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A Brief Overview on Plasma Therapy on Novel Corona Virus

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ABSTRACT

The corona virus disease (COVID-19) was first identified in Wuhan, China in December 2019. Corona virus is a group of related virus which is responsible for producing disease in mammals and birds. Corona virus is responsible for producing COVID-19 disease which produces respiratory illness in human. The objective of this article is that to identify the history of the corona virus, classification of corona virus, structure of corona virus, SARS CoV-2 control, prevention and possible treatment of corona virus disease (COVID-19) using plasma therapy. The world health organization (WHO) declared 'pandemic' situation because of the spreading of corona virus disease (COVID-19). As of December 2019, this epidemic had spread to 213 countries with 85 lakh confirmed cases, including 4.5 lakh deaths at 18 June 2020. There are various drugs and treatments are used to treat COVID-19 such as convalescent plasma therapy. The convalescent plasma therapy is method to transfer plasma of patients which is recovered from virus infection to the corona infected patients. The convalescent plasma contains antibodies against corona virus. The convalescent plasma therapy is not fully effective treatment for COVID-19 disease. The convalescent plasma therapy has great potential to treat COVID-19 disease in early stages but large scale in-vivo study is required to get a significant data to prove the efficacy of the treatment.

Key words:- COVID-19, SARS CoV-2, convalescent plasma, neutralizing antibodies,

INTRODUCTION

The Corona virus is a group of related RNA virus which is responsible for producing disease in mammals and birds. These viruses are commonly affect animal and birds but in these groups of virus some are affecting to human. The world health organization (WHO) has reported the new type of corona virus on 31 December 2019. [1] The WHO announced the current official name for the virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The corona virus can cause symptoms such as fever, sore throat from swollen adenoids, bronchitis (either viral bronchitis or secondary bacterial bronchitis) and pneumonia (either viral pneumonia or secondary bacterial pneumonia). [2][3] Most of the COVID-19 patients are asymptomatic or with mild symptoms of corona virus which is very difficult to detect. If the patient already suffering from diabetes disease or autoimmune liver disease, the mortality rate is higher in those cases. [4-6] It suggested that the population most at risk may be people with poor immune function such as older age people and those with renal and hepatic dysfunction. [7] By 18 June 2020 over 85 lakh people were infected with COVID-19 and caused over 4.5 lakh people deaths worldwide. [8]

The name 'Corona virus' is comes from Latin with meaning of 'crown' or 'wreath'. [9] These name is given because of their crown like shape. The human corona virus is firstly observed and studied by June Almeida and David Tyrrell. [10] Most of the members of corona virus that infect birds and mammals. There are only sex species of corona virus is infect human such as 229E , OC43, NL63, HKU1 (these cause common cold symptoms in immunocompetent

individual and the two other strains - severe acute respiratory syndrome corona virus (SARS-COV) and middle East respiratory syndrome corona virus (MERS-CoV). [11]

History:-

Corona virus is firstly discovered in chickens with acute respiratory infection caused by infectious bronchitis virus (IBV) in 1930. [12] The mortality rate was 40-90% in chickens. In 1940s, two more animal corona virus, mouse hepatitis virus (MHV) and transmissible gastroenteritis virus (TGEV) were isolated. [13] In 1960s, david tyrrell and Malcom Byone isolat noval common cold virus B814 which infect humans. [10] In 1965, tyrrell and Byone cultivated novel virus B814 by passing it through organ culture of human embryonic trachea. [14] In 1965, Dorothy hamre studied the tissue culture of students with cold, she discovered a new kind of virus, which became known as 229E. [15] In 1967, June Almeida show the two strains B814 and 229E by electron microscope. These two virus are morphologically related to infectious bronchitis virus (IBV). [16] The other human corona virus have since been identify including SARS-COV (2003), HCoV NL63 (2004), MERS-COV (2012), and SARS-COV-2 (2019). These new group of virus has a club like spikes in the surface of virus so that it known as Corona virus. [17]

Taxonomy :-

The formal taxonomical classification of virus is a responsibility of international committee on taxonomy of virus (ICTV). The ICTV has to classify the corona virus as shown in the table no.1. [18]

Unranked	Virus
Realm	Riboviria
Kingdom	Orthornavirae
Phylum	Pisuviricota
Class	Pisoniviricetes
Order	Nidovirales
Family	Coronaviridae
Subfamily	Orthocoronavirinae
Genera	Alphacoronavirus Betacoronavirus Gammacoronavirus Deltacoronavirus

The Alphacoronavirus and Betacoronavirus which infect mammals and Gammacoronavirus and Deltacoronavirus which infect birds. [19] The Alphacoronavirus ; species :- Human coronavirus 229E, Human coronavirus NL63, Miniopterus bat coronavirus 1, Miniopterus bat coronavirus HKU8, Rhinolophus bat coronavirus HKU2, ScotoPhilus bat coronavirus 512. And the Betacoronavirus ; species :- Human coronavirus OC43, Human coronavirus HKU1, MERS-COV, SARS-COV, SARS-COV-2. And the Gammacoronavirus ; species :- infectious bronchitis virus (IBV), Beluga whale coronavirus SW1. And the Deltacoronavirus ; species :- bulbul coronavirus HKU11, procine coronavirus HKU15. [18]

Structure :-

The 2019-nCoV was closely related (about 79% identity) to SARS-COV and (about 50% identity) to MERS-COV. [20] The coronavirus contain a positive-sense, single-stranded RNA genome of molecular weight 26 to 31 kilobases, the largest of any RNA virus group. They have petal shape spikes which is used to attachment of virus. [21] The viral envelope consists of lipid bilayer, in which the membrane, envelope and spikes structural proteins are anchored. [22] The viral envelope is used to protect virus and provide structural shape. The spikes of virus contain S glycoproteins which are used for attachment to the host receptor. [23] The M and E protein are important to form transmembrane structure which provides the shape of the virus. The N protein constitutes the only protein present in the nucleocapsid. The N proteins are bound to the positive sense single stranded RNA genome in continuous beads on a string type conformation. A fifth structural protein, the hemagglutinin-esterase (HE) is present in a subset of Beta-Coronavirus. [23] The average diameter of the virus particles is around 125 nm. [23]

Plasma therapy :-

The convalescent plasma therapy is method to transfer plasma of patients which is recover from virus infection to the corona infected patients. The recovered patients of COVID-19 have neutralizing antibodies titre, which can be an important donar source of convalescent plasma. It has been reported that these antibodies were administered to infected individual at an early stages, may magnificently reduce the viral load and the mortality rate is also reduce. [24] The convalescent plasma therapy has been used to treat patients with Machupo virus (Bolivian hemorrhagic fever), Junin virus (Argentinian hemorrhagic fever), Lassa fever and Ebola virus. In a study in Hong kong (80 patients) reported that, the efficacy of the convalescent plasma therapy is depends on how early you start the treatment of affected individuals after confirmed identification of infection. [25]

Mechanism of neutralizing antibodies :-

SARS-COV-2 have structural proteins include the spike (S), the membrane (M), envelope (E) and nucleic capsid (N) protein. [23] The corona virus initiates cell fusion via attachment of S protein with receptor on the host cell surface. The S protein comprises S1 and S2 units. The receptor-binding domain (RBD) within S1 directly interact with host receptor. [26] These S protein of SARS-COV-2 binds the Angiotensin converting enzyme 2 (ACE2) receptor on human alveolar epithelial cells.

The S protein of SARS-COV-2 is one of the major target for developing neutralizing antibodies to inhibit the binding and fusion of SARS-COV-2. [26] It has been reported that the sequence of SARS-COV-2 receptor-binding domain that directly contacts ACE2, is similar to that of SARS-COV, strongly suggesting that SARS-COV-2 uses ACE2 as its receptor. [27] The neutralizing antibodies comes from convalescent plasma, itself bind to the receptor-binding domain of SARS-COV-2 and prevent fusion of virus into the host cell. The mechanism of neutralizing antibodies are shown in fig.no.1

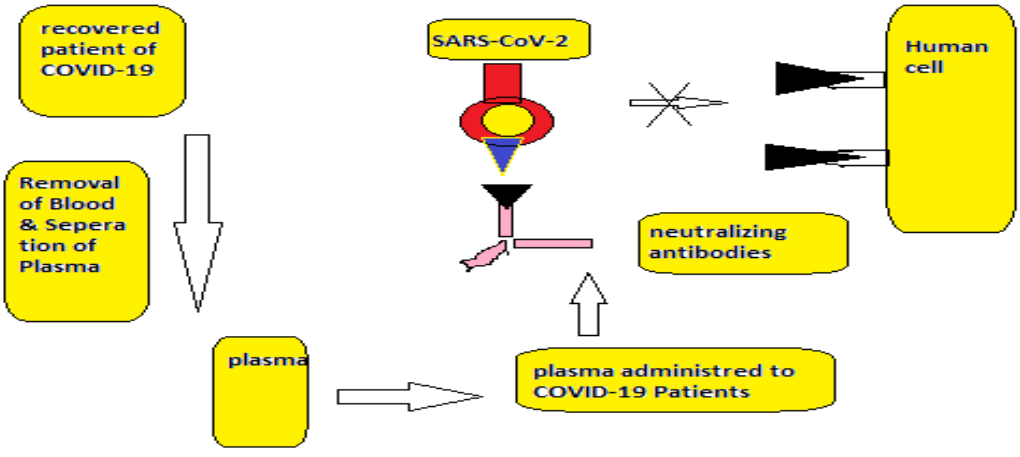

Fig.no.1 :- the mechanism of neutralizing antibodies. The neutralizing antibodies binds with SARS-COV-2 and prevent binding of ACE2 receptor on human cell.

The common steps to transfer plasma can be given as below [28] :-

1- The recruitment of the blood donors which has been recovered from COVID-19.

2- To check the donor eligibility criteria according to Drug controller general of India (DCGI).

3- The donar should be free from any sign of COVID-19 is to be checked.

4- The informed consent of the donor should be collected.

5- The blood group of donor should be checked.

6- The blood is to be withdrawn from recovered patients according to the standard parameters/established protocol.
7- The plasma has been separated by the blood.
8- The convalescent plasma is stored properly and transfers to the hospital for the transfusion.
9- Compatibility test has been carried out for COVID-19 patients.
10- The informed consent from a patient should be taken.
11- The clinical transfusion of convalescent plasma should be carried out according to the existing protocol.
12- The continuous monitor the patient, reduction in viral load, antibodies level and results of therapy is noted.
13- After transfusion of convalescent plasma, adverse effects (if identify) should be properly noted.

Risk factors for Convalescent plasma therapy :-

The risk of hepatitis B virus and hepatitis C virus transmitted through donated plasma should be thoroughly investigated. The transfer of HIV disease is possible if the donor have HIV virus. In Some patient, the adverse effects are also reported like nausea, itching, fever, and skin rashes. These adverse effects were resolved by symptomatic treatment or by reducing the rate of transfusion. [29]

Plasma therapy in India:-

In india, The Drug Controller General of India (DCGI) gives approval for convalescent plasma therapy at April 17 ,2020 to the Indian Council of Medical Research (ICMR). [32] The DCGI said this will be a phase II, open label, randomised controlled trial to assess the safety and efficacy of convalescent plasma. This trial has been approved on moderate disease patients. This trial will enrol 226 COVID-19 patients in group, who will receive plasma transfusion and 226 COVID-19 patients in group, who will not receive the treatment. [32] In India, various states like Maharashtra, Delhi, Kerala etc. show interest in plasma therapy after United States food and drug administration (US-FDA) approved the plasma therapy for COVID-19 patients. In initial study, there are five critically ill patients treated with plasma therapy in United States of America. The clinical status in all five patients improve after infusion of plasma with no dead and 3 patients were discharge and two patients continued to be stable on mechanical ventilation.

In China, 10 severely ill patients received the infusion of plasma (200 ml). The results of therapy show that there are no adverse effects of treatment and clinical status of all patients is improved. These study shows that the amount of neutralizing antibodies is different from individual to individual. [33]

In India, the first patients were recovered from COVID-19 and discharged from hospital on April 24, 2020. These patients have respiratory tract infection and further their condition worsened with type-1 respiratory failure. After the transfusion of convalescent plasma as per established protocol, the progressive improvement was observed in patients from 3-4 days of transfusion of plasma and at the end of 10 day of treatment the patient is successfully recovered from coronavirus infection. [30]

Plasma separation and storage :-

In whole blood, 45% part of blood cells and 55% part of plasma fluid. The plasma contains about 90% of water, with 10% being made up of ions, protein, dissolved gas, nutrients and wastes. The protein in plasma includes globulin protein (antibody), albumin (osmotic pressure), and fibrinogen (coagulation factor). [34]

The whole blood collected from recovered patients, is put into the commercially available anticoagulant-treated tubes e.g., EDTA-treated (lavender tops) or citrate-treated (light blue tops). The blood does not clot in the anticoagulant-treated tubes. The blood cells are removed from plasma by centrifugation for 10

minutes at 1,000–2,000 x g using a refrigerated centrifuge. Centrifugation for 15 minutes at 2,000 x g depletes platelets in the plasma sample. The blood cells settle down into the tube because of their high density and plasma is collected from supernatant portion. The supernatant, designated plasma is carefully removed from the cell pellet using a Pasteur pipette. [35]

The convalescent plasma separated from whole blood should be stored between +2°C to +6°C in blood bank refrigerator for up to 40 days. Alternatively, it may be frozen either within 8 hours of collection as 'Fresh Frozen Plasma' or within 18-24 hours of collection as 'Plasma Frozen Within 24 hours' and stored for up to 12 months at or below -18°C in a controlled plasma freezer. Appropriate labeling should be done to easily identify the convalescent plasma units. The convalescent plasma units should be transported in temperature controlled conditions. [36] Where there are no facilities to prepare convalescent plasma by centrifugation, it could be separated by stored vertically for 24 hours between +2°C to +6°C temperature; the supernatant plasma can then be transferred into the secondary bag and stored as a liquid plasma.

Caveats :-

1) In donor (recovered patients), the antibody level varies from individual to individual.
2) The amount of antibodies in, say, 250 ml (in india) of plasma transfused depends several factors, such as how long before the donor has been infected, whether the donor had severe or mild infection, whether the donor had other underlying illnesses that compromised her immunity and how long the plasma had been stored.
3) The high specificity means the antibody won't probably work against a different mutant or version of the virus.

Advantages of convalescent plasma therapy [31] :-

1) it is easily available, unlike specific drug or vaccine that takes time to develop, test and produce.
2) it is cheap. The only cost involved is in extraction and storage.
3) The antibodies are highly specific against the coronavirus.
4) The antibodies can have potential immunomodulator effect, reducing damage from the inflammatory response as the body mounts a severe response to the virus. Plasma treatment could help tone down the high immune response, which results in damage of normal tissue like those in the lungs, leading to lung injury and requiring the patient to be put on a ventilator.
5) It's generally safe and well tolerated and it's as safe as a blood transfusion.

DISCUSSION

In India, the clinical trials of convalescent plasma were initiated by the Delhi, Maharashtra, Kerala like State of India. The first patients in India were recovered by convalescent plasma therapy and discharge from hospital on April 24, 2020. [30] In India, the recovered patients of COVID-19 are ready to donate their plasma to save the life of other people. India, China, European countries are still working for success of the convalescent plasma therapy. Initially the results of convalescent plasma therapy is encouraging to treat COVID-19 disease but still more study and clinical trials are required to prove the efficacy of the CP therapy. The convalescent plasma therapy has a great potential to treat the COVID-19 patients. The CP therapy is used to highly reduce the viral load as well as remove the symptoms of SARS-COV-2. The structurally SARS-COV-2 is highly similar to the SARS-COV. In the present scenario the research is focused on identifying neutralizing antibodies. The researchers focused on to make artificial neutralizing antibodies to treat COVID-19 patients and make easily available to the treatment of COVID-19 disease.

REFERENCE

1. WHO. Novel Coronavirus–China. 2020. https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/. Accessed 1 Feb 2020.
2. Liu P, Shi L, Zhang W, He J, Liu C, Zhao C, et al. (November 2017). "Prevalence and genetic diversity analysis of human coronaviruses among cross-border children". Virology Journal. 14 (1): 230. doi:10.1186/s12985-017-0896-0. PMC 5700739. PMID 29166910.
3. Forgie S, Marrie TJ (February 2009). "Healthcare-associated atypical pneumonia". Seminars in Respiratory and Critical Care Medicine. 30 (1): 67–85. doi:10.1055/s-0028-1119811. PMID 19199189.
4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020 Mar 3. https://doi.org/10.1007/s00134-020-05991-x.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. J Am Med Assoc 2020 Feb 24. https://doi.org/10.1001/jama.2020.2648.
6. Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385e96.
7. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2001316.
8. https://www.worldometers.info/coronavirus/
9. "Definition of Corona by Merriam-Webster". Merriam-Webster. Archived from the original on 2020-03-24. Retrieved 2020-03-24.
10. Tyrrell DA, Fielder M (2002). Cold Wars: The Fight Against the Common Cold. Oxford University Press. p. 96. ISBN 978-0-19-263285-2.
11. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol 2016;24: 490-502.
12. Estola T (1970). "Coronaviruses, a New Group of Animal RNA Viruses". Avian Diseases. 14 (2): 330–336. doi:10.2307/1588476. ISSN 0005-2086. JSTOR 1588476
13. McIntosh K (1974). "Coronaviruses: A Comparative Review". In Arber W, Haas R, Henle W, Hofschneider PH, Jerne NK, Koldovský P, Koprowski H, Maaløe O, Rott R (eds.). Current Topics in Microbiology and Immunology / Ergebnisse der Mikrobiologie und Immunitätsforschung. Current Topics in Microbiology and Immunology / Ergebnisse der Mikrobiologie und Immunitätsforschung. Berlin, Heidelberg: Springer. p. 87. doi:10.1007/978-3-642-65775-7_3. ISBN 978-3-642-65775-7.
14. Tyrrell DA, Bynoe ML (June 1965). "Cultivation of a Novel Type of Common-Cold Virus in Organ Cultures". British Medical Journal. 1 (5448): 1467–70. doi:10.1136/bmj.1.5448.1467. PMC 2166670. PMID 14288084.
15. Knapp, Alex. "The Secret History Of The First Coronavirus". Forbes. Retrieved 2020-05-06.
16. Almeida JD, Tyrrell DA (April 1967). "The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture". The Journal of General Virology. 1 (2): 175–8. doi:10.1099/0022-1317-1-2-175. PMID 4293939.
17. Almeida JD, Berry DM, Cunningham CH, Hamre D, Hofstad MS, Mallucci L, McIntosh K, Tyrrell DA (November 1968). "Virology: Coronaviruses". Nature. 220 (5168): 650. Bibcode:1968Natur.220..650.. doi:10.1038/220650b0.
18. "Virus Taxonomy: 2018b Release". International Committee on Taxonomy of Viruses (ICTV). March 2019. Archived from the original on 2018-03-04. Retrieved 2020-01-24.
19. Wertheim JO, Chu DK, Peiris JS, Kosakovsky Pond SL, Poon LL (June 2013). "A case for the ancient origin of coronaviruses". Journal of Virology. 87 (12): 7039–45.
20. Roujian L, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;

https://doi.org/10.1016/S0140–6736(20)30251–8.
21. Cherry, James; Demmler-Harrison, Gail J.; Kaplan, Sheldon L.; Steinbach, William J.; Hotez, Peter J. (2017). Feigin and Cherry's Textbook of Pediatric Infectious Diseases. Elsevier Health Sciences. p. PT6615. ISBN 978-0-323-39281-5.
22. Lai MM, Cavanagh D (1997). "The molecular biology of coronaviruses". Advances in Virus Research. 48: 1–100.
23. Fehr AR, Perlman S (2015). "Coronaviruses: an overview of their replication and pathogenesis". In Maier HJ, Bickerton E, Britton P (eds.). Coronaviruses. Methods in Molecular Biology. 1282. Springer. pp. 1–23. doi:10.1007/978-1-4939-2438-7_1. ISBN 978-1-4939-2438-7. PMC 4369385. PMID 25720466. See section: Virion Structure.
24. Yeh K-M, Chiueh T-S, Siu LK, Lin J-C, Chan PKS, PengM-Y, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56(5):919e22.
25. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24(1):44e6.
26. Guangyu Z, Zhao Q. Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. Int J Biol Sci 2020;16(10):1718e23. https://doi.org/10.7150/ijbs.45123.
27. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol 2020. https://doi.org/10.1128/JVI.00127-20 [Epub ahead of print].
28. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id¼NTg2Mw¼¼.
29. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. Anesth Analg 2009;108(3):759e69.
30. https://www.theweek.in/news/india/2020/04/26/indias-first-covid-19-patient-to-receive-plasma-therapy-discharged.html.
31. https://scroll.in/article/960879/as-india-debates-using-plasma-therapy-for-coronavirus-patients-heres-what-you-should-know-about-it
32. https://www.thehindubusinessline.com/news/national/drug-controller□general-of-india-approves-clinical-trial-of-convalescent-plasma-therapy-in□covid-19-patients/article31375934.ece#.
33. Duhan K, et al. Effectiveness of convalescent plasma therapy in severeCOVID-19 patients. Proc Natl Acad Sci Unit States Am 2020. Latest Articles, www.pnas.org/cgi/doi/10.1073/pnas.2004168117.
34. https://www.news-medical.net/health/Blood-Plasma-Components-and-Function.aspx
35. https://www.thermofisher.com/in/en/home/references/protocols/cell-and-tissue-analysis/elisa-protocol/elisa-sample-preparation-protocols/plasma-and-serum-preparation.html
36. "Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks" by World Health organization 2014.

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