

DAWN PRISM

Plasma therapy for Covid-19: The hopes and the hype

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It is important to review the framework in which plasma therapy is permissible.

From the time we discussed Convalescent Plasma Therapy (CPT) for treatment of Covid-19 in Prism, putting forward the argument that we are sailing uncharted waters, there has been an explosion in the number of healthcare institutions across the world scrambling to try this therapy.

Pakistan has perhaps been a couple of steps ahead of the rest of the world, with CPT beginning to be regarded not only by the public at large, but also by the medical community as the magic elixir against Covid-19. Numerous posts on social media, including Facebook and Twitter, have seen individuals imploring

people who have recovered from the virus to donate their plasma in order to help save the lives of their loved ones.

A number of websites have cropped up to facilitate connecting potential donors with recipients. The great humanitarian side of Pakistanis has emerged. Quite similar to the way that people of Pakistan responded to the economic woes of daily wage workers by distribution of ration, altruistic individuals have joined hands in efforts to bring plasma donors and recipients together through the internet. Most people mean well. There is little debate in that.

The rapidly mounting numbers of sick patients and depletion of hospital beds has heightened the state of panic with calls being made from every podium possible to make CPT available to anyone who contracts this virus. After all, it can be argued that desperate times call for desperate measures.

However, when it comes to non-standard forms of treatment whose scientific merit has yet to be proven anywhere in the world, caution is in order. In our efforts to combat the disease, we must not lose sight of the fact that this is an experimental therapy, approved all over the world only within strict research parameters, and is not an over the counter drug like paracetamol, which anyone with a fever can have.

Nonetheless, between the month of April when we first wrote about this therapy, and now, CPT has become a household name.

It is important here to review the framework in which this therapy is permissible.

Pathways for administering a non-standard treatment

In cases of emergencies like Covid-19, when there are no proven remedies available, non-standard treatments may be administered to patients under strict parameters. But these non-standard treatments are not provided randomly, or on demand, but rather within strictly monitored research parameters so that their actual utility or otherwise may be assessed.

In the case of CPT, the research that has been permitted worldwide is generally under the pathway designated as "Monitored Emergency Use of Unregistered and Investigational Interventions" (MEURI). Since this kind of intervention requires strict monitoring, it is only permitted in approved centres, where patients fitting strict eligibility criteria may be enrolled, and their treatment monitored diligently. This is the framework under which the US Food and Drug Regulatory Authority (FDA) has allowed the experimental use of CPT in designated centres.

Situation in Pakistan

There is a two-tiered structure for regulation of clinical research in Pakistan. Each proposal has to be approved by the Research Ethics Committee (REC) of the National Bioethics Committee (NBC) and the Clinical Studies Committee of the Drug Regulatory Authority of Pakistan (Drap). Once approved by both, the study can commence recruiting patients strictly in accordance to agreed upon inclusion criteria and only at the approved centres.

According to the NBC website, there are two CPT studies approved in Pakistan under the MEURI framework. Typically, these trials can enroll from 50 to 500 patients to enable them to reach a conclusion that may dictate further course of action: adopting the intervention as approved therapy because it works, abandoning it because it does not work or is harmful, or continuing with a limited number of additional recruitment to gain a somewhat better understanding. The regulatory bodies review the interim analysis and the analysis after full recruitment in order to determine further course of action.

In fact, even interim analyses at times are of immense value and are reported in medical journals so that others can benefit from the information. A case in point here is the notable performance of dexamethasone in the recovery trial.

To the best of our knowledge, CPT are still continuing and their final or even notable interim conclusions have not been published. While one group of researchers claims to have attained "86% success", reportedly on an analysis of 14 patients only, there is no scientific evidence available to corroborate this claim.

The media has however eagerly lapped this up, with anchors on TV talk shows applauding the claims that plasma therapy is indeed the beacon of hope researchers seek worldwide. The researchers have enjoyed unlimited air time to declare success before the trial is actually concluded, and results computed and verified.

Even without verified results, campaigns are afoot to seek plasma donation from the recently recovered, using emotive appeals as a means of soliciting donations. Appeals have also been made to the prime minister to declare it mandatory for all recovered patients to donate their plasma. According to a news report, the National Disaster and Management Authority (NDMA) has also jumped into the plasma bandwagon to "facilitate" donations, again with no evidence that this therapy should be rolled out across the nation to all who test positive.

While it is important to provide hope in times of despair, one can question the ethics of providing false hope to the public. With so much plasma frenzy, it has become difficult to control the wildfire that has now spread. The evidence of this is demonstrated through various posts on social media, and people increasingly banking their hopes in this treatment.

Lack of regulation

There is evidence that CPT is now being offered in increasing numbers of hospitals across the country. With no verified evidence of success, how is it possible to roll out this therapy so widely? With multiple centres involved, oversight needs to be all the more stringent, and any expansion in the study design must be approved by competent governmental authorities. The cornerstone of research is controlled, measured experimentation so that no harm may come to the study participants. With this particular trial surfing the wave of popularity, patients on whom it may not be indicated may actually end up getting it.

There are anecdotal reports of patients with mild disease being made to get CPT just to be extra sure of cure. Plasma transfusion, like any kind of transfusion, carries its own hazards, and must never be undertaken unless medically necessary. The media hype is making both the public and in many cases physicians lose sight of this cardinal rule.

Commercialisation of plasma therapy

With CPT being celebrated as a miracle, it has now become a window of opportunity for a quick profit. While the investigators perhaps may not have anticipated this particular impact of their promotion of plasma therapy, it is now being seen as a business venture. There are reports of convalescent plasma being sold for up to Rs 800,00 to desperate patients, and even reports of fake donors who get money from recipients only to disappear. Commercial trade of human plasma is not only illegal in Pakistan and internationally, but this commodification of hope is also extremely unethical.

Evidence from the outside world

At present, there is only one clinical trial that has published its findings whereas the rest are still being conducted. Initiated in Wuhan, China, and eventually terminated as the number of cases decreased in the city, the trial showed that while CPT showed early promise, there was no statistically significant difference between the experimental group (52 patients which received the plasma) and the

control group (51 patients that received the standard supportive treatment). Moreover, since the trial was terminated early, it was likely to be an underpowered study signifying that the findings may be inconsistent at best, and misleading at worst.

Researchers have attempted CPT for the deadly Ebola outbreak in 2016 also. In a trial of 84 patients with Ebola Virus Disease, along with 418 historical controls (patients previously treated for Ebola using other forms of treatment), there was no significant improvement in survival of patients.

Covid-19 CPT trials are still underway and in time we will have more evidence. Currently however, things are very much in the experimental phase. As of today, a registry that contains a database of clinical trials being conducted all around the world shows that 187 studies, in various phases, are being conducted to determine the efficacy of plasma therapy for treatment of Covid-19.

While the Ebola epidemic died out before further trials could be conducted, this is not the case with Covid-19, which as it appears at present, does not seem to be going anywhere. Adhering to stringent scientific parameters, there is no doubt that scientists will find out if CPT works or not.

Way forward

It is natural to cling on to hope in times of despair and chaos but it is even more important to remember that medicine, particularly the provision of drugs and other treatments, are correctly regulated, primarily because the stakes are so high. The key concern is public safety. Therefore, while provision of non-standard treatments is considered in times of infectious disease outbreaks, it is still essential to adhere to scientific as well as ethical guidelines, the first and foremost of which is transparency. Such transparency appears to be missing within the context of Pakistan.

While we are not advocating that this treatment modality ought not be used within the Pakistani context, but that at this stage it needs to be monitored and regulated strictly. Therapies should not be administered under the "guise of compassionate use or panicked rhetoric about right-to-try" primarily because it will lead to weak science.

The public ought to be provided the correct information, and claims about benefits need to be made conservatively. Furthermore, the government and regulatory bodies should take steps to ensure that treatments under the MEURI protocol are

conducted at designated centres with proper data collection and oversight. This will hopefully help in curtailing the commercialisation of plasma therapy, a shameful occurrence in the context of such an outbreak.

It is reassuring to note that the Pakistan Society of Haematology has also issued a notification criticising the "massive advertisement and unnecessary media hype" in the absence of "scientific proof" that has led "general public as well as some health professionals to believe that convalescent plasma is the standard treatment option". The policy brief has also urged the health department and regulatory authorities to take strict action against the illegal trade of plasma and to ensure judicious use of this treatment.

Noting this disturbing trend, the Ministry of National Health Services and Regulatory Affairs (NHSRA) also came out with a statement cautioning the public against succumbing to the false hype around CPT.

Medical research using human subjects is an immensely serious undertaking. In addition to scientific responsibilities on the shoulders of researchers, they also carry the weight of moral responsibility. Of necessity, they are using patients and their illness as a means towards finding a remedy. Society expects the highest level of professional conduct from them, with diligence and discretion. Creating and then feeding media frenzy is unbecoming of researchers.