Comparison of Compliance of Animal Bite Patients to Two Different Routes of Post-Exposure Prophylaxis against Rabies.

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Abstract :

Introduction : Rabies is a 100% fatal zoonotic disease affecting humans. Intramuscular Anti Rabies Vaccination (ARV) has been the mainstay of management of post-animal bites for rabies. This prospective study was conducted to know the compliance of patients treated at ARV Clinics of the District hospital (IM route) and tertiary care hospital of Vadodara (ID route) and the reasons for delay or missing the Scheduled dosage of the same. **Method :** Among the 500 enrolled patients (250 patients from each institution), those who missed the scheduled dosage of ARV and never returned to the ARV Clinic were followed and their reasons for delay or missing the scheduled dosage were recorded. **Results :** Compliance was 62.8% and 70% in patients managed by intramuscular and intradermal route of ARV respectively, but the difference was not statistically significant (p value 0.0883). Personal or official workload followed by patient's forgetfullness about the scheduled date of vaccination were some of the main reasons for not coming regularly to receive next scheduled dosage of ARV. **Conclusion :** The compliance among patients managed by intradermal as well as with intramuscular route of ARV was similar. Use of intradermal method of ARV can be recommended to reduce ARV clinic visits and cost related to transportation.

Keywords : Animal bite, Rabies, ARV, Compliance, PEP.

Introduction :

Rabies is an acute viral disease causing fatal encephalomyelitis in virtually all the warm blooded animals. However, it can be prevented by local wound management, administration of ARV and use of immunoglobulins after exposure to rabid animals. Modern Cell Culture Vaccines (CCV) are now being used for post-exposure prophylaxis. Higher cost of intra-muscular administration of CCV is a limiting factor for its wider use. To overcome this problem, WHO has recommended use of efficacious, safe and feasible intra-dermal (ID) route of inoculation of CCVs. [1]

In many institutes, patients of animal bite are managed by intramuscular (IM) and/or intradermal (ID) route of Antirabies vaccination, the compliance of which needs to be compared. We carried out study at two sites namely Jamnabai Hospital (District Hospital) and SSG hospital (Tertiary care Hospital), Vadodara employing two different routes of ARV, intramuscular and intradermal routes respectively. Both these hospitals are government hospitals employing staff as per same Government norms and by policy it has been decided to administer a particular route of ARV to an animal bite victim at these institutions. The patients catered by these hospitals resemble each other in terms of socioeconomic profile. ARV charges were also similar for each dose in these hospitals.

Method :

This was a prospective study at SSG Hospital and Jamnabai Hospital over a period of 8 months April 2011 to November 2011. Upon relevant retrospective data collection from the data register of the clinic over a period of 5 months, compliance was found to be 69%. Taking desired precision as 5%, alpha risk as 5 and 95% confidence interval, the sample size was estimated at 248. Therefore 250 patients were enrolled in each intradermal and intramuscular group in the current study. The patients were followed up to their last dosage of ARV schedule.

Informed verbal consent was taken from the participants prior to their enrolment into the study.

Pretested semi-structured questionnaire was used for the interview. This study instrument included socio-demographic details and the history of animal bite on the first visit. On subsequent visits, the patients were asked about adverse events experienced after ARV and reasons for delay in scheduled dosage of ARV or missing of the dose, if any. Those who missed the scheduled dosage of ARV and never returned to the ARV clinic were contacted through the telephone and their responses for delay or missing the scheduled dose were recorded.

The patients were given 5 doses of 0.5ml ARV in I.M. group, while 4 doses of 0.1ml ARV over two sites in I.D. group.

The privacy of the patients was ensured during the entire process of data collection and confidentiality of the records was maintained.

Statistics :

Data was entered into Epi Info version 3.5.3 [2] and analysis was carried out using Bivariate & Multiple Logistic Regression.

Dependent variable : Compliance of the patients.

The principal outcome variable was patients' ability to complete ARV schedule. The patients were categorized as either completely vaccinated or incompletely vaccinated. Those who had taken all scheduled doses of ARV as prescribed by the physician according to the category of bite were labeled as completely vaccinated. This also included the patients who had received the vaccine later than the prescribed date of vaccination, but had taken all the doses of ARV. Others were labeled as incompletely vaccinated.

Independent variables : Demographic characteristics, category of animal bite, adverse reactions after vaccination and delay in scheduled dosage of ARV.

Statistical tests applied :

For bivariate analysis-Odds Ratio, Chi square test, Chi square for linear trends

For multivariate analysis-Multiple Logistic Regression

Results :

Majority of the 500 patients attending ARV Clinics of SSGH and Jamnabai Hospital (cumulative) belonged to age group 20-49 years (42.6%). Animal bite was more common among males (71.60%) in both hospitals but difference among them was not statistically significant (Chi-square test-0.1574, P value-0.6916).Around one fourth of patients had completed secondary education (8-10) and high primary education (6-8).

Almost 70% of the patients were APL Card holders and they received the antirabies vaccine by paying 100 Rupees for each dose, while Below Poverty Line (BPL) Card holders were given the vaccine free of cost (Currently, ARV is provided free of cost regardless of having APL or BPL card). The distribution of patients according to their APL/BPL card status was statistically significant in I.M. and I.D. groups (Chi-square test-4.1841, P value-0.0408). Only 30% of the patients were residing within 3 to 4 kilometres distance from ARV Clinic.

Compliance :

The patients managed by intradermal route of ARV showed 70% compliance to the ARV schedule, while those who were administered the vaccine by intramuscular route showed 62.80% compliance (Chi-square test-2.9045, p value 0.0883). However default rate was more among I.M. group. There were 20 patients in I.D. and 17 patients in I.M. regimen group who did not come for further dosage of ARV after receiving 1st dose of ARV. Table I shows that majority of the patients didn't come to receive last dose of ARV (Day 28). (Table 1)

Table 1 : Distribution of patients who missed the scheduled dosage of ARV according to the number of missed doses

Defaulter of ARV	I.D.(n=250)	I.M.(n=250)
Defaulter after 1st dose	20	17
Defaulter after 2nd dose	13	19
Defaulter after 3rd dose	42	21
Defaulter after 4th dose	-	36
Total	75(30%)	93(37.2%)

(As per table 2) There were 20, 24, 61, 102 and 43 patients in 0-5 years, 6-9 years, 10-19 years, 20-50 years and more than 50 years age groups respectively

in I.D. group, out of which 12, 15, 43, 71 and 34 patients had completed the ARV schedule. Similarly in I.M. group, there were 26, 23, 57, 111 and 33 patients in 0-5 years, 6-9 years, 10-19 years, 20-50 years and more than 50 years age groups respectively, out of which 16, 16, 43, 66 and 16 patients had completed the ARV schedule. In I.D. group, maximum compliance was observed among the age groups of 10-19 years (70.49%) and 20-50 years (69.61%), while patients of less than 10 years were comparatively less compliant to ARV Schedule (less than 63%). The commitment and perception of parents or guardian as well as two simultaneous pricks at each visit may be the contributing factor for less compliance in case of children. In I.M. group, patients of 10-19 years were comparatively more compliant (75.43%) than patients of more than 50 years age group (48.50%).

Table 2 : Contributing Factors related to patients ability to complete vaccination schedule of ARV

Characteristics	**Completely Vaccinated**	**Chi-square value**	
	I D Group(N=250) n (%)	**I M Group(N=250) n (%)**	**(P Value)**
Age group			
0-5 years	12/20(60)	16/26(61.5)	
6-9 years	15/24(62.5)	16/23(69.6)	Chi-square(trend)-
10-19 years	43/61(70.5)	43/57(75.4)	4.265(0.0389)
20-50 years	71/102(69.6)	66/111(59.5)	DF-1
More than 50 years	34/43(79.1)	16/33(48.5)	
Sex			
Male	130/181(71.8)	115/177(65)	0.008(0.9286)
Female	45/69(65.2)	42/73(57.5)	
Education			
Illiterate	32/45(71.1)	8/29(27.6)	
Primary	30/46(65.2)	32/45(71.1)	
High primary	27/42(64.3)	42/56(75)	18.122(0.0012)
Secondary and above	49/65(75.4)	40/67(59.7)	
Graduate and above	16/18(88.9)	11/15(73.3)	
Economic status			
APL	126/185(68.1)	101/164(61.6)	1.91(0.1670)
BPL	49/65(75.4)	56/86(65.1)	
Residential distance from ARV Clinic in Kilometres			
Less than 5	56/76(73.7)	93/145(64.1)	
5 to 10	105/146(71.9)	52/87(59.8)	Chi-square(trend)-
11 to 20	7/14(50)	8/12(66.7)	15.559(<0.0001)
More than 20	7/14(50)	3/6(50)	DF-1
Type of Animal			
Street Dog	153/219(69.9)	144/226(63.7)	1.875(0.3916)
Pet Dog	17/20(85)	9/15(60)	
Others (cat, rat etc.)	5/11(45.5)	4/9(44.4)	
Category of Bite			
Category 1	16/19(84.2)	22/26(84.6)	4.654(0.0976)
Category 2	148/216(68.5)	118/197(59.9)	
Category 3	11/15(73.3)	17/27(63)	
Adverse event following ARV Vaccination (n=250)			
Yes	24/36(66.7)	23/42(54.8)	0.0075(0.9311)
No	151/214(70.6)	134/208(64.4)	

Out of 181 males in I.D. Group, 130 males completed ARV schedule (71.8%) and 177 males in I.M. Group, 115 males completed ARV schedule (65%). The compliance rate was less among females than males in both groups.

The compliance level showed an increase with the level of education in both groups, with highest compliance rate in patients who had completed their graduation (92.3% in I.D. group and 71.4% in I.M. Group)

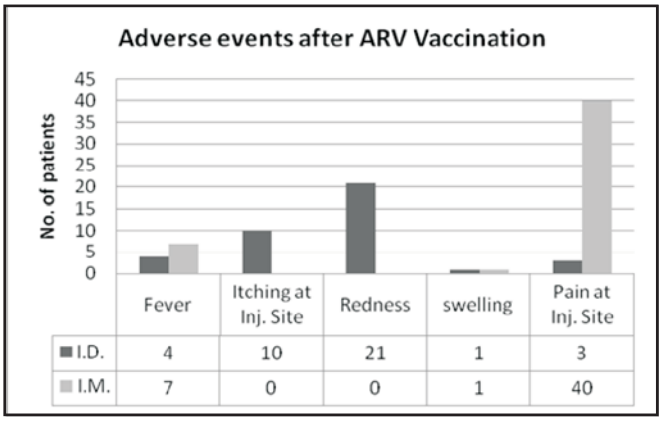
The BPL (Below Poverty Line) card holders were more compliant to the Vaccination Schedule than APL (Above Poverty Line) card holders in both groups.

Patients who reside within 10 kilometers from ARV Clinic showed better compliance (92% in both groups)to the ARV Schedule and the compliance decreased in patients who lived far away (more than 10 Km) from ARV Clinic.

Maximum compliance was seen in Category I patients (84.2% in ID and 84.6% in IM) while least compliance was seen in Category II patients (68.5% in I.D. and 59.9% in I.M. group) in both IM and ID patients. This difference was statistically significant in IM group (Chi-square test-6.007, p value-0.0496).

Figure 1 shows that adverse events were more common among the patients managed by intramuscular route of vaccination (54%). Pain at injection site was most common ADR in intramuscular route (95.24%), while redness was most common ADR (Adverse Drug Reaction) in intradermal route (58.33%) among the patients following Intradermal ARV. Itching and redness at

Figure 1 : Adverse events following ARV in I.D. and I.M. groups:



¥ Multiple responses are possible

On applying logistic regression, among different demographic characteristics of study population, we found age, educational status and residential distance in intradermal group while age and economic status in intramuscular group to be statistically significant factors for completely vaccinated patients as compared with incompletely vaccinated patients (Table 3).

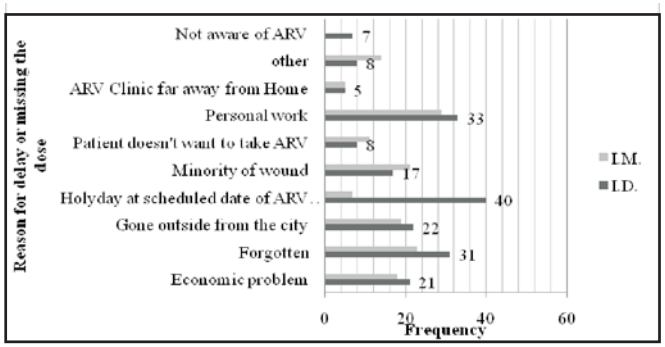
Table 3: Multivariate analysis of factors affecting compliance among patients managed by Intradermal and Intramuscular routes of ARV

Parameter	Intradermal Group			Intramuscular Group		
	Odds Ratio	Confidence Interval	P value*	Odds Ratio	Confidence Interval	P value
Age less than 20 years	**2.7350**	**1.1059-6.7637**	**0.0294**	**0.2512**	**0.0744-0.8481**	**0.0261**
Male sex	3.5817	1.0067-12.7429	3.5817	0.3232	0.0677-1.5429	0.1567
Literate patients	**1.7793**	**1.2512-2.5303**	**0.0013**	**1.3530**	**0.9114-2.0084**	**0.1337**
BPL Card holders	0.9315	0.3280-2.6455	0.8940	**4.3547**	**1.3563-13.9811**	**0.0134**
Residential distance less than 10 Kms from ARV Clinic	**0.9420**	**0.8910-0.9959**	**0.0353**	1.0238	0.8978-1.1675	0.7254
Past History of Animal bite present	3.5354	0.9701-12.8837	0.0556	0.2225	0.0217-2.2779	0.2054
Category I animal bite	0.9087	0.2522-3.2736	0.8836	0.4210	0.1052-1.6839	0.2213
Not Experienced ADR	1.1168	0.3127-3.9882	0.8650	1.9458	0.4599-8.2323	0.3657

*** p-value of less than 0.05 was considered to indicate statistical significance.**

Figure 2 shows patients' perspective for missing the ARV dose. Personal or official workload, patients' forgetfullness about the scheduled date of vaccination and their migration outside the city and economical constrains were major reasons for not coming regularly to the ARV clinic to receive next scheduled dosage of ARV in both groups. These reasons were almost the same in both the groups. However, patients unawareness about ARV services being available at emergency department was a major reason in I.D. group.

Figure 2 : Reasons for delay or missing the scheduled dosage of ARV



*** Multiple responses are possible**

Discussion :

Most of the factors affecting compliance in both the groups (IM and ID) were similar.The manner in which patients were segregated in the two groups was based on the way they approached the two institutions, by word of mouth, previous experience or nearness to their residential area.

Most common rabid animal to which patients exposed was the dog (96%) and among them 89% were due to stray dogs. Dog as a major biting animal was found in the present study and other studies also agree with this finding.[3-7]

Majority of the patients were of category 2 according to WHO classification. This was similar to the findings by Tiwari et al (2009) and Modi (2009).[6,8]

In the present study the compliance level towards ARV schedule was high among males, but difference between them was not statistically significant. On the contrarily, in a study by Rohi KR and Mankeshwar R compliance was seen more in female patients (68.7%) as compared to male patients (64.7%).[9]

In both groups, the patients were charged 100 rupees for each dose of ARV. The Patients with BPL card are given ARV free of charge. Compliance was less among non-BPL card holders due to the amount to be paid by them for the dose and 5% of them showed delay in taking scheduled dosage of ARV due to economical problems.

There was inverse relationship between residential distance from ARV Clinic and compliance to ARV schedule. The residential distance also adds to the travelling costs to the patients. Moreover ARV charges per dose and loss of daily wages also play a role in determining compliance to the ARV schedule. The least compliance level was observed among unskilled workers (66.67%) and loss of daily wages may be a contributing factor behind that.

In our study majority of the defaulter patients were for the last dose of ARV (4^{th} dose in ID group and 5^{th} dose in IM group). This may be due to complexity of ARV schedule or economical constraints or due to belief of the people that 3 or 4 doses are enough to protect them against rabies. The last dose (Day 28) of antirabies vaccination is 21 days after the 3^{rd} dose of ARV (Day 7) in ID group and 14 days after the 4th dose of ARV (Day 14) in IM group. This huge gap may be an anticipating factor for missing the last dose of ARV schedule in both the regimens.

Preliminary economic assessments support the cost savings associated with a reduced schedule of vaccination.[10, 11] The ACIP (Advisory Committee on Immunization Practices) Rabies Workgroup has estimated that, assuming 100% compliance with a recommended vaccine regimen, a change in recommendation from a 5-dose schedule to a 4-dose schedule would save approximately $16.6 million in costs to the U.S. health-care system. Persons who receive rabies vaccination might see some savings related to deletion of the fifth recommended dose of vaccine, measured in both the cost of the vaccine and the costs associated with the additional medical visit.[12]

There is no specific recommendation for the re-initiation of the vaccine schedule when the intervals between vaccine doses are not followed, since this does not significantly affect antibody levels. [13]

Therefore, it was decided to perform an intention to treat analysis (without considering correct intervals). Not following the recommended time intervals between doses does not affect the immunological response, just as an interruption in the vaccination schedule does not require its re-initialization.[14] Hence, those who completed all the doses, irrespective of the duration, were considered compliant for the sake of this study. Whether the antibody titre levels vary in patients who are given ARV immediately after animal bite and in those who delay in taking ARV, gives scope for further research.

Conclusion :

The compliance among patients managed by intradermal as well as with intramuscular route of ARV was similar. The compliance level increased with increase in the level of education in both the groups. BPL card holders and patients residing near to ARV clinics were found to be more compliant.

Non-compliance was more common for the last dose of vaccination in both groups. Personal or official commitments, holiday on scheduled date of ARV, their migration outside the city and economical constraints were major reasons for non-compliance in both groups.

Intradermal route of ARV can be recommonded as the compliance was similar to intramuscular regimen and it also reduces the ARV clinic visits and transportation costs associated with it.

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