Rabies Post-Exposure Prophylaxis Compliance of Bite Patients: The San Lazaro Hospital Animal B.I.T.E. (Bite Injury Treatment Experience) Study

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Background: Post-exposure prophylaxis (PEP) is the most important means of preventing rabies. Intradermal PEP was developed to improve compliance, still, many recipients fail to complete this regimen.
Objective: To determine the non-monetary factors contributing to non-compliance to PEP among patients in the Animal Bite Treatment Center (ABTC) of San Lazaro Hospital (SLH).
Methods: This was an analytical, cross-sectional study. The authors randomly reviewed patient records of SLH-ABTC for one-year period. We characterized the cases according to World Health Organization (WHO) parameters. They determined the day intervals between exposure, first consultation, PEP initiation and follow-up visits. Statistical analyses used were descriptive statistics, χ^2 test for independence and binary logistic regression.
Results: The authors evaluated 667 records. Patients mostly had Category III exposures (76.91%, 95%CI: 73.92%-80.62%). The chances of completing active immunization were more likely among patients exposed to unvaccinated animals (OR=1.85, 95%CI: 1.21-2.84, p=0.004). The chances of receiving passive immunization were higher for injuries on the head/neck regions (OR=8.18, 95%CI: 2.4-27.9, p=0.001). Overall, compliance to PEP was 70.21% and 40.70% for Categories II and III exposures, respectively. PEP compliance was moderately dependent on the exposure category (χ^2=38.14, df=1, p<0.001, φ=0.25).
Conclusion: Category II exposure patients had better compliance than Category III, since rabies immunoglobulins are not required. The authors did not identify any factors that significantly affected Category II regimen compliance. Among Category III patients, compliance was better if the injuries were bite-inflicted while those who were exposed from "healthy"-looking animals were less likely to comply.

Keywords: rabies, animal bite, post-exposure prophylaxis

Introduction

Rabies is a zoonotic viral infection that causes fatal encephalitis. It is transmitted through bites of an infected animal. Dogs have been implicated as important reservoirs in countries such as the Philippines.[1,2] Rabies predominantly affect children and young adults claiming approximately 55,000 lives in Asia and Africa alone.[1,3,4] This disease is highly fatal, but preventable by proper wound management with prompt and wise use of active and passive immunizations.[3,5]

Vaccination stimulates the immune system to mount its own defense against the virus. Rabies post-exposure prophylaxis (PEP) is given in a series of injections in order to induce immune response at the shortest possible time.[5] Prompt vaccine initiation and timely rabies immunoglobulin (RIG) administration are important to ensure infection prevention; however, many

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patients fail to practice these in actual settings.[3] The intradermal (ID) administration was devised to lower the cost of PEP without compromising patient safety.[6,7] Despite this, out-of-pocket spending is not totally eliminated because the full regimen is not provided for free. Since PEP cost is known to influence compliance, authors did not look directly on this aspect. They aimed to know the non-monetary factors that contribute to the patients' behavior to their PEP regimen. They believe that this is important to explore as it can contribute in the strategies to effectively deliver PEP and minimize vaccine wastage.

The study was conducted in the Out-patient Department (OPD) of San Lazaro Hospital (SLH), the oldest hospital in the Philippines with the distinction as the national referral center for infectious and communicable diseases. SLH's Animal Bite Treatment Center (ABTC) caters to approximately 90,000 animal bite cases annually, making it the largest ABTC in the country to date.

Methods

This was an analytical, cross-sectional study to determine patient compliance to rabies PEP and the non-monetary factors that contribute to their compliance behavior. The methodology process is summarized in Figure 1.

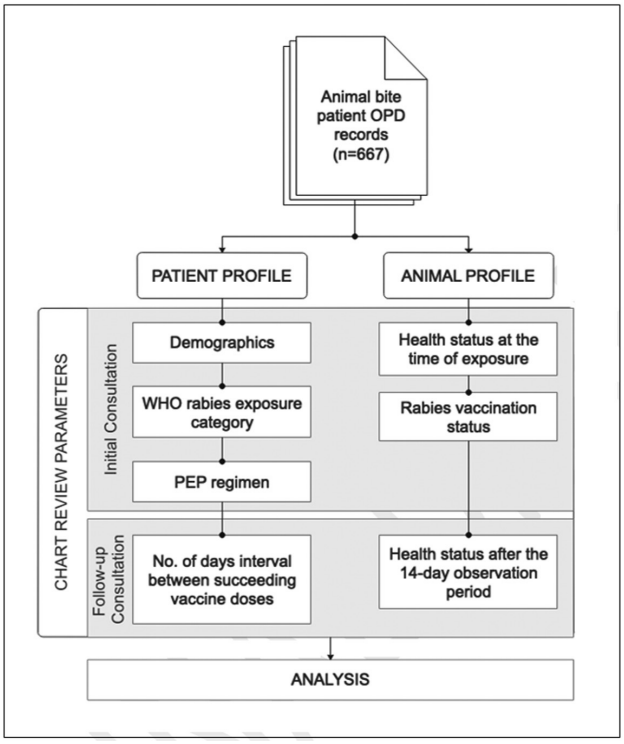

Figure 1. . Methodology flowchart.

Out of 106,674 SLH-OPD consultations from June 1, 2012 to May 31, 2013, 86,387 cases were bite/scratch exposures from dogs or cats, which served as the sampling frame. The authors used Epi Info™ 7 to compute for the sample size: with the population size of 106,674, the expected frequency of the factor under study was 80.98%, the acceptable margin of error set at 5% and the confidence level at 99.9%, the computed sample size was 667. The authors shuffled the cases listing from the sampling frame using the RAND function in Microsoft® Excel™ 2010.

The first 667 randomly generated cases that fulfilled the inclusion criteria were retrieved for analysis: completely filled records of patients with exposure from dogs/cats who were given ID regimen. Excluded were cases whose: exposures were from wild animals, wounds were rodent-inflicted, initial PEP were received from other institutions, and exposure were considered as Category I.

The authors defined "vaccine completion" as patients who: received the Day 28 (D28) vaccine dose without delay; received at least the D7 dose and the animal remained alive during the observation period; or had PEP in the past and received the D0 and D3 doses (short PEP). "PEP compliance" was defined as the probability of a patient to return for subsequent vaccine and RIG shots.

The patient demographic profile includes age, gender, weight, date and location of the exposure, and rabies immunization in the past five years. The profile of the biting animal includes mode of ownership, circumstances during injury infliction (i.e. whether the animal was provoked or not), and rabies immunization in the past 12 months. For animals that died within the 14-day observation period, the type of the death was recorded as "Died" if it was due to natural causes or "Killed" if the animal was sacrificed.

Described here are the types of exposure as: licks to broken skin, licks to mucous membranes, superficial abrasions or transdermal bites. Anatomical sites were identified and the wounds were characterized as single or multiple. Finally, the exposure was categorized based on the revised WHO Categories of Rabies Exposure 2010.[8]

The authors also determined the interval between the day of exposure and the first day of consult as well as the first vaccine (D0) dose. For Category III exposures, they determined the interval between the day of exposure and RIG administration, and the interval between D0 dose and RIG administration. They also determined the interval between the scheduled day of follow-up and the actual day of vaccine administration. "Vaccination delay" was defined as failure to come for follow-up visit, warranting modifications in visit schedules.[9] Although according to guidelines, the D28 dose may not be given in situations where the animal remained healthy beyond the observation period,[8] they still documented the delay for this dose.

They used Epi Info™ 7 for the descriptive statistics, used IBM® SPSS™ version 20 for binary logistic regression analysis and χ^2 test for independence.

This study was approved by the SLH Research and Ethics Review Committee prior to research implementation. The Medical Center Chief granted the authors access to patient records. Anonymity of data and confidentiality were observed during the conduct of the case review.

Results

Demographics

The mean patient age was 24.43 years (SD 19.08). Collectively, 51.43% belong to age bracket 1 to 20 years. Male to female ratio was 1.04:1. About a third of the patients were Manila residents (31.63%, 95%CI: 28.15%-35.34%). Approximately 93.25% (95%CI: 90.01%-94.98%) of the patients had no history of rabies vaccination. The non-monetary factors identified to influence compliance to both active and passive immunizations are listed in Table 1.

Animal Profile

Dogs (79.16%, 95%CI: 75.84%-82.14%) were predominant source of exposure. The animals were patient's own pet in 55.77% of cases (95%CI: 51.91%-59.57%), 34.03% (95%CI: 30.47%-37.79%) were owned by neighbors, and 10.19% (95%CI: 8.05%-12.81%) were stray. Only 15.29% (95%CI: 12.69%-18.3%) of the animals were known to have been vaccinated within the past 12 months. The rest were either unvaccinated (41.68%, 95%CI: 37.92%-45.53%) or unknown vaccination status (43.03%, 95%CI: 39.25%-46.89%), although most of these animals (92.5%, 95%CI: 90.17%-94.33%) were "healthy"-looking at the time of exposure. The health status of the animals after the 14-day observation period is summarized in Table 2.

Exposure Characterization

Six hundred forty of the exposures (95.95%) were bite-inflicted (95%CI: 94.09%-97.26%), mostly transdermal injuries. There were 513 cases (76.91%, 95%CI: 73.92%-80.62%) under Category III and the remaining 154 cases (23.09%, 95%CI: 19.98%-26.51%) were Category II.

Days Intervals and Delays

There were 625 individuals (93.7%, 95%CI: 91.51%-95.37%) who required the conventional PEP and 42 individuals (6.3%,

Table 1. Identified non-monetary factors that could affect the compliance to rabies post-exposure prophylaxis.

Variables for Vaccination Compliance	
Age	
Gender	Male Female
Body weight*	
Residence	Manilan Non-Manilan
Patient Vaccination Status Against Rabies in the Past 3 Years	<3 doses None Unknown
Type of Exposure	Lick Bite Scratch
Site of Exposure	Head/Neck* Trunk Arm/Forearm Hand Perineum/Genital/Gluteal Thigh Leg Foot
Number of Exposure	Single Multiple
Nature of Exposure	Licks to Mucous Membrane* Superficial Abrasion/Contusion† Transdermal Bites*
Type of Animal	Dog Cat
Mode of Ownership	Pet Neighbor Stray
Circumstances	Provoked Unprovoked
Animal Status at the Time of Exposure	Healthy Sick Unknown
Animal Vaccination Status in the Past 12 Months	Vaccinated Unvaccinated Unknown
Type of RIG	ERIG* HRIG*

* Factors that could affect compliance to Category III exposure regimen and RIG adherence only

† Factors that could affect Category II exposure regimen only

95%CI: 4.63%-8.49%) with past rabies vaccination requiring only the short PEP regimen. The number of patients given PEP from D0 to D28 according to exposure category are summarized in Table 3.

The mean number of days interval from the day exposure to the day of consult, giving of the D0 vaccine dose and RIG administration are presented in Table 4. It also shows the average number of days interval between the D0 vaccine dose and the day the RIG was given.

Delays in rabies PEP from the prescribed vaccination schedule are summarized in Table 5. The mean number of days delay was 0.26 day (SD 0.63) for D3 dose, 0.34 day (SD 0.86) for D7 dose and 1.7 days (SD 1.90) for D28 dose.

Vaccine Course Completion

Of the 625 patients requiring conventional PEP, 408 (65.28%, 95%CI: 61.38%-68.99%) were able to complete their schedule of at least the D7 dose. The remaining 217 cases (34.72%, 95%CI: 31.01%-38.62%) either did not complete the primary immunizing doses or did not receive PEP at all. Vaccine completion were more likely if patients were Manilans compared to non-Manilans (OR=0.68, 95%CI: 0.47-0.99, p=0.044) and among patients bitten by an unvaccinated animal compared to a vaccinated animal (OR=1.85, 95%CI: 1.21-2.84, p=0.004).

Adherence to RIG

Of the 513 patients who sustained Category III exposure, only 29 (5.65%, 95%CI: 3.88%-8.11%) have previous

Table 2. Health status of the injury-inflicting animal after the 14-days observation period.

Animal Clinical Status	Frequency	Percent	95% CI†
Healthy	263	39.43%	35.72% - 43.27%
Died	11	1.65%	0.87% - 3.02%
Killed	3	0.45%	0.12% - 1.42%
Sick	1	0.15%	0.01% - 0.97%
Unknown*	389	58.32%	54.47% - 62.08%
Total	667	100.00%	-

* For patients who did not complete their Day 28 (D28) vaccine dose, the true health status of the animal was not verifiable, and therefore placed under the "Unknown" category.
† 95% Confidence Interval

Table 3. Number of patients administered with rabies post-exposure prophylaxis (PEP) during the prescribed vaccination schedule.

Dose Schedule	Category II				Category III			
	Conventional 2-Site ID*		Short PEP		Conventional 2-Site ID*		Short PEP	
	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated	Vaccinated	Not Vaccinated
D0†	139	2	12	1	474	10	27	2
D3	117	24	11	2	359	125	27	2
D7	97	44	n/a**	n/a	304	180	n/a	n/a
D28	57	84	n/a	n/a	206	278	n/a	n/a

*Intradermal, **Not applicable, †Day 0

Table 4. Mean intervals (in days) between consultation, post-exposure prophylaxis (PEP) initiation and rabies immunoglobulin (RIG) administration.

Period	Mean (Days)	SD†
From exposure to consult	2.06	2.77
From exposure to initiation of PEP (D0)*	2.07	2.78
From exposure to RIG administration	3.57	3.87
From initiation of PEP (D0) to RIG administration	1.76	2.68

*Day 0, †Standard deviation

rabies immunization. Of the 484 cases that required passive immunization, only 208 (42.98%, 95%CI: 38.54%-47.53%) received RIG. Passive immunization was more likely received by patients with head/neck injuries compared to those with injuries to other parts of the body (OR=8.18, 95%CI: 2.4-27.9, p=0.001). RIG was favored for provoked bites compared to unprovoked (OR=1.61, 95%CI: 1.01-2.57, p=0.044). It was less likely administered if bitten by a "healthy"-looking versus a sick-looking animal (OR=0.23, 95%CI: 0.098-0.55, p=0.001).

Compliance to PEP

PEP compliance was moderately dependent on exposure category (φ=0.247, χ^2=38.14, df=1, p<0.001). The compliance for Category II exposures was 70.21% (95% CI: 61.94%-77.62%). Those with Category III injuries, 40.70% (95%CI: 36.31%-45.24%) received both active and passive immunizations. Among patients with past immunization, 38 (90.48%) out of 42 were able to comply with their short PEP regimen.

With Category II exposure, none of the factors in Table 1 had a significant association with PEP compliance. Among patients with Category III exposures, compliance seemed to be less likely for Manilan residents in contrast to non-Manilans (OR=0.60, 95%CI: 0.38-0.95, p=0.028), bite-inflicted injuries were more likely than other injuries (OR=3.48, 95%CI: 1.05-11.61, p=0.042). Compliance of patients bitten by a "healthy"-looking animal were less likely as compared to bitten by a "sick"-looking animal (OR=0.37, 95%CI: 0.16-0.86, p=0.021). Patients exposed to unvaccinated animals were more likely to be compliant than exposed to vaccinated animals (OR=1.87, 95%CI: 1.13-3.10, p=0.015).

Discussion

Children, particularly the age group 1 to 10 years old were the ones at higher risk of exposure. Majority of the bite victims had no history of vaccination. This was expected as rabies vaccination is not included in local immunization programs. Dogs remained the primary source of exposure and in more than half of cases, the patients' own pets were the culprit.[1,10] The rate of animal immunization was low indicating possible needs to further strengthen the programs on rabies control in domestic animals.

This BITE study was done to identify non-monetary contributors to PEP adherence. Similar to the findings in China[10] and India,[2] the results showed that patients had an average of 2-day lapse between exposure and seeking medical care. For follow-up vaccine doses, almost a quarter of patients were not able to come back for D3 dose and this further increased to 35.84% for D7 dose. The distance to the PEP provider and animal vaccination status were the only factors that significantly affected vaccine course completion. Since SLH is situated in Manila, the authors classified patients as Manilans or non-Manilans to simplify the proximity of vaccination center from their place of residence. Present data show that Manila residents were less likely to complete vaccination compared to non-Manilans. This was contrary to what they expected that adherence would be better if the residence was nearer to the PEP facility.[11] On the other hand, patients bitten by an unvaccinated animal were more likely to complete their vaccination. They presumed this is because of their awareness that the risk of contracting rabies is higher from an unvaccinated animal.

RIG is an essential part of PEP, particularly for Category III exposures. It was, however, not received by more than half of patients requiring passive immunization. For those who were given RIG, the lag was about four days from the day of exposure. Ideally, RIG should be given together with the D0 dose. However, in the actual setting, RIG was administered about two days after vaccine initiation. Patients who sustained injuries on the head/neck were more likely to have passive immunization. This indicates their awareness that the proximity of the injury to the central nervous system pose faster disease progression. Individuals bitten by "healthy"-looking animals were less likely to receive RIG, presumably because they are complacent that acquiring rabies is unlikely from asymptomatic animals. Patients bitten by provoked animals were more likely to have RIG administered compared to those exposed from an unprovoked animal. Surprisingly however, present data show that there was no significant correlation on bodyweight and RIG administration.

In the context of injury classification, compliance was better among Category II exposures, in contrast with Category III. They attributed this mostly on the failure of the latter to receive RIG administration. What was surprising was that patients residing outside Manila were more likely to comply than those living in Manila.

Inability to afford treatment has been associated with inadequate PEP delivery.[3,11] Since the implementation of the intradermal route, vaccine costs have been significantly reduced by 60% to 80%.[6,8] Despite this, vaccine costs have remained a substantial factor to inadequate compliance to PEP.[11] One particular disadvantage of intradermal PEP is vaccine wastage. About 20% to 25% vaccine wastage has been attributed to the ID regimen due to the limited shelf-life of the vaccine after reconstitution.[7,12] Overall, 35% of the patients failed to complete at least the first three vaccine doses.

Incomplete dosing contributes further to wastage since the administered vaccine does not guarantee to produce a protective antibody titer.[13,14]

Patients with Category III exposure tend to be more compliant if their wounds were bite-inflicted, likely because they perceive greater danger when there is a saliva-to-wound contact. Patients exposed to "healthy"-looking animals were less compliant, while those exposed to unvaccinated animals were more likely to comply to PEP. Compliance was high among individuals who had a history of rabies vaccination. This was expected since short PEP is a 2-dose regimen only. Short PEP cuts the vaccine costs to as low as one-eighth of its original price, and fewer clinic visits mean better compliance.

Conclusion

Patients with Category II exposure had better PEP compliance since this regimen does not require RIG administration. The authors did not identify any factors that could significantly affect the compliance rate with Category II exposure. Those who had Category III exposures would most likely comply to PEP if they sustain bite-inflicted injuries. Injuries acquired from a healthy-looking animals make patients reluctant of getting PEP.

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Declaration of Conflict of Interest

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