Title: AN EPIDEMIOLOGICAL APPRAISAL OF EFFECTIVENESS OF INTERCHANGEABILITY OF RABIES VACCINES FOR POST EXPOSURE PROPHYLAXIS IN BANGALORE CITY, INDIA

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Keywords Rabies, rabies vaccine inter changeablity, post exposure prophylaxis, India

Abstract This study was conducted to find out whether interchangeablity if rabies vaccines, including their routes of administration in postexposure prophylaxis (PEP) lead to any human rabies death in Bangalore city, India. During April 2005 to September 2011 a total of 1,55,842 antirabies vaccine (ARV) vials were used to treat 95,416 animal bite victims in Bangalore Municipal vaccine (PCECV) and purified duck embryo vaccine (PDEV)

Original Article

An Epidemiological Appraisal of Effectiveness of Interchangeability of Rabies Vaccines for Post Exposure Prophylaxis in Bangalore City, India

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ABSTRACT

This study was conducted to find out whether interchangeability of rabies vaccines, including their routes of administration in postexposure prophylaxis (PEP) lead to any human rabies death in Bangalore city, India. During April, 2005 to September, 2011 a total of 1,55,842 antirabies vaccine (ARV) vials were used to treat 95,416 animal bite victims in Bangalore Municipal Corporation hospitals. The three types of ARVs used were purified verocell rabies vaccine (PVRV), purified chick embryo cell vaccine (PCECV) and purified duck embryo vaccine (PDEV); and the five brands used were Abhayrab (PVRV), Indirab (PVRV), Rabipur (PCECV), Vaxirab (PDEV) and Verorab (PVRV). From April, 2005 to March, 2009 these vaccines were administered by intramuscular route and from April, 2009 to September, 2011 by both intramuscular and intradermal routes. From April, 2005 to March, 2012, from out of 35, 23 human rabies deaths which occurred in were reported from the Epidemic Diseases hospital of Bangalore city, complete information was available for 23 cases from the case record forms of the hospital. based on the information obtained from the clinical case records at the Epidemic Diseases Hospital Hence, as a follow up of these 23 cases it was possible to conduct and verbal autopsy done at household level in 13 cases. it It was found that none of these could be attributed to interchangeability of rabies vaccines and their routes of administration in PEP.

Key words: Rabies, rabies vaccine, vaccine interchangeability, postexposure prophylaxis, India

INTRODUCTION

Rabies is a viral encephalomyelitis caused by a RNA virus and the disease is almost always fatal. It is a zoonotic disease and usually transmitted to man following bite by a rabid animal mostly by dogs, cats, wild animals and other mammals. Hence, it is very important to institute timely and proper post-exposure prophylaxis (PEP) consisting of wound management, a course of modern rabies vaccines either by intramuscular (IM) or intradermal (ID) route; in severe exposures wherever anatomically feasible, local infiltration of wounds with rabies immunoglobulin (RIG). A course of vaccine consists of administering four or five doses of modern vaccine, either a cell culture vaccine (CCV) or purified embryonated egg vaccine (EEV). The two vaccine regimens that are approved for use in India are. (1) "Essen" consisting of five doses of given vaccine given on days 0, 3,7,14 & 28 (1-1-1-1-1) by IM route. (2) "Updated Thai Red Cross" consisting of four doses of vaccine given on days 0, 3, 7, and 28 (2-2-2-0-2) by ID route. The CCVs available in India are purified chick embryo cell vaccine (PCECV-Rabipur and Vaxirab N), purified verocell rabies vaccine (PVRV-Verorab, Abhayrab, Indirab, XP-rab), human diploid cell vaccine (HDCV- Rabivax) and EEV- purified duck embryo vaccine (PDEV- Vaxirab).

India is a "hot bed" of rabies as an estimated 20,000 human rabies deaths[1] and 17 million animal bites occur annually[2]. Majority of the bite victims being poor invariably go invariably go to government and municipal hospitals where rabies PEP is offered free of cost. But in these hospitals it is quite common to see that the rabies vaccines are interchanged in the course of a vaccination in a patient. This is because the vaccines are procured through public tendering process which is based on cost of vaccines and other factors. Besides following the introduction of intradermal rabies vaccination (IDRV) in the government and municipal hospitals sometimes even the route of vaccination is interchanged in a patient due to various factors. However, according to World

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Table-1
Details on type Type of ARV used, total no.number of animal bite cases treated at BBMP Bangalore city Municipal Corporation Hospitals & human rabies deaths reported in Bangalore city from April, 2005-March, 2012

Year	ARV vials used +	Proportions of ARV Types of ARV		Route of vacci-nation	Total No Number of animal bite cases treated	Total No. Number of human rabies deaths (n = 35)
		used+	used (%)+			
2005-06	28,702	Rabipur Verorab Abhayrab Vaxirab Indirab	60.0 3.9 25.0 0.1 11.0	IM IM IM IM IM	14,536	08
2006-07	18,979	Rabipur Abhayrab Indirab Vaxirab Verorab	40.0 40.0 03.0 07.0 10.0	IM IM IM IM IM	11,422	04
2007-08	22,647	Abhayrab Rabipur Indirab Vaxirab Verorab	59.0 14.0 13.0 04.0 10.0	IM IM IM IM IM	13,430	11
2008-09	24,457	Indirab Abhayrab Rabipur Vaxirab Verorab	40.0 41.0 10.0 07.0 02.0	IM IM IM IM IM	13,452	03
2009-10	27,596	Indirab Abhayrab Rabipur	63.0 31.0 06.0	ID/IM ID/IM ID/IM	16,098	04
20010-11	21,966	Indirab Abhayrab Rabipur	51.0 45.0 04.0	ID/IM ID/IM ID/IM	18,006	02
20011-12 (Till Sept)	11,495	Abhayrab Verorab Indirab	85.0 03.0 12.0	ID/IM ID/IM ID/IM	8,472	03
Total	1,55,842				95,416	35

Note:
+ Source: Vaccine store of Bangalore city Municipal Corporation –Referral Hospital, UFWC, Health centres & Dispensaries -Bangalore city Corporation
++ Source – Isolation HospitalEpidemic Diseases Hospital, Bangalore
Note -Rabipur: PCECV, Purified chick embryo cell rabies vaccine; Verorab, Abhayrab, Indirab: PVRV, Purified vero cell rabies vaccine; Vaxirab: PDEV, Purified duck embryo rabies vaccine

Health Organization (WHO), when it is impossible to complete post-exposure prophylaxis with the same CCV or EEV, another CCV should be used instead. However, since no study has been done yet on vaccine immunogenicity following changes in the route of vaccine administration (for example, from intramuscular to intradermal) during post-exposure prophylaxis, such changes should be the exception.[3] On the contrary, the product information of RabAvert, PCEC rabies vaccine available in the United States of America, states that there are no data on the interchangeable use of different rabies vaccines in a single pre- or post-exposure series. Therefore the vaccine from a single manufacturer should be used for the complete series whenever possible. If vaccines from other manufacturers are administered during the immunization series, an adequate antibody response should be confirmed by appropriate serologic tests[4]. Consequently, no clear information is available about this aspect of rabies prophylaxis which needs immediate attention.

Hence, this study was conducted to find out whether interchangeability of rabies vaccines, including their routes of administration in PEP has resulted in any human rabies death in Bangalore city.

MATERIALS AND METHODS

The Bangalore city is the capital of Karnataka, a southern state in India and has a population of about 8.4 million. It is endemic and enzootic for rabies[5&6]. The basic health services including rabies PEP are offered free of cost by Bangalore City Municipal Corporation through its network of health centres and hospitals. The medicines including rabies vaccines and immunoglobulins are procured through a public tendering process by the Bangalore City Municipal Corporation. The human rabies cases are usually admitted and managed in the Government run Epidemic Diseases Hospital (EDH), located in the city and considered a sentinel centre. Even rabies cases reaching other hospitals by convention are referred to EDH for management.

Table-2
Details of human rabies deaths in Bangalore city from April, 2005 to March, 2012

Total human rabies deaths	: 35
Information available from EDH records	: 23 (66%)
Verbal autopsy done at household level	: 13 (37%)
Reason for human rabies death	
- No ARV	19 cases (no PEP)
- 5 doses of ARV + No RIG	01 case (incomplete PEP)
- 3 doses of ARV + No RIG	01 case (incomplete PEP)
- 2 doses of ARV + No RIG	01 case (incomplete PEP)
- 1 dose of ARV + No RIG	01 case (incomplete PEP)

For the purpose of this study the information about vaccine procurement and supply was obtained from the central drug store of Bangalore city Municipal Corporation for the period April, 2005 to September, 2011. Similarly, the information about all human rabies cases admitted to EDH, Bangalore city from April, 2005 to March, 2012 was obtained. Additionally visits were made to other major hospitals in the city where remotely cases of human rabies might have been managed viz. National Institute of Mental Health and Neurosciences, where paralytic and atypical forms of human rabies are managed; Missionary hospitals often visited by poor and needy patients i.e. St.Johns, St.Philominas, St.Marthas, Baptist hospitals; and a corporate hospital, Manipal Hospital which occasionally is known to admit human rabies patients. However, in none of these hospitals a case of human rabies was admitted during this corresponding period.

Based on the information available from the EDH about the rabies case, wherever practically feasible, a house visit was made and a "verbal autopsy" was conducted using a structured proforma to reconfirm the cause of death and also know from the interviewees and the documents available at the household level whether there was any interchangeability of rabies vaccines and route of vaccine administration in these cases. All these activities were conducted by a public health (medical) professional well conversant with rabies prophylaxis; verbal autopsy and using structured proforma. For the purpose of this study the working definition of a PEP failure due to interchangeability of rabies vaccines/routes of administration (IM/ID) is "in a rabies exposed case, complete PEP given as per WHO categorization viz. wound management plus 5 doses of rabies vaccine received by IM route or 4 doses of rabies vaccine received by ID route; plus RIG in category III exposure, with interchangeability of vaccines (types/brands) with or without change of routes of administration i.e. IM and ID.

RESULTS

During April, 2005 to September, 2011 a total of 1, 55,842 antirabies vaccine (ARV) vials were used to treat 95,416 animal bite victims in Bangalore city Municipal Corporation hospitals. From April, 2005 to March, 2009 (4 years period) a total of 94, 785 ARV vials of Rabipur, Verorab, Abhayrab, Indirab and Vaxirab vaccines were given by IM route. From April, 2009 to September, 2011(2½ years period) 61,057 ARV vials of Abhayrab, Indirab, Rabipur and Verorab were given by IM and ID routes (Table -1).

From April, 2005 to March, 2012 (7 years period) 35 cases of human rabies from Bangalore city were reported at EDH. However, detailed information was available from 23 (66%) of these cases. In 13 (37%) cases a "verbal autopsy" could be conducted at the household level. It was revealed that in 19 (83%) cases " no PEP " was given ; of the remaining 4 (17%) cases of " incomplete PEP", in one case each, 5 doses of vaccine given without RIG; 3 doses of vaccine given; 2 doses of vaccine given and 1 dose of vaccine given (Table -2) .

DISCUSSION

Antirabies vaccines (ARVs) are antigens when administered produce antirabies antibodies in the vaccinees. Four types of ARVs are available in India viz. HDCV, PCECV, PVRV and PDEV of different brands. In routine clinical practice, these are used without interchangeability in the rabies exposed individuals. However, in government sector, often interchangeability of rabies vaccines occurs due to procurement of different brands over a period as a result of public tendering. This is in contrary to the recommendations of WHO[3] and a doubt arises whether interchangeability of rabies vaccines in PEP has lead to any failure of treatment and responsible for human rabies death in the person receiving such PEP. This is of serious public health concern more so when no data is available on immunogenicity of rabies PEP following interchangeability of rabies vaccines[3]. Hence, when this epidemiological scrutiny was made during the seven year period in Bangalore city it was found that five brands of rabies vaccines were used with "interchangeability" and even by routes of administration viz. IM and ID. However, none of the reported human rabies deaths during this period could be attributed to vaccine interchangeability. For the present this is reassuring as majority of the animal bite victims are poor and go to government and municipal hospitals where rabies PEP is offered free of cost. However, as in the given circumstances

"vaccine interchangeability" appears inevitable, it is strongly recommended that a well planned "prospective" immunogenicity study is conducted in individual cases of PEP receiving rabies vaccines interchanged in the Bangalore city Municipal Corporation hospitals.

Lastly, this study has some limitations like all human rabies deaths occurring during this period may not have been included, even among those reported in 12 (34%) cases complete information was not available and in the verbal autopsy done at the household level, due to "memory recall" and other factors the information provided by the surviving family members may not be accurate and complete.

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Announcement

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