DISCUSSION

Testing a low-cost approach to giving eRIG for rabies PEP: Ethical issues

RICHARD A CASH

Abstract

Ethical concerns in using a lower dose of equine rabies immune globulin (eRIG) to irrigate wounds from dog bites to prevent rabies are discussed. A lower dose of eRIG was used because of a general shortage of eRIG and the high market cost in the Himachal Pradesh state of India. The cost and availability of drugs in low- and middle-income countries (LMIC) often necessitates testing a lower dose of a vaccine or treatment than that recommended by international organizations (eg WHO). It raises the issue that recommendations may be designed for higher income countries without taking into consideration issues of supply and cost. Secondly a case-control design to compare dosages or delivery systems is usually not an option so investigators must often use historical data for comparison or other study designs. The ethical issues in the testing of drugs and vaccines in LMIC must be continuously reviewed by the international community

The author, Omesh Kumar Bharti, is to be congratulated on presenting a very clear narrative (1) on the rationale and development of the innovative preventive intervention that eventually led to changing the use of the World Health Organisation's Post Exposure Prophylaxis (PEP) for rabies. The principal ethical dilemma presented in this case occurred when researchers and clinicians attempted to evaluate the treatment or prevention of rabies, where standard recommendations were neither practical nor affordable. Low-resource settings are the primary venues where these situations play out as it happened in Himachal Pradesh.

The equine rabies immune globulin (eRIG) for Grade III exposure to a bite from an animal suspected of being infected with rabies is often unavailable and/or unaffordable to patients or institutions in the private market because of the large quantity of eRIG that is recommended by the World Health Organisation (WHO) prevention guidelines (2).

The first challenge to investigators is to define the "gold standard", in this case the recommendation by WHO (2). What is it? How was it arrived at? Is it the result of expert opinion only, or is it based on solid scientific evidence? Did the standard take into consideration where the treatment/prevention would be implemented? Does the 'gold standard' only apply to wealthy countries where cost is not a factor and availability is assured? When Dr Bharti approached the Institutional Ethics Committee (IEC) with his proposed intervention of applying a reduced amount of eRIG at the site of the wound and eliminating the intra-muscular (IM) injection of the same drug, the IEC was initially reluctant to approve because of the WHO recommendations (1). But the WHO recommendations for the use of eRIG were based more on the opinion of WHO experts and less on solid research evidence. Control studies in humans could not be conducted and, therefore, did not inform the WHO recommendations. But opinions did. Dr Omesh Bharti, his colleagues, their patients, and the IECs were prisoners of opinions and not facts. The "gold standard" PEP guidelines may have reflected the concern of the "experts'" in insisting on the maximum intervention dose, given the high rabies mortality. But they did not take into consideration the difficulty in obtaining, or the cost of the PEP. Faith-based rather than evidence-based guidelines were given legitimacy by WHO. It is when shortages in the supply of PEP arose that the PEP standard was challenged.

A somewhat similar issue arose during an outbreak of yellow fever in the Democratic Republic of the Congo (DRC) in 2016 when there was a shortage of the vaccine (3). The government took a decision, with the support of WHO, to reduce the recommended dose of the vaccine to 1/5th of the standard so that larger numbers could be vaccinated to stem the epidemic. Though seroconversion rates had indicated that the lower dose of the vaccine could be effective, the actual efficacy could not be determined until the population immunised with the lower dose yellow fever vaccine was observed over a period of time to determine the incidence of the disease and the mortality in that population.

In Dr Bharti's view he did not conduct a study but rather a clinical intervention to save lives. It was, in fact, an innovative preventive intervention (4). There was no control group, and one method was not compared prospectively with another. Does this mean that the intervention should be held to a different standard than if it had been a research study? It could be thought of as the preventive side of innovative therapy, which is defined as a newly introduced or modified therapy with unproven effect or side effect undertaken in the best interest of the patient (4). But it must be conducted within an

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ethical framework that recognises that the intervention is not the standard.

Dr Bharti takes the position that this was not research but a clinical intervention and, therefore, research guidelines and ethical clearance had to prevail. Approval from his local IEC proved to be difficult because of prevailing opinions on the rabies PEP. Some IEC members were concerned that the use of cheaper eRIG would lead to anaphylactic reactions; however, data from Thailand recorded only 2 cases of anaphylaxis among 150,000 patients who received eRIG at that institution (5). Finally, a champion, a recognised rabies expert, stepped forward to argue the case and convince the IEC of the validity of the study. Consent was taken, a protocol was developed and rigidly adhered to, and patients were followed for up to a year post-prophylaxis. All rabies deaths were investigated for whether the patient had received post-exposure prophylaxis. Human rabies has essentially a 100% mortality, so a comparative study randomly assigning patients to one of two treatments was unacceptable.

A major ethical dilemma would have occurred if the hospital had deliberately withheld the eRIG recommended by WHO. But this is not what occurred. The hospital developed its policy based on the availability of eRIG in the market and at the hospital. Prior to this hospital policy, all patients in Himachal Pradesh, except for the very poor, had to potentially purchase eRIG in the market; and this was often not available or was far too expensive for many. One of the cases presented in the article documents the death of a woman who could not find eRIG in her local hospitals or the market even though she could afford to purchase the drug. What are the ethics of Himachal Pradesh or any state having a policy which requires a patient to purchase a life-saving drug from the market? Why wasn't eRIG available to all Indian citizens?

Low resource environments rightly challenge high cost preventions and interventions for diseases, especially for those common in their environments. There is a long history of the development of clinical interventions (eg, ORT to treat cholera and other diarrhoeas) as well as preventive efforts (eg, lower dose vaccines). What is important is that these innovations are conducted in an ethical framework that takes into consideration the quality of the information available, and the context in which the intervention will be implemented. Context is critical in defining the ethical issues. This has been well demonstrated in the recent Ebola outbreaks where ethical guidelines for the evaluations of new therapies and vaccines were developed taking the context and urgency of the issue into account (6, 7).

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Exemplary operational research on an important public health problem

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Abstract

Rabies is a fatal disease once contracted, and a serious public health problem. Immunisation was unaffordable and inaccessible for most affected people in India. Omesh Bharti's operational research allows us to reduce the unit dose needed for life saving rabies immunoglobulin (RIG) for class 3 rabid animal bites thereby raising hopes that access to this drug will improve. This study also suggests how public health research should question established guidelines that are rooted in impractical biomedicine without considering sociopolitical realities. The randomised controlled trial as a standard of research methodology is not only impractical but unnecessary. We discuss some of the challenges such as stockout of life saving medicines like RIG and suggest possible solutions. There is still a need to determine the correct RIG dose and the best technique for administering, storage and timing of this important drug.

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