Feasibility of WHO Recommended 3 visit fractional dose Intra-dermal Rabies Vaccine regimen (IPC) and only wound infiltration of RIG in Rabies Post Exposure Prophylaxis to I84, 955…

Article *in* Journal of the Indian Medical Association · May 2023

CITATIONS
0

READS
105

1 author:

Omesh Kumar Bharti
Indira Gandhi Medical College
195 PUBLICATIONS **510** CITATIONS

SEE PROFILE

Original Article

Feasibility of WHO Recommended 3 visit fractional dose Intra-dermal Rabies Vaccine Regimen (IPC) and only Wound Infiltration of RIG in Rabies Post Exposure Prophylaxis to I,84,955 Patients — Evidence from India

Omesh Kumar Bharti[1]

Background : In 2018, WHO recommended a 3 visit IPC regimen replacing 4 visit TRC regimen after due consultations and the field evidence but many countries are reluctant to follow this new IPC vaccine regimen thinking it to be risky and also practical difficulty of ID vaccine administration.

Method : We at our clinic in DDU Hospital, Shimla had started Pooling Strategy for sharing of Rabies Vaccine vials to optimize costs to patients since 2008. Later, only wound infiltration of eRIG was started since June 2014 owing to non-availability of RIG. Authors got brain samples of local freshly dead animals tested for FAT and found all of them to be positive including that of wildlife apart from getting serum samples of 30 patients for RFFIT after 3 ID injections. All patients were having titers ranging from 4.5 IU/ml- 30 IU/ml on day 14.

Results: Since May 29, 2018 we have followed new WHO guidelines and in four years time, we have vaccinated I84, 955 patients with IPC regimen in state of HP, India with only one confirmed failure of PEP reported due to injury to facial nerve of a girl child near Shimla.

Conclusion: IPC regimen is dose and cost sparing and equally effective to save lives of even those patients bitten by rabid dogs however additional local wound infiltration of RIG is must when indicated in lacerated wounds. Pooling Strategy is the most cost effective way to administer fractional doses of Rabies Vaccine and RIG free of cost to all and to achieve the objective of zero rabies by 2030.

[*J Indian Med Assoc* 2023; **121(8):** 46-8]

***Key words* : IPC regimen, Pooling Strategy, Rabies Prophylaxis, Rabies, Free PEP.**

Rabies is a viral zoonotic disease responsible for an estimated 59,000 human deaths and over 3.7 million Disability-Adjusted Life Years (DALYs) lost every year[1]. Most cases occur in Africa and Asia, with approximately 40% of cases in children aged <15 years. Dogs are the most important reservoir for rabies viruses and dog bites account for >99% of human cases[2]. Rabies can be prevented if timely prophylaxis is given to the bite victims in the form of rabies vaccine and Rabies Immunoglobulin (RIG) injection into the bite wounds [3].One of the reasons for non-compliance to seek rabies Post Exposure Prophylaxis (PEP) after bite is its high cost. Recently two low cost solutions have been proposed by the new WHO guidelines 2018. Intradermal administration of rabies vaccine on days 0,3 and 7 (IPC Regimen) and only wound infiltration of RIG (Himachal Method). Both these strategies require sharing of vials and for that we at Anti Rabies Clinic & Research Centre (ARCRC) at DDU Hospital Shimla, started first pooling Centre in 2008 so that vials of vaccine and later that of RIG can be shared.

[1]MBBS, DHM, MAE (Epidemiology), State Epidemiologist and State Master Trainer IDRV, HP, India, State Institute of Health & Family Welfare, Kasumpti 171009 and Corresponding Author

Received on : 08/06/2022
Accepted on : 24/04/2023

Editor's Comment :

- Pooling Strategy is the most cost effective way to administer fractional doses of rabies vaccine and RIG free of cost to all and to achieve the objective of zero rabies by 2030.

Materials and Methods

We started this pooling strategy in 2008, when there was scarcity of Rabies vaccine in Himachal Pradesh in specific and in India in general. We thought of an idea of pooling the patients to optimize the vaccine use[4]. All nearby health centers in Shimla city were asked to send animal bite patients to a centralized place to DDU Hospital in Shimla, called “Pooling Centre” for vaccination after wound wash and first aid. Each patient was asked to purchase one vial of Rabies vaccine while coming for first dose of vaccine and rest we would give “FREE”. Actually it was not free, we used to divide one vial among four patients by Intradermal (ID) vaccination and keep rest 3 vials of vaccine in the fridge, pull out next vial on subsequent visits and share among four and so on till the completion of 4 visit PEP. Later, author started to look for alternatives to make RIG also affordable to poor and developed a protocol of only wound infiltration of RIG for poor in 2013. While we were in the process of implementing this new protocol of only wound

infiltration among poor patients by sharing of RIG vials on the analogy of sharing of Rabies Vaccine in our pooling centers and took ethical clearance for the same, the RIG was out of stock not only in our state but throughout of Himachal Pradesh in 2014. We contacted CRI Kasauli, a Government owned manufacturer of eRIG to supply few vials of eRIG for at risk patients to save their lives. After due IEC approval, we now started to inject only wound/s of not only poor but everyone as RIG was not available in the market. These pooling centers came handy for sharing of RIG vials as now one vial of eRIG was being shared among 10-20 patients depending on the size and depth of the wound/s[3] left out eRIG was used next day. With sharing of vaccine and RIG vials[5] the total cost of PEP came down to just few dollars[6] that lead our Government to give complete PEP including eRIG free to all since May 2018 in Himachal Pradesh.

Results

Cost of USD 35 for 6 Intramuscular (IM) injections then came down to USD 6 for four visit ID vaccinations following TRC regimen. The patient load increased to 2.8 times and poor patient load increased to 3.2 times[7]. All these patients sought rabies vaccination for PEP after paying for only one vial of Rabies Vaccine rest of doses were shared by pooling. Patients from faraway places used to attend the clinic for cheaper prophylaxis as ours was the first clinic to start intradermal vaccination by adopting pooling strategy for the benefit of patients in the state of Himachal Pradesh and India. Later due to very small cost involved, the health authorities declared rabies vaccination free to all in the state of Himachal Pradesh. Now more than 90 "Pooling Centers" are operational in the state of Himachal Pradesh, some of them in land locked areas, where trained staff gives PEP by using intradermal strategy. Earlier four visit bilateral intradermal injections used to be given but now after WHO recommended three visit IPC schedule, only three visit bilateral intradermal Rabies Vaccination is administered as 2-2-2 schedule that have saved hundreds of vaccine vials for wider use saving costs of the Government and money of thousands of patients for visiting the clinic for the fourth dose. Further cost saving was done by omitting Rabies Vaccination to those who had consumed raw milk of a rabid cow or buffalo as per latest recommendation of WHO to not to give vaccination to those people having consumed raw milk of rabid cow or Buffalo. This saved large number of vaccine vials for PEP as vaccine remains in scarcity all over (Table 1).

Over a four years time, I84,955 PEP were given that have now exceeded 200,000 PEP mark by May 2022. Out of more than I84,955 PEP administered for dog bites in Himachal Pradesh with 3 visit 2 ID dose IPC regimen and only wound infiltration of eRIG there has been no confirmed PEP failure except in a girl child who was bitten on her face and her facial nerve was torn by the rabid dog[8].

Table 1 — *Dog Bite PEP using 3 visit IPC in Himachal Pradesh, India (Does not include PEP administered due to bites of other animals like Monkeys, Mongoose, Languor and Cats etc*

Year	Dog Bite PEP	Deaths due to suspected/Confirmed Rabies
2018	34279	1
2019	36227	4 (1 lab confirmed)
2020	48543	2
2021	65906	3 (1 lab confirmed)
Total	I84,955	10

For 48,543 PEPs administered in 2020 in the state of Himachal Pradesh (HP) vaccine vials (0.5 ml) used were 50,114 and eRIG vials(5ml) used were 23,133 indicating cost saving potential of Pooling Strategy adopted at 90 pooling centers of HP.

Discussion

While we were excited to have implemented this "Pooling Strategy" in the state leading to free distribution of the Rabies Vaccine to patients, mostly poor, we were worried about few reports of some of the patients dying despite Rabies Vaccination as rabies immunoglobulins were either scarce or not available at all. Human RIG (HRIG) was costing about USD 500 and equine RIG (eRIG) about USD[9]. Doctors would not prescribe eRIG for fear of anaphylaxis reaction and HRIG if prescribed, was not within the reach of majority of patients, so they would not purchase it and remain satisfied after taking Rabies Vaccine leading to some deaths due to rabies. This lead us to think of only wound infiltration of eRIG that proved to be successful in bringing cost down and save lives. We also provide/ advise Pre-Exposure Prophylaxis to people who come to our clinic to seek advice about it having a pet dog at home or having lots of stray dogs roaming around their locality and likely to be bitten by them. Equally high numbers of patients availing PEP at pooling centers are those bitten by monkeys as monkeys have been found to be rabid in Himachal along with other wildlife animals[9] including Mongoose[10] and squirrel[11]. An Estimated 20 million people who receive PEP each year[12] and 60% of them require RIG as per data of our clinic having type-III wounds. Our method of only wound infiltration[3,5,6] can help reduce costs[13] by 60 % from 120 Million USD to 10 Million USD per year globally a saving of 110 Million USA annually considering Current eRIG costs@$5per 5 ml vial.

Conclusions

The evidence of successful PEP among thousands of patients proved without doubt that 3 visit IPC regimen recommended by WHO along with only wound infiltration of eRIG is life saving and giving rest of RIG into muscle as IM is not of any benefit. WHO recommended only wound infiltration of RIG except in rare circumstances where wound is not available for infiltration e.g. aerosol exposure etc.RIG is in limited supply world over and only wound infiltration would not only save costs[14,15] but also spare up to 60% of RIG volume for India[16] and other countries where RIG is not available[17].

With such a low cost for eRIG due to only wound infiltration, the Himachal Government made total Rabies PEP free to all in 2018 that has enabled us to reach almost zero death due to Rabies in Himachal Pradesh. With free PEP to all the total PEP has gone up 4-5 times in the state of Himachal and yearly deaths due to Rabies have come down from about 35 in 2005[18] to almost zero now (Table 1) mostly for not availing free PEP. The Himachal Model needs to be implemented in other states of India and other countries need to adapt to this new Pooling Strategy of Himachal to achieve the WHO goal of Human Rabies free world by 2030. Therefore, adopting pooling strategy globally to administer fractional doses of Rabies vaccine and RIG free of cost to all by sharing vials can help us achieve zero by 30 fast and with minimum cost, saving thousands of lives annually and sparing costly rabies biologicals for wider patient use.

Funding : Self-funded.

Conflict of Interest : None.

References

1 Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, et al — Correction: Estimating the Global Burden of Endemic Canine Rabies. *PLOS Neglected Tropical Diseases* 2015; **9(5):** e0003786; https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003709

2 Fooks A, Cliquet F, Finke S — Rabies.Nat Rev Dis Primers 3, 17091 (2017). https://doi.org/10.1038/nrdp.2017.91;https://www.nature.com/articles/nrdp201791#rightslink

3 Bharti OK, Madhusudana SN, Gaunta PL, Belludi AY — Local infiltration of rabies immunoglobulins without systemic intramuscular administration: An alternative cost effective approach for passive immunization against rabies. *Hum Vaccin Immunother* 2016; **12(3):** 837-42. doi:10.1080/21645515.2015.1085142

4 Bharti O, Damme W, Decoster K, Isaakidis P — Breaking the Barriers to Access a Low Cost Intra-Dermal Rabies Vaccine Through Innovative "Pooling Strategy", *World Journal of Vaccines* 2012; **2(3):** 121-4. doi: 10.4236/wjv.2012.23016. https://www.scirp.org/journal/paperinformation.aspx?paperid=21524

5 Bharti OK, Madhusudana SN, Wilde H — Injecting Rabies Immunoglobulin (RIG) into wounds only: a significant saving of lives and costly RIG. *Hum VaccinImmunother* 2017; **13(4):** 762-5. https://pubmed.ncbi.nlm.nih.gov/28277089/

6 Bharti OK, Thakur B, Rao R — Wound-only injection of rabies immunoglobulin (RIG) saves lives and costs less than a dollar per patient by "pooling strategy". Vaccine 2019; **37 Suppl 1:** A128-A131. https://www.sciencedirect.com/science/article/pii/S0264410X19310084?via%3Dihub.

7 Bharti O, Damme W, Decoster K, Isaakidis P — Breaking the Barriers to Access a Low Cost Intra-Dermal Rabies Vaccine Through Innovative "Pooling Strategy", *World Journal of Vaccines* 2012; **2(3):** 121-4. doi: 10.4236/wjv.2012.23016.

8 Bharti OK, Tekta D, Shandil A — Failure of postexposure prophylaxis in a girl child attacked by rabid dog severing her facial nerve causing possible direct entry of rabies virus into the facial nerve. *Human vaccines & Immunotherapeutics* 2019; **15(11):** 2612-4. https://doi.org/10.1080/21645515.2019.1608131

9 Bharti OK — Human rabies in monkey (*Macacamulatta*) bite patients a reality in India now!, *Journal of Travel Medicine* 2016; **23(4):** taw028, https://doi.org/10.1093/jtm/taw028

10 Bharti OK, Sharma UK, Kumar A, Phull A- Exploring the Feasibility of a New Low Cost Intra-Dermal Pre & Post Exposure Rabies Prophylaxis Protocol in Domestic Bovine in Jawali Veterinary Hospital, District Kangra, Himachal Pradesh, India. World *Journal of Vaccines* 2018; **8:** 8-20. https://www.scirp.org/journal/paperinforcitation.aspx? paperid=82278

11 Bharti OK — Rabies in Squirrel and other wild animals, APCRI Journal; Volume XXII, Issue I, June 2020. https://www.researchgate.net/publication/344295752_RABIES_IN_SQUIRREL_AND_OTHER_WILD_ANIMALS

12 WHO Technical Report Series No. 1012, 2018; https://apps.who.int/iris/bitstream/handle/10665/272364/9789241210218-eng.pdf

13 Request for Reinstatement of Equine Rabies Immune Globulin to the EML and EMLc; available from; https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/applications-for-addition-of-new-medicines/a.12_equine-rabies-ig.pdf?sfvrsn=772b7a5d_6; accessed on June 9, 2022

14 Suijkerbuijk AW, Mangen MJ, Haverkate MR — Rabies vaccination strategies in the Netherlands in 2018: a cost evaluation. *Euro Surveill* 2020; **25(38):** 1900716. doi:10.2807/1560-7917.ES.2020.25.38.1900716. https://pubmed.ncbi.nlm.nih.gov/32975187/

15 Worathitianan B, Chockchalermwong S, Reongkhumklan S — Economic impact of revised rabies immunoglobulin administration protocol 2018 in the Emergency Department, NakhonPathom Hospital. *Dis Control J [Internet]* 2019; **45(3):** 293-04. Available from: https://he01.tci-thaijo.org/index.php/DCJ/article/view/174399

16 Sudarshan MK, AshwathNarayana DH, Jayakrishnappa MB — Market mapping and landscape analysis of human rabies biologicals in India. *Indian J Public Health* 2019; **63(Supplement):** S37-S43. doi: 10.4103/ijph.IJPH_379_19. PMID: 31603090.https://pubmed.ncbi.nlm.nih.gov/31603090/

17 Sreenivasan N, Li A, Shiferaw M, Tran CH, Wallace R — Working group on Rabies PEP logistics. Overview of rabies post-exposure prophylaxis access, procurement and distribution in selected countries in Asia and Africa, 2017-2018. Vaccine 2019; **37Suppl 1:** A6-A13. doi: 10.1016/j.vaccine.2019.04.024. Epub 2019 Aug 27. PMID: 31471150.https://pubmed.ncbi.nlm.nih.gov/31471150/

18 Suraweera W, Morris SK, Kumar R — Deaths from symptomatically identifiable furious rabies in India: a nationally representative mortality survey. *PLoSNegl Trop Dis* 2012; **6(10):** e1847. doi:10.1371/journal.pntd.0001847.