**Retracted papers on role of Hydroxychloroquine and Chloroquine in SARsCoV-2 pandemic : What did we learn?**

Abstract-

Frauds in clinical trials have been a concern for years. Medical ethics , integrity and truthfulness are supposed to be pillars of scientific research. In last few deacdes incidences of scientific misconduct are on the rise .As a reflection, there have been many retractions of published papers. Retraction of the recent article on increased mortality with use of Hydroxychloroquine and Chloroquine (a multi centre registry analysis) in Lancet in June 2020 has ignited the debate on scientific misconduct mainly due to data fraud. Also concerns have been raised regarding the process of editorial and peer review in the prestigious high impact factor journals during the pandemic times. Medical literature is replete with numerous trials resulting in retracted papers within varying time intervals. The said study was published in a time of SARs Covid -2 pandemic and was perceived to have impact on changing medical practice and public health.

It is high time ,we learn lessons from these kind of scientific research fiascos where data is manipulated with a strategic approach. The readers of such journals and articles need to be analytical of the details of the study and use their clinical discretion before implementing the proposed therapy/technique in practice. The editors and peer reviewers should be entrusted with the responsibility of strict review process and data scutiny before publication. Formal investigations into the unrevealed aspects of motivational forces ( if any) behind these fraudulent studies should be explored and dealt appropriately.

Key words- COVID 19, Retracted papers, fraudulent trials, Hydroxychloroquine

Frauds in clinical trials have been a concern for years. Medical ethics and integrity are expected to be fundamental aspect of clinical research.Unfortunately lack of these principles have bred ground for unethical scientific trials and misconduct.

US Public Health Service has defined research misconduct as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Fabrication means when data or results are made up and reported .Honest error or differences of pinion are not included in reseach misconduct.1

The ongoing pandemic caused by SARsCoV-2 has grappled the entire world. Mankind is in a desperate stage to find a wonder drug which may offer healing to the suffering .Hence scientific reseach related to such therapy and trials have immense implications for public health and medical practices.

Numerous drug trials and therapies are underway in research in order to find either a preventive or curative therapy to curb the disease. Many drugs like Hydroxy chloroquine(HCQ), Ivermectin, steroids , Remdisivir , Fabinavir ,convalescent plasma therapy and others are under various stages of investigations for their possible role as a therapy in Covid related illness. Controversies continue to cloud the efficacy and complications of these drugs. Due to circumstantial challenges and logistics ,it is difficult to plan and conduct randomised control trials in the pandemic times, which is conventionally the best way to generate high grade and reliable evidence.

In this context, recently Mehra et al published a multi registry analysis regarding use of HCQ in SARs CoVid -2 cases sighting increased mortality and cardiovascular complications due to use of HCQ with or without macrolide .2 They had apparently analysed data of 96,032 patients from different countries. Soon after, serious doubts were casted on the genuinity of database and an open letter was sent to the authors and editor of The Lancet.3

Among series of heated debate on the veracity of data discussed , the said paper was retracted on 3rd June by The Lancet with apologies from the authors. 4-6There are have been many hue and cries and media releases on this as well.7-12

The retracted article on HCQ is the most recent one during the current pandemic. Also another article on ACE inhibitors by same authors ( Mehra et al) in NEJM was retracted.13

History of scientific research is replete with examples of scientific misconduct. Stroebe et al have sighted around forty fraudulent trials .14 In a study by Sovocool et al ,there is a list of eleven high profile cases.15 More than 2000 scientific articles have been retracted over the last 40 years, most of which are in biomedical sciences. In recent years ,the number of retractions has increased significantly and research misconduct especially data fraud is the most common cause of these retractions. 16

So what did we actually learn from this fiasco ?Following are few points worth consideration:

1. ***Editorial board and peer review:***

The accountability of the board of editors and peer reviewers of the journals who publish results of such so called large analysis based on close to a million patients from across the world is of paramount importance. It is easily comprehended that the article was published in a short period and without detailed verification of the data .It compels the scientists and readers of the prestigious journal to ponder who is in fact to be held responsible for checking the genuinity of the data before it is acepted for publication considering it has immnese implication and influence on medical practice concerning a serious illness like SARs CoV-2.

In near future, numerous studies related to Covid -19 are to going to conclude and may publish. It is understood that few journals have adopted fast rack review process for COVID related articles. All such studies should be scrutinised thoroughly before relased for publication because these may change clinical practice.

The impact of the article in discussion was to an extent that World Health Organisation stopped recruiting patients in its HCQ trial right after the article in Lancet and so did in UK trial.After retraction notice, both trials have resumed recruitment again. 17 So in futrure it will be more imperative on the journals to conduct a thorough review along with data check before publishing.

1. ***Statistical analysis***

The stastistical analysis behind many such trials are intriguing many times and leave a reader perplexed. Understanding complex statistical models is beyond comprehension of many journal readers and hence the flaws (if any) are not generallydemonstrable. These may create bias in results.

***c. Authors***′ ***apology –***

The concerned authors ( Mehra et al) have floated some explanations with apologies . Are such apologies enough to erase the effect of the scientific misconduct of such gravity. We understand further investigation is underway. Paper retractions with apologies published and letter of explanations are not sufficient enough to be construed as a process to obliviate the fraud. The retraction was one of the quickest one in scientific literature so far.16

***d. Investigations into the scientic misconduct***

There is ongoing further investigations into the yet unravelled aspects like the motive behind the trial to mislead the medical fraternity and influence practice which has implications for millions of lives .There have been many claims and statements in media on the possible link between drug industry, politics and the trial which remains to be investigated. 7-12The perpetrators of such fradulent trials are an organised force with a strategy .They use science and suffering of patients to frame and the extract advantages which may be personal or social or combined. It is highly unethical.

After investigation , all associated personnel (direct and indirect) and the purported motivational forces( if any) like industry and socio-political factors should be handled as per standing rules and regulations of medical ethics.Such actions will desist researchers from venturing into such exercises in future .

***E .Future publications-***

In future any such landmark or large trial is published in the high impact factor journal,as a reader ,it may generate speculations and suspicions abouts its authenticity.In clinical medicine it as such a challenging task to keep upto the latest updates and evidences amidst enormous loads of clinical work and limited health care infrastructure.

***f.*** ***Apporach to published articles-***

Most of the high impact journals offer paid subscriptions only and article submission is also on payment basis for many. So acquiring some information from such scientific studies in the prestigious journals which later prove to be fraudulent and then undoing it aftre retraction of the paper leaves the reader in dilemma .In addition, it reduces confidence in published studies and the journal credibility in future times. It is therefore, a prudent approach to conduct a 360 degree analysis of all such articles, espcially the ones which have impact to change clinical practice . This includes in depth scrutiny of the study design , materials and methods , data acquistion , statistical analyses of the data and the logistics involved. Conflicts of interests declared by authors and funding associations are key elements of an article which is often ignored by readers. The above proposed simple exercise will unravel the important aspects of the study whereby, the readers can infer themselves. Thorough scrutiny with existing knowledge and experience shall indicate if such papers should change our practice.

This retracted paer has drawn global attention in a short span and rekindled the debate on scientific misconduct once again. Honesty and transparency are essential components of research necessary to uphold the expectations and faith of the scientific community. We sincerely hope in coming times ,there will be more scientific research of high quality and ethics which we will pave path to find a solution to for prophylaxis and cure for SARs CoV-2 related illness.

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