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Transfusion and Apheresis Science 61 (2022) 103398

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

SARS-CoV-2 variants inactivation of plasma units using a riboflavin and ultraviolet light-based photochemical treatment

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ARTICLE INFO

Keywords:
Pathogen reduction
SARS-CoV-2
Variants of concern
Convalescent plasma donor
Neutralizing antibodies
Plasma transfusion therapy

ABSTRACT

Background: Test the ability of Mirasol Pathogen Reduction Technology (PRT, Terumo BCT, Lakewood Co, USA) treatment with riboflavin and ultraviolet light (R + UV) in reducing SARS-CoV-2 infectivity while maintaining blood product quality.

Material and methods: SARS-CoV-2 strains were isolated and titrated to prepare cell free virus for plasma units infection. The units were then under treatment with Mirasol PRT. The infectious titers were determined before and after treatment with an in house microtitration assay on Vero E6 cells. Thirty-six plasma pool bags underwent PRT treatment.

Results: In all the experiments, the measured titer following riboflavin and UV treatment was below the limit of detection of microtitration assay for all the different SARS-CoV-2 strains. Despite the high copies number detected by RT-PCR for each viral strain after treatment, viruses were completely inactivated and not able to infect VERO E6 cells.

Conclusion: Riboflavin and UV light treatment effectively reduced the virus titers of human plasma to the limit of detection in tissue culture, regardless of the strain. These data suggest that pathogen reduction in blood products highlight the safety of CP therapy procedures for critically ill COVID-19 patients, while maintaining blood product quality.

1. Introduction

Passive immunotherapy with convalescent plasma (CP) from recovered subjects is an historic therapeutic tool widely used and a pillar of basic immunology [1]. Indeed, the use of immunoglobulins in the prophylaxis and treatment of viral infections is an irreplaceable tool for the post-exposure prevention of several viral infections like VZ and rabies since long time [2]. When a new infectious agent appears passive immunotherapy, is the only weapon available to solve public health emergency. Recently, therapy with convalescent plasma was applied in Western Africa Ebola (2013–2016) and MERS epidemic, (2014–2015) [3]. During the SARS-CoV-1 epidemic caused by a Coronavirus, a 23 % reduction in mortality was reached when convalescent plasma was administered at the early stages of disease [4]. Furthermore, the high levels of safety of plasma therapy was confirmed with the daily transfusion practice of plasma products [5]. At the beginning of COVID-19 pandemic, experts debated whether asymptomatic transmission was possible due to the findings of viral RNA in multiple samples tested (including blood), raising considerable concern regarding the safety of convalescent plasma [6]. Viremia was found in 15 % of patients from Wuhan, China, with a median PCR cycle threshold of 35.1 suggesting a very low RNA copies number [7]. Several reports found viremia in asymptomatic patients, posing a potential risk in blood donation due to the possibility to escape current health screening performed at the time of donation. Starting from March 2020 until now, in response to the outbreak of the SARS-CoV-2 pandemic, convalescent plasma (CP) has

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome virus 2; COVID-19, coronavirus disease 2019; TCID50, median tissue culture infectious disease; PRT, Pathogen Reduction Technology; CP, convalescent plasma.

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https://doi.org/10.1016/j.transci.2022.103398
Received 3 December 2021; Received in revised form 24 January 2022; Accepted 12 February 2022
Available online 16 February 2022

been used for the treatment of severe COVID -19 patients [8] due to the lack of an established therapeutic strategy.

Pathogen reduction systems (PRS) have been also widely implemented to increase the safety of COVID-19 CP, considering that most CP donors have no donation history and thus their donations should be considered at higher infectious risk. The Mirasol Pathogen Reduction Technology (PRT) System (Terumo BCT, Lakewood Co, USA) combines the use of a UV light source and riboflavin (vitamin B2) loading to an irreversible damage to nucleic acids. This system inactivates viruses, bacteria, parasites and white cells, while red blood cells, platelets and plasma proteins are preserved. Our hospital was the first in Italy to use CP for the treatment of critical COVID-19 patients [9,10] during the first pandemic wave in March 2020. In compliance with the recommendations of National authorithy (Centro Nazionale Sangue) we adopted the Mirasol PRT technology to inactivate CP produced at Tranfusion Service. In the present experimental study, we used infectivity assays to evaluate the reduction of SARS-CoV-2 infectivity after inoculation of different viral variants into plasma samples and subsequently treated by Mirasol PRT system.

2. Methods

2.1. Plasma products

Plasma products were prepared from 25 whole blood units collected in Citrate Phosphate Dextrose (CPD) from regular healthy blood donors, separated on an automated blood system and discarded by local Blood Bank Processing and Validation Center of Fondazione IRCCS Policlinico San Matteo according to the Italian law decree of Ministry of Health, November 2, 2015, "Provisions relating to the quality and safety requirements of blood and blood components". The products were released as PF24 (plasma frozen within 24 h after phlebotomy to ≤-20 °C). After thawing in a water bath at 37 °C, plasma units were pooled and divided in sets of 36 plasma bag units in order to reduce donor variability that might affect the assay's outcome.

2.2. SARS-CoV-2 variants culture protocol

SARS-CoV-2 strains, including wild type Chinese-derived strain (D614), Italian strain PV10734 (D614 G), Alpha strain (501Y.V1 lineage B.1.1.7), Gamma strain (501Y.V3 lineage P.1), Beta strain (501Y.V2 lineage B.1.351) and Delta strain (B.1.617.2) were isolated from infected patients' nasal swabs. The viruses were propagated in Vero E6 cells [VERO C1008 (Vero 76, clone E6, Vero E6, ATCC® CRL-1586™] with the addition of respiratory medium: EMEM plus 1% penicillin, streptomycin, glutamine and 5 γ/mL of trypsin. Mediums were harvested from infected cells, clarified by centrifugation and each strain was titrated and frozen at -80C in aliquots until use. The identity of SARS-CoV-2 strains were established by sequencing [11] and confirmed with a database of sequence data of the viruses, submitted to GISAID under the following reference numbers (EPI_ISL_568579; EPI_ISL_1403609-11). Virus propagation occurred in BSL-3 laboratory. All virus concentration results are presented in median tissue culture infectious doses ($TCID_{50}$).

2.3. Pathogen reduction study

Pooled plasma derived from blood donors was divided in 36 equal volume into illumination bags (Mirasol Illumination Bag, Terumo BCT, Lakewood, CO). Riboflavin solution for virus inactivation (35 mL) and heparin (Epsoclar, 2500 unit in 0,5 mL, Pfizer NY, US) were added to each bag (230 mL total final volume) to avoid plasma coagulation during microtitration assay. An aliquot of plasma sample was removed from each bag and tested for the presence of specific SARS-CoV-2 IgG and neutralizing antibodies (NT-Abs). In addition, a specific real-time RT-PCRs targeting RNA-dependent RNA polymerase and ORF8 genes was used to detect presence of SARS-CoV-2. In each plasma bag 200 $TCID_{50}$ of virus (6 bags respectively for each strain) was added, according to stock titer. Plasma bags were placed into the Mirasol Illuminator for UV inactivation that consists of exposure to 6.24 J/mL UV light for an average time of 10 min, according to the manufacturer guidelines (https://www.terumobct.com/mirasol). A pre- and post-treatment sample was obtained for viral titer determination with in-house microtitration assay.

2.4. Microtitration assay

Titration of SARS-CoV2 variants after treatment were defined according to reported protocol [12]. Briefly, 50 µl of plasma sample from each pool bag were diluted in 50 µl (1:2) of respiratory medium in two wells of a flat bottom tissue culture microtiter plate (COSTAR, 13 Corning Incorporated, NY 14831, USA) and titrated up to 1:128 in a serial 1:4 dilution. $3x10^4$ VERO E6 cells [VERO C1008 (Vero 76, clone E6, Vero E6); ATCC® CRL-1586™] in 50 µl were added and incubated at 33 °C 5% CO2. After 72 h plates were scored for cytopathic effect (CPE), stained with Gram's crystal violet solution (Merck KGaA, 64271 Damstadt, Germany) plus 5% formaldehyde 40 % m/v (Carlo ErbaSpA, Arese (MI), Italy) for 30 min and washed under running water. Blue staining of wells indicated the absence of cytopathic effect. Virus titrations were calculated using Reed-Muench method [13]. Every treated bag was tested in duplicate with each variant.

2.5. Calculation of limit of detection and log reduction

When, in the post treatment samples, no virus was detected in the lowest dilution, the limit of detection for the assay was reached [14]. All values at the limit of detectability of our test were considered less than or equal to the calculated theoretical detection limit. LOD (limit of detection) and log reduction was calculated using the following equations:

$$LOD = \log [1 / (N \times V)]$$

$$\text{Log Reduction} = \text{Log (Starting Titer)} - \text{Log (Final Titer)}$$

N stands for the number of replicas tested at the lowest dilution per sample; V is the volume used for viral titration (volume inoculated/ well in mL). No cytotoxicity occurred at the lowest dilution.

2.6. Quantitative SARS-CoV-2 S1/S2 IgG and neutralizing antibodies (NT-Abs) measurement

Plasma samples were analyzed using a chemiluminescent immunoassay (CLIA) (LIAISON® SARS-CoV-2 S1/S2 IgG; DiaSorin, Saluggia (VC), Italy) for the quantitative characterization of SARS- CoV-2 anti-S1 and anti-S2 IgG antibodies, according to the manufacturer's instructions. Results were given as AU/mL and a cut-off of 15 AU/mL was considered for definition of positive samples. Results ranging from 12 to 15 AU/mL were considered borderline or weak positive and IgG titres <12 AU/mL were given as a negative result.

For SARS-CoV-2 neutralizing antibodies a titer <1:10 was defined as negative whereas a titer > 1:10 was considered positive [12].

2.7. SARS-CoV-2 genome detection

Commercial SARS-CoV-2 specific real-time RT-PCRs (MGISP-NE384, MGI Tech Co., Ltd., China) targeting RNA-dependent RNA polymerase and ORF8 genes was performed to detect the presence of SARS-CoV-2 genome in plasma samples collected before virus inoculum and post UV treatment, according to the manufacture guidelines. SARS-CoV-2 RNA amounts are reported as quantification cycle (Cq).

Table 1
Log reduction of SARS-CoV-2 and variants of concern after PRT treatment of pooled plasma units at volume of 230 mL.

Strain/inoculum	UNIT NUMBER	PRETREATMENT VIRAL TITRE (Log)	POST-TREATMENT VIRAL TITRE (Log)	LOG REDUCTION
Italian				
200 $TCID_{50}$	1	2,20	≤1	≥1,20
	2	2,12	≤1	≥1,12
	3	2,26	≤1	≥1,26
	4	2,18	≤1	≥1,18
	5	2,25	≤1	≥1,25
	6	2,28	≤1	≥1,28
	average	2,21	≤1	≥1,13
	SD	0,059	N/A	N/A
	CV	1,705%	N/A	N/A
	UNIT NUMBER	**PRETREATMENT VIRAL TITRE (Log)**	**POST-TREATMENT VIRAL TITRE (Log)**	**LOG REDUCTION**
Chinese				
200 $TCID_{50}$	7	2,10	≤1	≥1,10
	8	2,15	≤1	≥1,15
	9	2,18	≤1	≥1,18
	10	2,10	≤1	≥1,10
	11	2,12	≤1	≥1,12
	12	2,14	≤1	≥1,14
	average	2,13	≤1	≥1,13
	SD	0,031	N/A	N/A
	CV	1,466%	N/A	N/A
	UNIT NUMBER	**PRETREATMENT VIRAL TITRE (Log)**	**POST-TREATMENT VIRAL TITRE (Log)**	**LOG REDUCTION**
Alpha				
200 $TCID_{50}$	13	1,60	≤1	≥0,60
	14	1,42	≤1	≥0,42
	15	1,48	≤1	≥0,48
	16	1,40	≤1	≥0,40
	17	1,41	≤1	≥0,41
	18	1,49	≤1	≥0,49
	average	1,48	≤1	≥0,48
	SD	0,075	N/A	N/A
	CV	5,133%	N/A	N/A
	UNIT NUMBER	**PRETREATMENT VIRAL TITRE (Log)**	**POST-TREATMENT VIRAL TITRE (Log)**	**LOG REDUCTION**
Gamma				
200 $TCID_{50}$	19	1,10	≤1	≥0,10
	20	1,18	≤1	≥0,18
	21	1,12	≤1	≥0,12
	22	1,16	≤1	≥0,16
	23	1,13	≤1	≥0,13
	24	1,12	≤1	≥0,12
	average	1,13	≤1	≥0,13
	SD	0,029	N/A	N/A
	CV	2,599%	N/A	N/A
	UNIT NUMBER	**PRETREATMENT VIRAL TITRE (Log)**	**POST-TREATMENT VIRAL TITRE (Log)**	**LOG REDUCTION**
Beta				
200 $TCID_{50}$	25	2,28	≤1	≥1,28
	26	2,23	≤1	≥1,23
	27	2,18	≤1	≥1,18
	28	2,20	≤1	≥1,20
	29	2,21	≤1	≥1,21
	30	2,23	≤1	≥1,23
	average	2,22	≤1	≥1,22
	SD	0,034	N/A	N/A
	CV	1,544%	N/A	N/A
	UNIT NUMBER	**PRETREATMENT VIRAL TITRE (Log)**	**POST-TREATMENT VIRAL TITRE (Log)**	**LOG REDUCTION**
Delta				
200 $TCID_{50}$	31	1,71	≤1	≥0,71
	32	1,54	≤1	≥0,54
	33	1,76	≤1	≥0,76
	34	1,82	≤1	≥0,82
	35	1,27	≤1	≥0,27
	36	1,47	≤1	≥0,47
	average	1,59	≤1	≥0,59
	SD	0,207	N/A	N/A
	CV	13,010%	N/A	N/A

SARS-CoV-2 and variants viral titer reduction after pathogen reduction treatment (PRT). Each condition was tested in duplicate, including two replicas for each bag strains group. Pooled plasma bags were inoculated with a known quantity of coronavirus and each one was treated independently. After virus inoculum titration occurred before and after PRT treatment. TCID50 = median tissue culture infectious dose. 200 TCID50 Is the stock inoculum value, Log viral titer is the higher dilution number of inoculated samples that can produce observable cytopathic effect, log ≤1 mean no cytopathic in the lowest dilution.

Table 2
Sars-CoV-2 specific real-time RT-PCRs quantification cycle (CQ) in pooled plasma.

sample after PRT	Sars-CoV-2 specific real-time RT-PCRs quantification cycle (CQ)					
Post UV treatment plasma Bag N#	6	10	14	19	25	32
ORF8 Gene (CQ)	28	28	28	31,8	26	26,9
RdRp Gene (CQ)	27,6	27,7	28	31	25	27,1
Strain	ITALIAN	CHINESE	ALPHA	GAMMA	BETA	DELTA

Quantification cycles of SARS-CoV-2 variants is reported as aquantification cycle (CQ) in six pooled plasma bags, analysed post pathogen reduction treatment (PRT).

2.8. Data analysis

All analyses reported including descriptive statistics for pathogen reduction were performed using GraphPad Prism software (version 5; GraphPad Software Inc., La Jolla, CA), including mean, standard deviation, coefficient of variation (CV) and numbers of samples analyzed (N).

3. Results

Thirty-six (N = 36) PF24 pooled plasma units were evaluated using Mirasol PRT system against SARS-CoV-2 and its variants of concern. In order to exclude prior virus neutralization by immune components in the plasma products, we performed a quantitative SARS-CoV-2 S1/S2 IgG and NT-Abs detection that tested negative. Moreover, the investigation by a SARS-CoV-2 specific real-time RT-PCRs for the presence of viral genome in plasma bags before inoculation of the different variants, was negative.

The data collected are shown in Table 1. The in vitro microtitration assay demonstrated that the pathogen reduction treatment of plasma bags inoculated with SARS-CoV-2 was able to reduce infectious titer to the limit of detection by ≥ 1,21 log for Italian, ≥ 1,13 log for Chinese, ≥ 0,48 log for Alpha, ≥ 0,13 log for Gamma, ≥ 1,22 log for Beta and ≥ 0,59 log for Delta strain. Indeed all thirty-six treated units were reduced to the limit of detection (≤ 1 log10). All samples were tested immediately before and after Mirasol treatment. Furthermore, we tried to isolate the viral strains after treatment, inoculating plasma samples on VERO E6. Despite the high copies number detected by RT-PCR for each viral strain (Table 2) after treatment, viruses were completely inactivated and not able to infect VERO E6 cells (Table 3).

4. Discussion

Convalescent plasma, a source of anti-SARS-CoV-2 antibodies, has been widely used as a treatment for COVID-19 during the present pandemic. The safe use of CP depends mainly on the accuracy in donor screening for transmitted transfusion diseases, potentially harmful for the recipient, considering that many CP donors could be first time donors [15].

The Mirasol PRT treatment of CP is a safe method that significantly reduces the risk of possible transmitted transfusion infections and, importantly, does not impair plasma quality (e.g.:antibody function [16]). In the study by Keil et al., the Mirasol PRT system significantly reduced the load of viral agents tested in plasma and platelet products [17]. This method provides a proactive layer of blood safety through its broad-based effectiveness against a wide range of known pathogens.

The European Center for Disease Prevention and Control (ECDC) suggests a precautionary deferral from blood donation for 21 days after any possible exposure for confirmed COVID-19 patients [18]. Despite SARS-CoV-2 virus was detected at very low levels in blood products [19] and there is no evidence of transfusion transmission at this time, the theoretical and potential risk of SARS-CoV-2 and their variants of concern to be transmitted through transfusion is unknown. Recently Shawn et al. reported the efficacy of Mirasol PRT system in reducing SARS-CoV-2 (Chinese derived isolate, USA-WA1/2020) strain in plasma and platelets without impairing product quality e.g.: antibody function [20]. During a pandemic, pathogen reduction approach may provide an important first line of defense against the transfusion transmission of an unknown outbreaking agent along with reducing residual risk of co-infections.

SARS-CoV-2 is a pathogen characterized by frequent mutations since its first isolation in December 2019, prone to develop different strains that can escape immunity. Our results show that riboflavin and UV light effectively inactivate different variants of SARS-CoV-2 as demonstrated by the results of the in vitro microtitration assay. These data confirm previous results obtained with MERS-CoV [21], suggesting that Mirasol system is effective against different coronaviruses. Furthermore, the comparison between the results of molecular assay after plasma inactivation with Mirasol system and virus isolation on VERO E6 show that the Mirasol PRT system is a safe and reliable method for the inactivation of Sars-CoV-2 contamination, highlighting the safety of CP therapy procedures for critically ill COVID-19 patients, maintaining the plasma quality.

5. Conclusion

Pathogen reduction Riboflavin and UV light treatment greatly reduced the virus titer of SARS-CoV-2 and its variants in human plasma, resulting in inactivated viruses unable to infect tissue culture and consequently not transmittable through transfusion. Although the risk of

Table 3
Viral isolation from pooled plasma sample after PRT.

	Sars-CoV-2 plasma isolation results					
Post UV treatment plasma Bag N#	6	10	14	19	25	32
virus isolation result	negative	negative	negative	negative	negative	negative
Strain	ITALIAN	CHINESE	ALPHA	GAMMA	BETA	DELTA

Viral genome detected in pooled plasma after pathogen reduction treatment (PRT) is not able to infect VERO E6 cells. At 120 h post incubation with VERO E6 cells, plates were scored and showed no cytopathic effect (CPE) due to inactivation of the viral genome.

viral transfusion transmission is suspected to be low, implementation of pathogen reduction technology might result in a better protection of plasma transfusion recipients during this and future pandemic.

Data availability

Data will be made available on request.

The data that has been used is confidential.

Funding

This work was supported by Ministero della Salute-Ricerca Finalizzata COVID-2020-12371817, Fondazione IRCCS Policlinico San Matteo Ricerca Corrente no. 80206 and Horizon 2020 European Project ATAC.

Authorship contributions

Conceptualization, P.C., E.P., C.D.F. and A.F.; methodology, A.F., C. D.F, J.C.S., and A.F.; software, A.F. and C.M.; formal analysis, S.D.V. and E.B.,; resources, F.B.; data curation, A.F. and I.C.; writing—original draft preparation, A.F. and E.P.; writing—review and editing, E.P., I.C., P.C., C.D.F. and F.B.; visualization, F.B.; investigation, D.T. and F.P.; funding acquisition, F.B. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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