

RABIES VACCINATIONS AND PARAMETERS AFFECTING EARLY VACCINATION IN ISTANBUL WHERE HUMAN RABIES CASES ARE RARE

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ABSTRACT

Introduction: Contact with domestic or wild mammals poses a risk of rabies. Accurate evaluation of wounds, early wound care, and vaccination and immunoglobulin therapy reduce the risk.

Materials and methods: In this study, the data obtained from Rabies Vaccination Center in Istanbul between 2008-2015 were analyzed. Those who applied to the center were divided into two groups as early and late applications. The gender, vaccine type, number of vaccines, wound characteristics, animal characteristics, distance from the vaccine center (residence) of these patients were examined.

Results: During the study period 3819 patients applied. 79.4% of them applied to our center within the first 24 hours after contact with animals. There were positive correlations between dog bite, male sex, stray animal contact, wound depth and early administration. It was found that those arriving from a distance of 20-30 km applied in the early period, and those arriving from a distance of 30+ km applied in the late period.

Conclusion: There was no difference between individuals with early and late admission in terms of completing the vaccination program and the site of injury. Animal species, sex, wound depth and the distance between the place of residence and the center are parameters that significantly affect the post-contact application time.

Keywords: Rabies, post-exposure prophylaxis, vaccination, pre-exposure prophylaxis, anti-rabies immunoglobulin.

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Introduction

Approximately 29 million people worldwide receive Post-exposure prophylaxis (PEP) for rabies every year⁽¹⁾. In Turkey, this number is around 250000⁽²⁾. Most of the previous rabies cases in Turkey are associated with dog bites, and unfortunately, rabies development has been reported despite appropriate prophylaxis^(3,4).

It is of note that although rabies is rarely seen in jackals (*Canis aureus*) around Istanbul, it has been shown that transmission to dogs occurs as a result of spread from this endemic reservoir⁽⁵⁾. There have been no cases of human rabies reported in the İstanbul region since 2007. In some countries, access to rabies vaccination is still difficult⁽⁶⁾. However, pre-

exposure and post-exposure prophylaxis vaccines are free in Turkey and there is no problem in access. Therefore, human rabies is very low and risky contact with rabies is one of the most frequently reported infectious diseases⁽⁷⁾.

The best method of preventing rabies is pre-exposure vaccination with the 3-dose vaccine before contact⁽⁸⁾. PEP includes washing the bitten area with soap, rabies vaccine and administration of rabies immunoglobulin (RIG) when necessary⁽⁹⁾.

The administration of RIG is performed to neutralize the virus before entering axons until the effectiveness of the vaccine begins⁽¹⁰⁾.

All patients requiring PEP are evaluated in accordance with the Ministry of Health's rabies field guide in Turkey⁽¹¹⁾.

In this study, we evaluated the data derived from 2008 to 2015 from a Center for Rabies Vaccination in Istanbul.

Materials and methods

All patients who came to the Center for Rabies Vaccination of the hospital with an animal bite were clinically evaluated by the emergency care practitioner and the specialist by consulting.

The registration, wound washing, care, vaccinations and the RIG applications were performed in this center. The patients were given vaccination schedule cards and they were followed for ten days by signing the card after each shot. If the animal is alive, the vaccination process is terminated after the 3rd dose. The data matrix of the vaccines is recorded in the Ministry of Health Vaccine Tracking System with the dates and personal information of the patients. A horse-derived Ig is administered to the site of injury (wound) at a dose of 40 IU / kg RIG (purified Vero cell rabies vaccine (Abhayrab 2.5 IU / 0.5 ml)). The design of the study was planned as a retrospective cohort.

The forms of all patients who applied to our center between 2008-2015 were retrospectively analyzed. Patients' characteristics, such as age, gender, wound, animal type and vaccine were combined in a spreadsheet file and classified. The patients who applied within the first 24 hours were accepted as "early application", and those who applied after 24 hours were accepted as "late application". The wound depth was classified as superficial, deep or very deep. The wound site was categorized as head-face, hand, arm, leg, multiple or trunk. Early and late applicants were analyzed by using the Chi-square method to assess the distribution of gender, vaccination completion, wound characteristics, biting animal features and types of vaccination.

The distance from the patients' residence to our vaccination center was calculated. The effect of the distance on the duration of the application and the completion of vaccination was examined.

Results

PEP was applied to 3728 of the 3819 patients (97.6%). Among these patients, the male/female ratio was 2.47 and the mean age was 26.58 ± 18.32 . 64% of the patients who applied were over 15 years old. Five doses of rabies vaccine (Essen regimen) were applied to 39.5% of the patients (n = 1508)

and four doses were applied to 9.1% (n = 349) of them. We also found that three doses were applied to 31.2% (n = 1191) of patients, while the 2-1-1 Zagreb regimen was applied to 2.7% (n=104). It was also noted that two doses were applied to 15.1% (n = 576), whereas 2.4% (n = 91) of the patients did not require vaccination. The 5-dose vaccine was the most used (p=0.002). The application time (after contact) was recorded in 3758 (98.4%) of the patients and 79.4% (n= 2994) of them applied within the first 24 hours. The patients bitten by dogs (pet and stray) were found to have applied significantly earlier (p <0.001) (Table 1). Horse-derived immunoglobulin (ERIG) was administered to 4.49% (n= 166) of the patients. There were no allergic reactions recorded.

Animal		Early	Late	Total	Chi-square	p
Pet dog	n	644	148	792	33.739	<0.001*
	%	81.3	18.7	100		
Stray dog	n	1125	238	1363		
	%	82.5	17.5	100		
Pet cat	n	100	52	152		
	%	65.8	34.2	100		
Stray cat	n	991	301	1292		
	%	76.7	23.3	100		
Other animals	n	70	15	85		
	%	82.4	17.6	100		
No data-prophylaxis	n	64	10	74		
	%	86.5	13.5	100		
Total	n	2994	764	3758		
	%	79.7	20.3	100		

Table 1: Animal characteristics in patients whose application time was recorded.

According to wound depth, 3159 (82.7%) patients had superficial wounds, and 660 (17.3%) had deep or very deep wounds. According to application time to the hospital, 73% of those with superficial wounds applied early while 84.2% of those with deep/very deep wounds applied early (p = 0.009). The average number of days for late applications was 5.6 days. 45% of the patients who were vaccinated with the 2-1-1 Zagreb regimen arrived later than 24 hours after contact.

Among the 3684 patients, 58.4% had contact with dogs and 39.2% had with cats. Only 26.5% (n= 977) of the animals were pets. Among stray animals, 1363 of 2740 (49.7%) were dogs while in pet animals 792 of 944 were dogs (83.9%). There were no reports of a wild animal bite. The ratio of certification of pets for rabies vaccine was 35.1% in dogs and 12.6% in cats. The complete data for animal bite sites were recorded in only 1645 (43%) patients (Figure 1). Males were bitten more frequently than females (p <0.001). In addition, males were bitten

mostly by dogs ($p < 0.001$) and, more by stray animals ($p < 0.016$) and, they applied earlier to the hospital ($p < 0.028$). Females were injured mostly in the hand and while males were in the leg ($p < 0.001$). There was no difference between genders in terms of data reporting on a bite ($p = 0.256$), wound depth ($p = 0.513$), need for wound care ($p = 0.313$), rabies number of vaccines ($p = 0.065$).

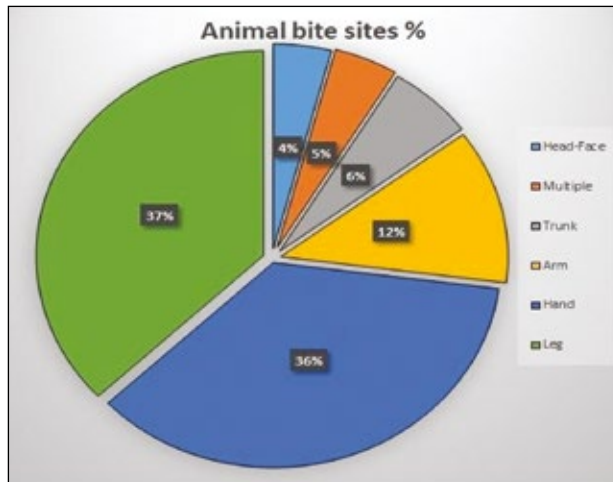


Figure 1: Animal bite sites.

		5/2-1-1/4 Doses	3 Doses	Missing Dose	Total	Chi-square	p
Early	n	1503	946	438	2887	3.247	0.197
	%	52.1	32.8	15.2	100		
Late	n	421	243	99	763		
	%	55.2	31.8	13	100		
Total	n	1924	1189	537	3650		
	%	52.7	32.6	14.7	100		

Table 2: The vaccination posology of patients whose application times were recorded.

People who were bitten by pet cats applied later than those who were bitten by other animals. There was no significant difference between patients who applied early and late in terms of age ($p = 0.422$). On average, the time of admission to our center for patients under 18 years of age was significantly earlier than patients over 18 years of age (1.32 ± 0.93 days versus 1.10 ± 0.30 days, $p = 0.035$). Patients aged between 0-15 and those aged 56 years and older were bitten on the hands more often, while patients aged between 16-25 and 36-45 years were bitten on the legs more frequently ($p < 0.001$). The superficial injuries were more common in all age groups ($p < 0.001$). There was no relationship between vaccination posology and application times ($p = 0.197$) (Table 2).

When the application times were evaluated in the 1010 patients (27%) with residency data, it was found that those arriving from a distance of 20-30 km applied earlier, and those coming from a distance of 30+ km applied later ($p = 0.033$) (Table 3).

According to the records, the most frequently recorded data were gender, age and wound care. Wound depth and wound site were found to be incomplete in 21.1% and 43.1%, respectively.

Distance		Early	Late	Total	Chi-square	p
0-10 km.	n	448	216	664	8.725	0.033*
	%	67.50	32.50	100.00		
10-20 km.	n	127	76	203		
	%	62.60	37.40	100.00		
20-30 km.	n	66	18	84		
	%	78.60	21.40	100.00		
30+ km.	n	35	24	59		
	%	59.30	40.70	100.00		
Total	n	676	334	1010		
	%	66.90	33.10	100.00		

Table 3: Application time and distance distribution of the patients whose addresses are recorded.

Discussion

The application of PEP was utilized at a frequency of around 97% at our center. This rate is similar to those reported by previous studies from our country^(12,13). In some studies conducted, lower PEP rates were also reported^(14,15).

Before 2018, the Rabies Guideline in Turkey recommended 5 doses of vaccination. For this reason, this was the most applied vaccine in our center, similar to other centers at that time⁽¹⁶⁻¹⁸⁾.

The high rate of PEP application can be related to the existence of rural settlements close to the city center in our region and the sensitivity of people to the subject in social and medical terms. It was found that 80% of the patients applied within the first 24 hours of contact and 93% of them applied within the first 48 hours. In the studies conducted in Turkey, the first-day application rate was reported as 72% and above⁽¹⁷⁻¹⁹⁾. Vaccination for rabies is most effective when administered immediately after suspected exposure. Therefore, the patient should be informed about starting prophylaxis immediately and completing the vaccines. It is recommended to apply Rabies IG together with the vaccine as soon as possible for exposures that are deemed to be high-risk^(20,21).

The obligation to continue the vaccination process for 4 or 5 different days may reduce compliance. However, most of our patients had completed the vaccination program, similar to the reports from other regions in Turkey^(14,18). There was

no difference in the completion of the vaccination program between early or late applicants. According to the Ministry of Health guidelines, if animals can be observed and are alive after 10 days of surveillance, the vaccination process is terminated after the 3rd dose.

In a study conducted by Tran et al., it was found that females, those under the age of 15, those with leg bites, category 1 injuries, bat bite, and those living in provinces with high rabies risk had higher rates of completing the vaccination program⁽²²⁾.

In the study of Şevken et al., it was found that those who applied in the spring and summer months, females and those who started prophylaxis late were more likely to comply with the PEP⁽¹⁹⁾. In our study, it was found that gender and the date of application did not affect the completion of immunization. Although the efficacy of the 2-1-1 Zagreb regimen is similar to the classical 5-dose Essen regimen, the use of this vaccination option is lower⁽²³⁾.

The awareness of applying to the vaccination center in the early period after a suspicious contact is high in Turkey. However, the number of stray animals is rather high in Turkey. In such cases, since the animal is difficult to observe, 5-dose vaccination is usually performed. In cases with observable animals, the 3-dose vaccination is still utilized.

In the present study, 2.38% of the patients (n = 91) were not vaccinated. The recorded reasons were: the dog was vaccinated, the bite occurred with animals such as mice and snakes, the person was vaccinated within the last year, and non-penetrating exposure (saliva from clothes etc.). The rate of non-vaccination was between 9-13% in other studies conducted in Turkey^(12,14). The reason for this low rate could be not registering patients who did not need vaccination.

In a study conducted in the United States, only 6.7% of all bite cases were vaccinated. The vaccination rates were around 80% in wild animal bites (such as raccoons and bats)⁽²⁴⁾. The cost of vaccination in low-to-moderate risk patients may also affect patient decisions. The mean age of the patients was 26.6, similar to the literature^(14-18,25). As expected, most of the patients were in the 0-15 age group.

Dogs are the most common cause of animal contact that requires an application to a health center in the world and Turkey. Men are more likely to be injured through such contact^(4,14-17,19,24-27). In our study, men were injured more frequently and mostly with stray dogs. The frequency of injury after dog

contact is above 60% in Turkey^(12-15,25). It was also found that the applications after dog bites were made significantly earlier. This may be because society considers dog bites more dangerous compared to other stray animals and pets.

In our study, the majority of injuries were superficial and the need for RIG application was less than 5%. However, in deep and very deep bites, this rate exceeded 45%. RIG applications were mostly done on the same day and directly from the wound site. RIG application rates in our country vary between 8-59%. However, this rate may vary depending on the total number of applications, injury type and whether the RIG is a horse or human origin^(14,17,18).

Immunoglobulin administration was found to be statistically higher in patients who received five doses of vaccine than those who received 3 doses of vaccine (p = 0.002). The wound depth was greater (p = 0.019) and the contact with stray animals (p <0.0001) was more frequent in patients who received 5 doses of vaccine. These three results may be associated with the patients' perception in deeper and more serious wounds, the high incidence of stray animal bites, and also the attending physician's approach to PEP application.

Overall, 26% of the animals (n = 977) were pets. This low rate compared to similar studies may be due to the high number of stray animals in our city^(14,19,29). In our study, it was found that the documented vaccination rate in pet dogs was around 35%, while this rate was even less in cats. In the study of Kılıç et al., only 17% of the animal owners could present a rabies vaccine certificate⁽¹⁵⁾. However, it must be noted that stray dogs are regularly vaccinated by the local authorities.

The information about wound depth was found to be neglected rather frequently in the records of our hospital. Most of the recorded wounds were superficial. The frequency of deep wounds was between 8-41% in some studies, depending on the evaluation criteria⁽¹²⁾. If the injury is in rural areas, the frequency of deep wounds may increase up to 63% (17). In our study, the deep and very deep bites were identified in 17.26% of the patients, and their application time was significantly earlier. It can be thought that deeper wounds are considered to be more important, not only for rabies immunization but also with regard to the need for wound care and medication.

The current study showed that data about the site of injury was recorded in nearly half of the patients.

Similar to many previous studies, limb injuries were at a higher frequency in our study^(14-16,26,28). Males were injured in the leg and females were injured in the hand most commonly. There was no relationship between the injury site and early application.

In our study, there was no difference between genders in terms of data reporting, wound depth, vaccination rates, and completion of the vaccine program. These indicate that the health system provided equal access to rabies vaccination services in the majority of the population.

It was found that patients coming from an average distance of 20-30 km had applied earlier compared to patients coming from a distance of 30 km or more (who mostly applied in the late period) ($p = 0.033$). Most bites had occurred in rural areas (56%)⁽¹⁵⁾. The late applications may be related to the disadvantage of being far from the health services, being in a rural area, and ignoring the injury during the initial period.

The limitations of our study were that there was some missing information, most importantly, wound depth. For this reason, proportioning and calculations were based on the recorded data in all evaluations. Lastly, due to the limited number of address records, the residency data of patients may have been skewed.

In conclusion, considering the number of vaccinations, risky contact with stray animals continues to be an important public health problem in our country. According to the results of our study, it was seen that males were bitten more frequently by stray dogs, and children under the age of 18 were brought to the center significantly earlier. In addition, the full dose vaccine was preferred more frequently in animal bites with a greater wound depth requiring RIG than 3 doses of treatment. Those living 20-30 km from the center, those who were bitten by a stray dog and deeply injured applied earlier.

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List of Abbreviations:

PEP: Post-exposure prophylaxis

RIG: Rabies immunoglobulin

ERIG: Equine rabies immunoglobulin

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics 20 Committee of Bakırköy Sadi Konuk Training and Research Hospital (2018/437).

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