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How Safe Is COVID-19 Convalescent Plasma?



To the Editor: We read with interest the systematic review and metaanalysis by Klassen and colleagues,¹ recently published in *Mayo Clinic Proceedings*. The investigators included in their analysis 30 randomized clinical trials (RCTs) and matched control studies, documenting that COVID-19 convalescent plasma (CP) transfusion, especially when it is given within 3 days of hospital admission, is associated with lower mortality of patients with COVID-19 compared with standard treatment. Adverse events analysis, in combination with benefits analysis, is essential to make an informed decision about health intervention. For this reason, we would like to add safety data to the analysis of Klassen and coworkers.¹

Through an online systematic search on PubMed and MEDLINE (range, January 1, 2020, to May 15, 2021), we identified 30 studies (14 RCTs and 16 non-RCTs with matched control group) that were downloaded and analyzed for safety data (Supplemental Table, available online at http://www.mayoclinicproceedings. org). Overall, severe (serious and grade 3-4) and thromboembolic adverse reactions were recorded and analyzed. In addition, we collected and evaluated the prevalence of overall and severe adverse reactions to CP transfusion in the selected studies. The study weight was calculated using the Mantel-Haenszel method, and statistical heterogeneity was assessed using the I^2 statistic. Measures of treatment effect were risk difference (RD) together with 95% CI. All calculations were conducted using Review Manager, version 5.4 software (Cochrane Collaboration).

The mean prevalence (standard deviation) of all and severe CP infusion—related adverse events was 2.1% (2.6%) and 0.7% (1.4%), respectively. As reported in

	(CP	Control			Risk difference	Risk difference
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% Cl	M-H, random, 95% Cl
1.1.1 RCT							
Al Qahtani	3	20	0	20	1.9%	0.15 [-0.02, 0.32]	
Bajpal	1	14	I	15	1.6%	0.00 [-0.18, 0.19]	
Balcells	4	41	0	0		Not estimable	
Li	2	52	0	51	11.8%	0.04 [-0.02, 0.10]	+
Libster	0	79	1	80	28.2%	-0.01 [-0.05, 0.02]	
O'Donnell	96	147	40	72	2.9%	0.10 [-0.04, 0.24]	
PlasmAr Study	153	228	66	105	4.3%	0.04 [-0.07, 0.15]	
Recovery trial	1433	5267	1427	5128	49.3%	-0.01 [-0.02, 0.01]	
Subtotal (95% CI)		5848		5471	100.0%	0.01 [-0.02, 0.03]	•
Total events	1692		1535				
Test for overall effect	t: Z=0.45 ((P=.65)	0 (1 .2.	5),1 25	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
	4	59	0	0		Not estimable	
Subtotal (95% CI)		59	0	Ő		Not estimable	
Total events	4		0	-			
Heterogeneity: Not a Test for overall effect	applicable t: Not appl	icable					
Total (95% CI)		5907	,	5471	100.0%	0.01[-0.02, 0.03]	•
Total events	169	96					Ĩ
Heterogeneity: Tau ² =0.00; Chi ² =7.80, df=6 (P=.25); I ² =23%					3%	0.5	
Test for overall effect: $Z=0.45$ ($P=.65$)						-0.5	
Test for subgroup differences: Net applicable							Favors CP Favors control
Test for subgroup dit	fference: N	Not appl	icahle				

FIGURE. Forest plots of comparison of convalescent plasma (CP) vs standard treatment. A, Outcome: all adverse reactions. Data are from 8 randomized clinical trials (RCTs) and 1 non-RCT. B, Outcome: severe adverse reactions. Data are from 9 RCTs and 1 non-RCT. C, Outcome: thromboembolic adverse reactions. Data are from 7 RCTs and 2 non-RCTs. MH, Mantel-Haenszel. *Figure continued on next page*.

	CP		Control			Risk difference	Risk difference			
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% Cl	М-Н,	fixed, 95%	CI	
1.2.1 RCT										
Al Qahtani	0	20	0	20	2.9%	0.00 [-0.09, 0.09]	-			
Bajpal	0	14	0	15	2.1%	0.00 [-0.12, 0.12]				
Balcells	3	41	0	0		Not estimable				
ConPlas-19 Study	6	38	7	43	5.9%	-0.00 [-0.16, 0.16]		_		
Li		51	0	52	7.6%	0.02 [-0.03, 0.07]				
Libster	0	79	0	80	11.7%	0.00 [-0.02, 0.02]		+		
O'Donnell	39	147	26	72	14.3%	-0.10 [-0.23, 0.04]				
PLACID trial	_3	235	0	229	34.2%	0.01 [-0.00, 0.03]		-		
PlasmAr Study	54	228	19	105	21.2%	0.06 [-0.04, 0.15]			_	
Subtotal (95% CI)		853		616	100.0%	0.00 [-0.03, 0.03]		•		
Total events	106		52							
Heterogeneity: Chi ² =	5.02, df=7	' (P=.66); I ² =0%							
Test for overall effect	:Z=0.25 (P=.81)								
1.2.2 Non-RCT										
Panna	1	59	0	0		Not estimable				
Subtotal (95% CI)		59	0	ñ		Not estimable				
Total events	1	57	0	0		Notestimable				
	ا		0							
	ipplicable									
lest for overall effect	: Not appi	icable								
Total (95% CI)		912		616	100.0%	0.00[-0.03, 0.03]		•		
Total events	107		52							
Heterogeneity: Chi ² =	5.02, df=7	' (P=.66)); I ² =0%			_0.5	_0.25	0	0.25	
Test for overall effect: $7=0.25$ ($P=.81$)					-0.5	5.25 F aura C	, -	0.2J	0.5	
Test for subgroup diff	Tact for subgroup differences: Not applicable						Favors Ch	' Fav	ors control	
B	ici ci ices. I	vot appi	icable							

	(P	Con	trol		Risk difference	Risk o	difference	
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95% Cl	M-H, fiz	xed, 95% Cl	
1.3.1 RCT									
Al Qahtani	0	20	0	20	0.4%	0.00 [-0.09, 0.09]			
ConPlas-19 Study	I	38	2	43	0.7%	-0.02 [-0.10, 0.06]			
Li	0	52	0	51	0.9%	0.00 [-0.04, 0.04]		+	
Libster	0	79	1	80	1.4%	-0.01 [-0.05, 0.02]	-	-	
O'Donnell	6	147	3	72	1.7%	-0.00 [-0.06, 0.06]	-	+-	
PlasmAr Study	4	228	0	105	2.6%	0.02 [-0.00, 0.04]			
Recovery trial	73	5267	87	5128	92.3%	-0.00 [-0.01, 0.00]			
Subtotal (95% CI)		5831		5499	100.0%	-0.00 [-0.01, 0.00]			
Total events	84		93						
Heterogeneity: Chi ² =	3.75, df=6	(P=.71); I ² =0%						
Test for overall effect	:Z=1.17 (P=.24)							
1.3.2 Non RCT									
Balcells	0	41	0	0		Not estimable			
Duan	0	10	0	0		Not estimable			
Subtotal (95% CI)		51		0		Not estimable			
Total events	0		0						
Heterogeneity: Not a	pplicable								
Test for overall effect	: Not appl	icable							
Total (95% CI)		5882	2	5499	100.0%	-0.00[-0.01, 0.00]			
Total events	84		93			Γ	1	1	
Heterogeneity: Chi ² =	:375 df=6	(P = 7)	$1^2 = 0\%$			-0.5	-0.25	0 0.25	0.5
Test for overall effect: $7=1.17$ ($P=24$)						Favors CP	Favors control		
Test for subgroup diff			icable						
	ierences. r	чог аррі	ICADIE						
0									
GURE. (continued).									

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Figure A and B, treatment with CP did not increase the risk of overall adverse events (RD, 0.01; 95% CI, -0.02 to 0.03; P=.65) and severe adverse events (RD, 0.00; 95% CI, -0.03 to 0.03; P=.81) compared with standard treatment. Similarly, the rate of thromboembolic events did not differ between the study groups (1.4% in the CP arm vs 1.7% in the control arm; RD, 0.00; 95% CI, -0.01 to 0.00; P=.24; Figure C). In addition, the funnel plot of comparison of all 3 outcomes (all, severe, and thromboembolic adverse reactions; Supplemental Figure, available online at http:// www.mayoclinicproceedings.org) appeared to be symmetric, suggesting a substantial homogeneity among the included studies and the lack of publication bias.

In conclusion, the results of this updated meta-analysis confirm the safety of CP transfusion and, in particular, document the very low rate (0.7%) of CP transfusion-related serious adverse reactions, similar to that reported in the large US Expanded Access Program.² Differing from the previous systematic reviews, we have focused our analysis on the CP-related thromboembolic risk, considering the particular critical setting of COVID-19, with a hyperinflammatory and hypercoagulative state, and the concerns from some clinicians.³ After a careful analysis of the published literature, we can conclude that the addition of CP to the COVID-19 treatment does not increase the patients' thromboembolic risk. Finally, we personally think that considering the lack of valid anti-COVID-19 therapies, the relatively low costs, and the high safety profile, CP collection and use should be endorsed and implemented by governments of developing and developed countries, without waiting for conclusive evidence of its efficacy.4

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinic proceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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In Reply—How Safe Is COVID-19

Convalescent Plasma?

To the Editor: We would like to thank Franchini and Cruciani for their letter in response to our systematic review and meta-analysis studying the effect of convalescent plasma therapy on the mortality of patients diagnosed with coronavirus

disease 2019 (COVID-19).¹ This letter highlights important new metaanalytical data based on 30 controlled studies (including 14 randomized clinical trials) demonstrating that convalescent plasma transfusion does not increase the risk of adverse events, including thromboembolic events, compared with patients diagnosed with COVID-19 who either were not transfused or were transfused with standard fresh frozen plasma. This new safety analysis supports the viewpoint that human convalescent plasma has a favorable risk-benefit ratio, particularly when it is reviewed in the context of the mosaic of evidence supporting some degree of effectiveness of convalescent plasma therapy for COVID-19.² Taken as a whole, these data support the continued use of convalescent plasma as the COVID-19 pandemic endures, especially in regions with limited vaccine access and in immunocompromised patients who cannot mount effective immune responses to vaccines.³

At the onset of the COVID-19 pandemic, several theoretical safety risks regarding convalescent therapy were plasma raised. the potentiation including of COVID-19 respiratory deterioration through antibody-dependent enhancement or cytokine storms, transfusion-associated circulatory overload, and enhanced thromboembolic risk.⁴ However, the metaanalytical safety data presented in the letter by Franchini and Cruciani along with the consistent signatures of safety emerging from worldwide use of convalescent plasma, including in the United States under the Expanded Access Program and Emergency Use Authorization. have generally allayed these safety concerns.^{5,6} Convalescent plasma safety can