran. Kharameh is one out of 23 counties of this province. It is located about 80 kilometers northeast of Shiraz (the capital city of the province), and is geographically positioned at 29°50'20" N and 53°31'24" E, and about 1500 m above the sea level. Kharameh with an area of 1,590 km² and population of 61580 individuals is considered as one of the main important areas of ZCL in Fars province, southern Iran (Figure 1).

In this investigation, based on the CL accessible data collected from Center for Disease Control (CDC) of Shiraz University of Medical Sciences, regarding the incidence of CL cases and demographics of natives, all villagers were checked by physical examination, and the incidence rate of this disease was reviewed. Afterwards, five out of 95 villages from Kharameh were selected. Indeed, Mehrabad, Moezabad, and Sofla villages were considered as target villages. In addition, Soltan-Shahr and Abshor were selected as the control (un-treated) villages. Fipronil and IVM procedures (indoor residual spraying, outdoor spraying of the patients' houses, and the thermal fogging) were carried out in Mehrabad village, whereas fipronil systemic insecticide was merely performed in Moezabad and Sofla villages. In the two control villages of Soltan-Shahr and Abshor, without any specific control advice, the routine traditional controls (using a brodifacoum-impregnated bait) were carried out.

The collected data were analyzed using Chi square and descriptive statistics test in SPSS 16 and a P value of <0.05 was considered as significant.

Fipronil-Impregnated Bait Method

According to a study, the concentration of insecticide was determined as 100 mg/kg for preparation of fipronil bait, which had the highest effect on sand flies and the least side effect on rodent reservoirs of ZCL.[23] Consequently, 50kg of wheat, combined with 5gr of fipronil and 2.5 liters of soya bean oil was used to create enough adhesion and taste for rodents, and it was placed on rod bait.

To find active colonies of rodents, their burrows were destroyed up to 500 meters around the villages of Mehrabad, Moezabad, and Sofla two days before fipronil bait procedure started. After 48 hours of rodent burrow destruction and a day before the peak activity of sand flies in early June, which was determined by previous studies in Kharameh focus,[24] the active burrows of the rodents were revealed and about 15gr of fipronil-impregnated baits (concentration of 100-mg/kg) were carefully put in a depth of 10 cm of burrows and these were blocked again to prevent the use of other non-target animals.

Spraying Method

At the same time, during the peak activity of sand flies in early June and September, spraying was carried out three times by indoor residual spraying (IRS) and outdoor spraying of the patients' houses by the thermal Fog machine (Golden Eagle mark, USA) by cypermethrin (EC 40%) insecticide to remove the

Figure 1: Map of the studied areas of Kharameh in Fars province, southern Iran

vectors of CL in Mehrabad. Then, routine control programs were carried out using a brodifacoum-impregnated bait in the villages of Abshor and Soltan–Shahr.

Results

The incidence outcome of CL revealed that despite its value was 28.91 per thousand in 2016, and it reduced to 3.40 per thousand in 2017 after CL control programs were performed. In fact, CL declined by 25.51 per thousand in Mehrabad village, where all the above-mentioned control methods were carried out. Indeed, the number of CL patients reduced from 17 to 2 cases, showing a significant difference level compared to the control villages (P=0.01) (Table 1).

Similarly, the incidence rate of CL was 54.92 per thousand during 2016 in two villages of Sofla and Moezabad, but after exclusive use of fipronil-impregnated bait in the intervention program, the incidence rate of CL reduced to 5.97 per thousand in 2017, which was a reduction of 48.95 per thousand after 1 year. Indeed, the number of CL patients was reduced from 92 to 10 cases. Consequently, new results indicated a significant difference level (P<0.001) compared to the control villages. Also, these results (Fipronil-impregnated bait) revealed a significant difference between Mehrabad village (IVM), and Sofla and Moezabad villages (Fipronil-impregnated bait) (P=0.01) (Table 1).

In addition, the incidence rate of CL was 30.02 per thousand during 2016, but it declined by 18.53 per thousand in the control villages of Asbshor and Soltan Shahr in 2017; it decreased by 11.49 per thousand in 2017. The number of CL patients reduced from 81 to 50 cases (Table 1).

Discussion

Fars province is currently considered as the most important center of CL in Iran, and the number of cases of this vector-borne disease has increased dramatically in almost all areas of the province in recent years.[25, 26] This increase reveals the possibility of formation of a new and important CL endemic center in these areas.[27, 28] Considering the topographic condition of Fars province and the continuous dispersion of the vectors and reservoirs in different regions of the province, it may possibly spread to other areas in the province. In this study, the incidence rate of the disease declined by 48.95 per thousand after using fipronil-impregnated bait for one year. In addition, using the IVM method (including fipronil and spraying) could also reduce the incidence rate by 25.51 per thousand, and this reduction was statistically significant compared to the incidence reduction in the control villages.

Mascari et al. (2013) examined the effect of fipronil on the mortality of sand flies and revealed that this insecticide affected the mortality of both larvae and adults of sand flies, and was able to suppress the vector population living near the reservoir hosts.[23] In this study, this reduction significantly (P=0.01) occurred in CL infections (reduced from 92 to 10 patients), particularly in villages where merely fipronil was used. Another investigation evaluated the effect of fipronil on the mortality of Phlebotomus papatasi larvae and adults. This investigation indicated that 2 days after feeding, up to 90% of female sand flies died. Also, after six weeks, 80% of the total sand flies' population were decreased.[29] This was consistent with the current study, with an incidence reduction of 48.95 per thousand in villages where only fipronil was used. Another study was conducted by Mascari et al. (2008) on an ivermectin systemic insecticide. Accordingly, they showed that the mortality and survival rate of the larvae fed on hamsters treated with ivermectin insecticide were significantly changed.[30] In another research, the effect of fipronil insecticide on the mortality of larvae and matures of P. argentipes in India was evaluated. In this study, cows were fed with fipronil-impregnated bait. Results then showed that all larvae and adult sand flies which were fed on cow blood and stool died (100% mortality) in a 21-day period after a dose of fipronil was used.[31]

A field experimental study was conducted in southeast Kazakhstan to evaluate the efficacy of fipronil bait (0.005%) in reducing Xenopsylla and Phlebotomus species populations, which used the rodent burrows for oral uptake. The bait resulted in 100% mortality in Xenopsylla flea species about 3 months after treatment. Gravid Phlebotomus population decreased between 72% and 100% during

Table 1: Incidence rate of ZCL before and after different control implementations in the study areas of Kharameh in Fars province, southern Iran during 2016-2017

Village(s)	Method(s)	Population	Before intervention		After intervention		Total reduction		P value
		(no.)	*Inf. (no.)	**Inc./tho.	Inf. (no.)	Inc./Tho.	Inf. (no.)	(Inc./Tho.)	
Moeazbad & Sofla	Fipronil bait	1675	92	54.92	10	5.97	82	48.95	0.01
Mehrabad	IVM	588	17	28.91	2	30.4	15	25.51	0.02
Abshor & Soltan-shahr	routine	2698	81	30.02	50	18.53	31	11.49	0.001
Total	-	4961	190	113.85	62	54.9	128	85.95	

*Infected; **Incidence/thousand; ***Integrated Vector Management

3 weeks of insecticide treatment. However, sand fly decrease was not noticeably seen after the third week and the findings showed that ecological factors may significantly influence the abundance of sand flies.[32]

In conclusion, two methods of fipronil poison bait and IVM significantly reduced the incidence of the disease (P=0.02), and fipronil method was more effective than IVM procedure. However, it seems that fipronil systemic insecticide baits eaten by rodents are able to remove the ZCL vectors without killing the rodent reservoirs, and suggested to be effective as a low-cost control procedure. However, investigating the effect of other systemic insecticides on the control and/or reduction of sand flies is suggested. Also, designing a large scale study in a wider area with more villages and evaluating the effectiveness of this method over a multi-year period to reduce the incidence of disease are beneficial. Moreover, laboratory examination of insecticides on adults and larval stages of carriers may result in more detailed findings under controlled conditions of insectarium.

Acknowledgment

This investigation was extracted from an approved master's degree dissertation (No. 95-01-04-12528) written by Ehsan Saki and financially supported by the research vice-chancellor of Shiraz University of Medical Sciences, Fars Blood Transfusion Organization, and Fars Governance ("Samat" code no. 15398135899).

Conflict of Interest: None declared.

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