Is this the Right Direction for Dengue Fever Research in India?

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Sir

Very interesting to read the article titled “A multi-centric, double-blind, placebo-controlled, randomized, prospective study to evaluate the efficacy and safety of Carica papaya leaf extract, as empirical therapy for thrombocytopenia associated with dengue fever” by Kasture et al in June 2016 issue. It is encouraging to see that there is important research going on in conditions like dengue fever which is a major problem of the developing world and in which the multinational pharmaceuticals are unlikely to invest. We would like to highlight a few points.

We hope the trial has been reviewed by a statistician to determine the sample size of the study. If the power is determined just for the platelet count then the number is adequate, but for mortality and toxicity the sample size is grossly inadequate. It would have been ideal if the authors mentioned the details of statistical calculations especially on what assumptions sample size was based on for a randomised control trial without much evidence from small studies.

You have concluded that “drastic fall of the platelets being one of the concerns in dengue cases, this novel option of Carica papaya leaf extract (Caripill) can be optimum offering which is simple, convenient, cost effective, safe and efficacious adjuvant in the treatment of thrombocytopenia”. The improvement in platelet count in the group of patients you studied is of doubtful clinical significance. There are researches to suggest that bleeding in dengue fever is dependent on lot of factors including endothelial injury, activation of coagulation and fibrinolysis besides the platelet count. It is noticeable that the trial excluded patients with platelet count below 30000, the group in which the thrombocytopenia is more significant, we know that counts above 30000 barely make any difference in patient outcome. I think the authors should make a recommendation at the end that the clinical practice in Dengue should not change in any way from the recommendations made by WHO and physicians should not start prescribing this drug based on this trial.¹ This trial probably will help the pharmaceuticals to promote their sales which has already been marketed in the false identity of an ayurvedic product. It is doubtful that any ethics committee of the western world would approve such a study.²

For a drug to develop in modern medicine, even if it is a natural extract, there should be attempts to identify the active ingredients of the extract. There have been attempts to do this in previous studies by other groups.³ The next step is to identify which ingredient/ingredients are the active component by doing in vitro studies and possibly animal models. It should be followed by healthy volunteer study to find the major toxicity, a dose finding study, a phase 2 study on limited number of patients to find out the efficacy followed by randomised controlled studies to compare the efficacy to placebo. It looks like all those steps have been bypassed by this study under the pretence that this is an ayurvedic product and has been in the market for few years. This has been marketed as an ayurvedic product with very limited evidence. It is unusual for physicians practising modern medicine to conduct this trial without adequate preliminary evidence. We think the major difference between an ayurvedic product and a modern medicine drug treatment is not in the content but in the strength of evidence to identify the efficacy and toxicity of the product.

There is no declaration of conflicts of interest or about the sponsorship of the trial. As one of the authors is from the pharmaceutical industry it is likely that the trial is sponsored by the Micro Labs. It is unfortunate to see that an attempt to answer an important research question in India has not followed the steps advised by the Indian Council of Medical Research (ICMR). There may be an active thrombopoietic or immunomodulatory agent in the papaya extract, which the researchers should endeavour to extract and conduct the research in an accurate way without bypassing the essential steps, which can sometimes put life of several patients at risk. If we make an attempt to identify the component in the precise way this may be helpful in lot of other haematological conditions also. This type of research will only facilitate the sale of similar products which will be a gain for the pharmaceutical share holders, unfortunately will not add any clinical benefit for our patients but rather will be an additional financial burden and occasionally can be dangerous.

References