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REVIEW

TRANSFUSION

Impact of different pathogen reduction technologies on the biochemistry, function, and clinical effectiveness of platelet concentrates: An updated view during a pandemic

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Abstract

Standard platelet concentrates (PCs) stored at 22°C have a limited shelf life of 5 days. Because of the storage temperature, bacterial contamination of PCs can result in life-threatening infections in transfused patients. The potential of blood components to cause infections through contaminating pathogens or transmitting blood-borne diseases has always been a concern. The current safety practice to prevent pathogen transmission through blood transfusion starts with a stringent screening of donors and regulated testing of blood samples to ensure that known infections cannot reach transfusion products. Pathogen reduction technologies (PRTs), initially implemented to ensure the safety of plasma products, have been adapted to treat platelet products. In addition to reducing bacterial contamination, PRT applied to PCs can extend their shelf life up to 7 days, alleviating the impact of their shortage, while providing an additional safety layer against emerging blood-borne infectious diseases. While a deleterious action of PRTs in quantitative and qualitative aspects of plasma is accepted, the impact of PRTs on the quality, function, and clinical efficacy of PCs has been under constant examination. The potential of PRTs to prevent the possibility of new emerging diseases to reach cellular blood components has been considered more hypothetical than real. In 2019, a coronavirus-related disease (COVID-19) became a pandemic. This episode should help when reconsidering the possibility of future blood transmissible threats. The following text intends to evaluate the impact of different PRTs on the quality, function, and clinical effectiveness of platelets within the perspective of a developing pandemic.

KEYWORDS

in vitro quality, pathogen reduction technologies, platelet concentrates

1 | INTRODUCTION

The safety procedures to prevent transfusion-related pathogen transmission start with careful screening of donors and include regulated blood testing for known pathogens. Tests introduced for the detection of human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C virus (HCV) in donor samples have dramatically

improved the safety of transfused blood products.[1] Additional tests have been progressively implemented to detect other blood-borne viral and parasitic infections. Traditional methods of donor screening and mandated testing have limited ability to prevent emerging infectious agents like the dengue or chikungunya viruses and parasites such as *Plasmodium falciparum* or *Leishmania*, from reaching blood therapeutic products.[2] It is increasingly complex and impractical to respond to new pathogen threats by simply adding additional detection tests,[3] and the risk of bacterial contamination during platelet storage remains significant. Pathogen reduction technologies (PRTs) provide an additional safety layer to reduce the risk of emerging infections undetectable through current testing.[1,4]

PRTs initially introduced for plasma products[5] have substantially improved safety, and their potential deleterious action on the plasma quality has not been challenged. PRTs were later adapted to treat platelet products with a triple-intent: to prevent bacterial contamination,[6] to prolong the shelf life of platelet concentrates (PC) up to 7 days, and to provide an additional safety layer against emerging blood-borne infectious diseases. In contrast to their detrimental actions on the quality of plasma products, PRT-induced changes in platelet products are intensely scrutinized. The following text will attempt to place in perspective the advantages and disadvantages of PRT applied to platelet products. The contents of this review are of particular relevance during the COVID-19 pandemic as these technologies may protect the blood supply from future blood-borne epidemic threats.

2 | METHODOLOGIES—AVAILABILITY AND EFFECTIVENESS IN PATHOGEN REDUCTION

Three technologies are currently available for pathogen reduction in PCs, each utilizing exposure to UV light. Two of these technologies, INTERCEPT and MIRASOL, introduce a photosensitive compound to PCs before activation with UV. The third technology, THERAFLEX, uses short-wave UV alone.

The INTERCEPT Blood System (Cerus Corporation, Concord, CA, USA) obtained the CE mark for platelets in 2002. This technology uses amotosalen as a photosensitizer, before its activation by exposure to UVA illumination (320–400 nm). A removal process reduces residual amotosalen to trace levels avoiding possible toxicity.[1,7] INTERCEPT PRT, in use for >18 years in over 30 countries, has been approved for platelets by the US Food and Drug Administration (FDA).

MIRASOL (Terumo BCT, Lakewood, CO, USA)[8] uses riboflavin (vitamin B2) as a photosensitizer, followed by activation at UVA-UVB spectral regions (265–370 nm). Riboflavin does not need to be removed from the exposed product. This methodology obtained the CE mark for platelets in 2007 and is being used in >20 countries.

THERAFLEX UV-Platelets (MacoPharma, Mouvaux, France), developed more recently, does not require a photosensitive agent. This PRT uses short-wave ultraviolet light (UVC wavelength range 200–280 nm) applied to PCs under agitation. This technology obtained CE mark for platelets in 2009 and was recently evaluated in the clinical setting.[9]

PRTs are unlikely to sterilize the transfusion product to the point of zero risk of pathogen transmission,[10] and therefore, the "reduction of pathogen load" is a better definition of their objective.[11,12] Extensive literature has confirmed that the PRTs referred to in this text have demonstrated substantial benefits by inactivating high levels of a range of clinically relevant bacteria, viruses, and parasites, in both plasma and PCs. Comprehensive reviews on the three technologies are available.[13–19] Furthermore, these PRTs have shown effectiveness at mitigating transmission of West Nile virus and coronaviruses.[4,19–21] MIRASOL was recently shown to be effective at reducing SARS-CoV-2 in plasma, platelets, and whole blood.[22,23] INTERCEPT does also efficiently inactivate SARS-CoV-2 in human plasma and similar actions could be expected for THERAFLEX.

3 | IN VITRO QUALITY OF PLATELET CONCENTRATES

The term "storage lesion" was coined to describe a series of structural and functional alterations during the storage of red cells and has also been applied to PCs. This lesion starts early during the process of collection, increases progressively during storage, and compromises the in vivo function of transfused platelets.[24] Improvements in plastic containers, additive solutions, and collection procedures have alleviated the problem, but have not substantially improved the quality of PCs stored for longer periods.

Tests to evaluate the in vitro quality of stored platelets fall in two major groups: (a) indirect parameters of platelet quality (platelet count, metabolism, structure, presence of receptors or activation markers);or (b) direct measurements of adhesive, aggregating, and procoagulant activities of platelets.[25] Metabolic changes in PCs stored for 5 days are characterized by reduction in glucose levels, augmented lactate production, and pH lowering, indicating enhanced anaerobic metabolism. These metabolic changes are associated with alteration of platelet morphology, reductions in glycoproteins,

enhanced expression of platelet activation- and apoptotic markers, and reduced functional responses.

For the purpose of this review, we have identified a total of 53 relevant publications, 20 evaluating the in vitro quality of PCs subjected to INTERCEPT,[26–45] 23 using MIRASOL,[46–68] 5 using THERAFLEX,[19,69–72] and 5 studies that have compared INTERCEPT versus MIRASOL.[73–77] Details of these studies are summarized in the Supplemental Table 1.

3.1 | Impact of PRTs on biological and metabolic indicators

INTERCEPT enhances anaerobic metabolism in treated PCs. Increased glucose consumption, lactate accumulation, and acidification are consistently reported in buffy-coat[28–30,32,35,36,38,39] or apheresis PCs[27,37–39,41–43] after exposure to INTERCEPT. These changes were followed by alterations in platelet morphology, slight reductions in swirling, and altered resistance to hyperosmotic shock (HSR). Moderate reductions in GPIb with the activation of GPIIb-IIIa,[37,38,42,43] with enhanced expression of P-selectin, have been confirmed by numerous investigators.[27,28,30–33,35,36,38,39,42–45] The increased expression of P-selectin parallels enhanced signs of apoptosis with the exposure of anionic phospholipids, binding of annexin-V, and release of microparticles.[32,33,35,39,41,42,45] Introduction of classic or newer formulations of platelet additive solutions (PASs) does not prevent the deterioration observed after INTERCEPT.[28,35,37,39,42–45] A reduction of citrate concentration in PAS may slightly reduce platelet activation.

Alterations induced by MIRASOL are similar to those observed with INTERCEPT—increased anaerobic metabolism and subsequent acidification after treatment of buffy-coat,[52–54,56,63,66,68] or apheresis-derived PCs.[46,48–51,55,57–59] Metabolic changes were accompanied by morphological alterations, reductions in swirling, and altered HSR.[48,52,53,55,57–60,63,64,66,68] Moderate reductions in GPIb with the activation of GPIIb-IIIa have been similarly reported after MIRASOL exposure,[48,52,53,55,57–60,63,64,66,68]

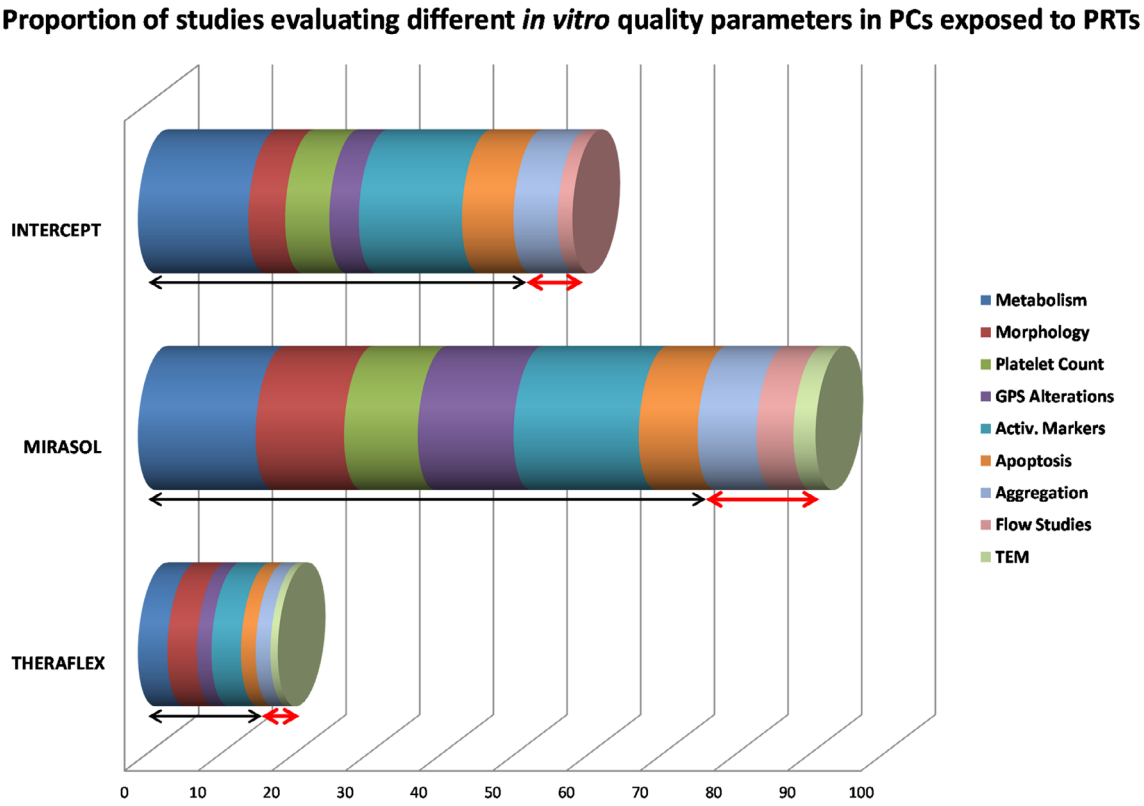

FIGURE 1 Bar diagrams represent comparative percentages of in vitro quality parameters assessed in the publications evaluated in this review. As shown by the double pointed arrows the majority of studies have concentrated on indirect markers of platelet quality (black arrows). Because of their higher complexity, fewer proportions of studies have concentrated on the evaluation of functional parameters of platelets in the pathogen-reduced concentrates (red arrows). Differences in qualitative aspects explored for a certain PRT that have not been evaluated by other technologies may depend on tests available at the time of the studies or expertise of research groups with them. Data were compiled from a total of 20 publications on INTERCEPT, 23 on MIRASOL, 5 on THERAFLEX, and 5 studies that have compared INTERCET versus MIRASOL (GPS = glycoproteins)

TABLE 1 In vitro evaluations of adhesive, aggregating, or procoagulant platelet functions in platelet concentrates exposed to various PRTs

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
8-MOP Procaccini et al.[26]	Volunteers, platelet-rich plasma exposed to psoralen + UVA	—	—	—	—	—	ADP ↓, Coll↓ Risto, Arachidonic Acid	Abnormal platelet aggregation to ADP and Coll with elevated concentrations of 8-MOP	No detectable abnormality in platelet function in vivo after ingestion
INTERCEPT versus Control Picker et al.[30]	Buffy-coat 7 days	Glucose ↓1–7 days Lactate ↑ 3–7 days pH ↓ 1–7 days	HSR = 1–7 days Swirl = 1–7 days	—	CD62 ↑ 3–7 days	—	Risto ↓ 3–7 days	Aggregation decreased significantly in all PCs during storage, with lower values in PRT-units	Platelet count ↓ PRT caused various alterations of in vitro data. Although significant these changes were relatively modest.
INTERCEPT Different bags Jansen et al.[32]	7–11 days PAS-III	Glucose ↓ 7 days Lactate ↑↑ 4–7 days ATP ↓ 7 days	HSR = 2–7 days	—	CD62 progress from 2–11 days (n.s)	ANV ↑ from 2–11 days	ADP = (low) Coll ↓ 2,7 days Thrombin ↓↓ 2,4 days	Significant reduction in aggregation capacity with collagen and thrombin	Characteristics of containers could affect the in vitro quality of PCs subjected to PRT
INTERCEPT Lozano et al.[34]	Buffy-coat 5–7 days	—	—	—	—	—	Global Test Perfusion	Adhesive and aggregating capacities under flow conditions remained well preserved for up to 7 days	Platelet Count ↓ 10% after 5 days.
INTERCEPT Johnson et al.[36]	INTERCEPT versus Control Buffy-coat 7 days SSP+	Glucose ↓↓ Lactate ↑ pH ↓, ATP ↓	—	—	CD62 ↑ 5–7 days	Cytokines RANTES ↑	Collagen ↓↓ ADP=	Alterations in aggregating responses were more evident from day 5 of storage.	Platelets suspended in SSP+ with reduced plasma carryover are of suitable in vitro quality following PRT.

TABLE 1 (Continued)

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
INTERCEPT Abonnenc et al.[40]	INTERCEPT versus Control or UV Buffy-coat PAS Intersol	—	HSR ↓ 7 days	PAC-1 ↑ 7 days CD42 ↓ 7 days	CD62 ↑ 7 days	ANV JC-1 ↓	ADP ↓ 7 days Coll ↓ 2 days ↑ 7 days AA = TRAP = + Static adhesion on fibrinogen	Variable alterations of PLT aggregation. % of adherent platelets increased on days 4 and 7 compared to control units.	Platelet count ↓ UV alone make negligible contributions to the changes in aggregation observed
INTERCEPT Stivala et al.[41]	INTERCEPT versus Control Apheresis 7 days	—	—	CD42b ↓	—	ANV ↑ =	Collagen ↓↓ 1 day Thrombin ↓↓ 1 day + Microfluidic on collagen and VWF ↓d	Reduced platelet aggregation. Reduction in platelet coverage on Coll and VWF surfaces In vivo Survival	Phosphorylation p38 ↑↑ (apop) Bak↑↑ Enhanced apoptosis and accelerates clearance
MIRASOL Perez-Pujol et al.[47]	versus Control Apheresis Impact of UV intensities 6.2 or 12.3 J 5 days	—	—	↓ CD42 GPIb 5 days 12.3 J/ml	CD62 ↑3–5 days 12.3 Jul/ml CD63 ↑ 3–5 days 6.2 or 12.3 J/ml	ANV ↑3–5 days 12.3 Jul/ml	Global Tests Perfusion studies with blood flowing through damaged vessel segments	Treatment with 6.2 J/ml preserve adhesive and cohesive functions of platelet to levels compatible with those observed in control PCs.	Platelet count ↓ 3–5 days Alterations more pronounced with 12.3 J/ml
MIRASOL Picker et al.[48]	versus Control or G-irradiation Apheresis 7 days	Glucose ↓↓ Lactate ↑↑ pH↓ 5–7 days	Swirl ↓↓ 5–7 days HSR ↓↓ 1−/	—	CD62↑↑ 5–7 days	—	↓ Risto	—	Platelet count ↓↓ (due to dilution) modifications similar to G-irradiation M slightly better than historical data with I
MIRASOL Ostrowski et al.[54]	versus Control Buffy-coat 8 days	pH ↓ 3–8 days	Swirl ↓ = control MPV ↑ 2–8 days	—	—	—	ADP ↓ = Coll ↓ 6–8 days TRAP ↓↓ 3–8 days + TEG	Impaired aggregation. Reductions in maximum clot strength	Platelet count ↓ 7–8 days PRT significantly reduced platelet aggregation, but

(Continues)

TABLE 1 (Continued)

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
							MA 7–8 days	(maximum amplitude, no changes in initial fibrin formation, clot growth rate (alpha)	had a minimal influence on clot formation.
MIRASOL Galan et al.[55]	versus Control Apheresis 7 days various PAS-III versus PAS-IIIM	Glucose ↓ 3–7 days Lactate ↑ 3–7 days pH ↓ 5–7 days variations among PAS	Swirl ↓ 5–7 days	GPIb ↓ 7 days GPIIb-IIIa ↑ 7 days	CD62 ↑ 3 days CD63 ↑ 7 days	ANV ↑ 3, 7 days	Global test Perfusion studies Blood flowing through damaged vessel segments	PCs stored in PAS presented similar reactivity than that observed for untreated PCs. Moderate reductions in cohesive properties in PRT-PAS-III PCs, but not in PRT-PAS-IIIM PCs, at day 7.	Quality was reasonably preserved in PCs stored in PAS for 5 days. PAS-IIIM better than PAS-III at 7 days
MIRASOL Johnson et al.[56]	versus Control Buffy-coat 7 days PAS-IIIM	Glucose ↓ 2–7 days Lactate ↑ 2–7 days pH ↓ (5–7 days)	—	GPIIIa =	CD62, CD63 ↑ 2–7 days	ANV ↑ 2–7 days Mitochondrial permeability = CD40L =	ADP = Coll ↓ 5–7 days	Platelet aggregation with ADP low but maintained through storage. Reduced platelet aggregation with Coll.	M treatment and storage in PAS is no more detrimental than storage in plasma.
MIRASOL Picker et al.[58]	versus Control Apheresis 8 days PAS SSP+	Glucose ↓ 1–8 days Lactate ↑ 1–7 days pH ↓ 1–8 days) ATP ↓ 8 d	Swirl ↓ 7–8 days HSR ↓ 8 days	—	CD62 1–8 days	ANV ↑ 5–8 days JCT-1 ↓ 8 days	Coll ↓ 1 day= 5–8 days TRAP ↓ 5–8 days + Cone-Plate Impact-R	Reduced platelet aggregation. Surface covered in the Impact-R decreases with storage time, but similar to controls	Platelet Count ↓ 8 days. Results with M in PAS were comparable to plasma preserving ATP and mitochondrial function.

TABLE 1 (Continued)

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
MIRASOL Middelburg et al.[60]	versus Control Buffy-coat 10 days	—	Thrombolux ↓ 6–10 days	—	CD62↑ 5–8 days	ANV ↑ 2–10 days	ADP ↓ 2–10 days Coll↓ 2–10 days TRAP ↓ 2–10 days + TEG Angle = ↓ Max Ampl	Impaired aggregation responses. Maximum amplitude in TEG started lower and decreased faster after PRT. No differences between PRT-PLTs and untreated PLTs for the angle,	Plat count ↓ Platelet quality decline during 10-day storage of standard and M-treated PCs in plasma.
MIRASOL Zeddies et al.[61]	versus Control Buffy-coat 8 days	—	—	CD42b 5–8 days CD41 = CD61 ↑ 5 days	—	—	PMA ↓ Convulxin ↓ RI ↓ day 8 + Platelet spreading on Coll	Aggregation to convulxin and ristocetin was significantly lower and influenced by storage time. Spreading of platelets o Coll was reduced	M leads to hyperreactive PLTs, which aggregate and degranulate over storage time.
MIRASOL Terada et al.[62]	versus Control Apheresis 5 days	—	—	PAC ↓-1 1–5 days CD41 ↑ 3–5 days Fgn ↑ 1–5 days	—	—	Global test Perfusion studies Evaluated Flow studies measuring platelet retention on collagen columns	The retention rate of the PRT-treated PLTs was significantly higher than that of the control PLTs throughout the storage period	PRT leads to the enhancement of thrombus formation on collagen, which is related to the activation status of αIIbβ3,
MIRASOL Van Der Meer et al.[63]	versus Control Buffy-coat PAS SSP+ 8 days	Glucose ↓ 6–8 days Lactate ↑ 6–8 days	HSR ↓ 6–8	—	CD62 ↑ 6–8 days	ANV ↑ 6–8 days JC-1 ↓ 6–8 days	Coll ↓ 6–8 days ADP ↓ 6–8 days	Aggregation was lower immediately after preparation. A	Storage in SSP+ after PRT has some beneficial action on pH, lactate

(Continues)

TABLE 1 (Continued)

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
		pH ↓ 6–8 days						further decline was observed being more pronounced for the units in SSP1	production an ANV expression
MIRASOL Ignatova et al.[64]	versus Control or G-irradiation Apheresis Plasma SSP+ 5 days	—	Alterations 3–5 days	PAC-1 ↑1–5 days	CD62 ↑ 1–5 days	ANV ↑ 1–5 days Mitochondrial potential ↓ 0–5 days	Coll ↓ 3–5 days	On the day 3, 50% of Mirasol-treated units did not respond to activation;	Platelet Count ↓ (dilution) Clinical interventions in patients lower number of febrile reactions wit SSP+ stored PCs
MIRASOL Terada et al.[65]	Apheresis Before and after	—	—	—	—	—	Thrombus Formation on collagen Microfluidic Cone-plate Assay -	PRT leads an immediate enhancement of PLT thrombus formation and thrombus stability on collagen.	Enhanced thrombus formation disappeared in the presence of aIIbb3 inhibitor.
MIRASOL Lachert et al.[66]	versus Control Buffy-coat 5 days	Glucose ↓ 3–5 days pH ↓ 1–5 days	HSR =	CD42b =	CD62 ↑ 1 day	B-trombo-globulin ↑	ADP ↓ =	Aggregation dropped after PRT, and further decreased in both groups at d 5 No statistical differences observed respect to control group	Platelet count ↓ Alterations in parameters after M comparable to those in control group
MIRASOL Ballester-Servera et al.[68]	versus Control Buffy-coat T-PAS + 14 days	Glucose ↓ 1–14 days Lactate ↑ 3–14 days pH ↓ 3–14 days	Swirl ↓ 7–14 days	—	—	—	TEG R = Angle ↓ 7–14 days MA ↓ 7–14	TEG detects moderate alterations in maximal amplitude and angle at later storage times	PRTs accelerate platelet storage lesion.

TABLE 1 (Continued)

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
MIRASOL Abbonnenc et al.[67]	versus Control or UV Buffy-coat PAS+ versus PAS-IIIM 10 days	Glucose ↓ 5–9 days Lactate ↑ 5–9 days pH ↓ 5–9 days for UV or M	HSR ↓ 2–7 days UV, M	PAC-1 ↑ 2–7 days UV, M CD42b ↓ =	CD62↑ 2–7 days UV, M	ANV↑ 5–7 UV, M	Coll+Epi ↓ 7 days ADP + Epi ↓ 2–7 days	The use of Epi, potentiated aggregating responses, but aggregation of PRT-PLTS was reduced at day 7.	Platelet count ↓ with UV and PRT. PLTs more activated, showed, higher apoptosis markers and a lower HSR. PAS-IIIM preferable UV radiation alone is causing platelet lesions
INTERCEPT MIRASOL Picker et al.[73]	Apheresis 8 days PAS	Glucose ↓ = C Lactate ↑ 5–8 days pH↓ 1–8 days ATP↓ 8 days for I	Swirl ↓ 7 days for I or M HSR	—	CD62 ↑↑ 5–8	ANV↑↑ 5–8 JC-1 (mitochondrial enzymatic activity)) Altered 7–8 days	Coll ↓↓ 7–8 days TRAP-6 ↓ 5–8 days for I or M	M was significantly superior over I for HSR, aggregation with TRAP-6	PRT-treated PLTs remained comparable to untreated units throughout 7 days of storage. Slightly better ATP maintenance and in vitro function for M during the last storage period
INTERCEPT MIRASOL Picker et al.[75]	Triple dose Apheresis	—	—	CD41 ↑ 5–8 days	CD62 ↑ 5–8 days	—	TRAP ↓ 1–8 days Cone and Plate	Aggregation ↓. no differences between study groups. Shear-induced adhesion significantly decreased in I units remained stable in M units during the entire 8-day observation period.	Irrespective of storage-related changes in PLT activation and turbidometric aggregation response, M-based PRT seemed to benefit shear-induced PLT adhesion

(Continues)

TABLE 1 (Continued)

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
INTERCEPT, MIRASOL or UV alone Abonnenc et al.[76]	Buffy-coat 8 days PAS Intersol	Glucose ↓ 5–7 days Lactate ↑ 5–7 days pH ↓ 5–7 days for M or UV LDH ↑ 5–7 days for I	HSR ↓ 2 7 days for M or UV	PAC-1 ↑ 2,7 for I PAC-1 ↑↑ 2, 7 for M or UV	CD62,↑ 2, 7 days for M or UV	ANV ↑ 2, 7 days for M or UV JC-1 ↓ (mitochondrial) 2, 7 days for M or UV	Adhesion on fibrinogen ↑ from day 2, for M or UV	The capacity of riboflavin/UVB- and UVB-treated PLTs to adhere to fibrinogen decreased at the end of the storage period.	Platelet storage lesion is increased by M or UV compared to untreated PCs or I. These lesions are caused by the UVB radiation alone.
INTERCEPT MIRASOL or G-Irradiation Van Aelst et al.[77]	7 days	—	—	GPIb ↓ PAC- 1 Altered	CD 62 ↑	ANV ↑	Coll ↓ 2–7 days, TRAP=, RI ↓ 2–7 days M Coll ↓ 2–7 days, TRAP↓ 2–7, RI ↓ 2–7 days microfluidic chambers over immobilized collagen or VWF	Both PRTs decreases the rate of thrombus formation in microfluidic flow chambers	I M mainly accelerate platelet storage lesion
THERAFLEX Mohr et al.[19]	Buffy-coat UVC UVB versus G-irradiation 6 days PAS-IIIM	Glucose ↓ 6 days	Swirl = HSR =	—	CD62 ↑ 6 days	ANV =	Coll ↓ 4–6 days	Aggregation with low concentrations collagen was impaired UVC UVB versus γ-irradiation Proteomic and Pathogen inactivation studies	Spontaneous aggregation 6 days. HIV-1 was only moderately inactivated
THERAFLEX Johnson et al.[71]	versus Control Buffy-coat 7 days SSP+	Glucose ↓ 7 days	HSR ↓ 1–7 days	PAC-1 ↑ 1–7 days	CD62 =	ANV ↑ 7 days Mitochondrial membrane =	ADP = Coll = +	Platelet aggregation was reduced but not	Reducing the plasma <30% did not significantly

TABLE 1 (Continued)

References	PRT	Metabolism	Morphology	Flow Cytometry/activation markers			Functional tests	Comment	Conclusions
				GPs	CD62	Other			
		Lactate ↑ 1–7days pH ↓ 5–7 days ATP =				Procoagulant activity supernatant ↓	TEG <30 plasma = A	different from controls. TEG parameters were not affected by UVC treatment.	affect the overall quality of platelets following T

Note: 8 MOP = psoralen + UVA precursor of INTERCEPT PRT; PAS, PAS-III, PAS-IIIM, Intersol, SSP+, Intersol, = Platelet additive solution with different compositions; ↓ or ↑ indicate marked reductions, often statistically significant, in the mentioned parameter; MPV = Mean Platelet Volume; HSR = Hypertonic Shock Resistance; CD42b = GPIb; CD41 = GPIIb; CD41/CD61 = GPIIb-IIIa; PAC1 = Activated GPIIb-IIIa; CD40L = CD40 ligand; CD62P = p-Selectin; ANV = Annexin- V; JC-1 = Mitochondrial enzymatic activity; ADP = Adenosin diphosphate; Coll = Collagen; Ri = Ristocetin; TRAP = Thrombin receptor activating peptide; M = MIRASOL; I = INTERCEPT.

with enhanced expression of platelet activation markers and indicators of apoptosis[46–53,55–60,63,64,66] The type of bag and cell separator used may have some impact on quality parameters.[59] Newer formulations of PAS may partially mitigate the effects of PRT when results are compared with those in classic PAS,[63] but overall do not have a critical effect on the in vitro quality alterations.[50,53,55–58,63,64,68]

Information on the impact of the newer THERAFLEX technology on the quality of platelets is sparse and mainly based on buffy-coat PCs[19,69–72] (Figure 1). Metabolic and morphological changes in treated platelets follow the pattern described earlier for INTERCEPT or MIRASOL and run with moderate alterations in swirling and reduction of the HSR. Changes in the presence of glycoproteins, enhanced expression of P-selectin, and increased binding of annexin-V have also been reported,[69–72] although they seem—relatively—less pronounced than with INTERCEPT or MIRASOL.

3.2 | Modifications of functional responses

Table 1 summarizes a selected group of studies focused on the direct functional (adhesive, aggregating, or procoagulant) integrity of platelets in PCs subjected to PRT. Several studies have reported decreased aggregating response of platelets to ADP, collagen, or thrombin after INTERCEPT treatment,[30,32,36,41] and to ADP, collagen, TRAP, or other agonists after MIRASOL treatment.[54,56,58,60,61,63,64,66] Aggregating responses to ADP and collagen were reasonably preserved after THERAFLEX,[19,71] although the published evidence with this technology is sparse relative to INTERCEPT or MIRASOL PRT (Figure 1).

Studies under flow conditions allow for a more precise evaluation of adhesive and cohesive functionalities of platelets. In a model where reconstituted blood is perfused over damaged vascular segments, adhesive and aggregating properties of INTERCEPT-treated platelets were similar to control PCs and were well preserved for up to 7 days of storage.[34] Stivala et al., however, reported that INTERCEPT reduced the adhesion and aggregation of platelets to von Willebrand factor-collagen substrata.[41] MIRASOL-treated buffy-coat PCs preserved adhesive and cohesive functionalities comparable to the respective control PCs.[47] Galan et al. evaluated the effect of MIRASOL on apheresis platelets during storage in PAS-III or PAS-IIIM in studies with flowing blood.[55] Functional properties were preserved in PRT-treated concentrates stored in PAS for 5 days, with PAS-IIIM providing better preservation than PAS-III after 7 days of storage. In the cone-plate

approach,[58] MIRASOL reduced platelet aggregation and surface coverage, with the responses decreasing with storage time similar to controls. In another set of flow studies measuring platelet interactions with collagen substrata, the authors found MIRASOL treatment enhanced platelet retention[62] and increased thrombus formation on collagen surfaces.[65] The enhanced thrombus formation disappeared in the presence of GPIIb-IIIa inhibitors indicating an early activation of this receptor by this PRT. THERAFLEX attenuated thrombus formation kinetics *in vitro* in microfluidic flow chambers, but only at later stages of storage. Overall, these data suggest that the PRT-induced functional reductions noted in in vitro aggregation assays are less pronounced in reconstituted blood samples subjected to shear rate conditions.

Thromboelastometric assays have been applied more recently to the global evaluation of the quality of PCs. These assays measure the viscoelastic properties of clot formation and subsequent lysis under low shear conditions and thereby reveal the contribution of thrombin generation, fibrinogen, platelet glycoproteins, and cytoskeletal assembly to the clot formation process. Studies have reported reductions in maximum clot strength in buffy-coat PCs stored in PAS solution exposed to MIRASOL.[54,60,68] In a separate study, the viscolelastic parameters were minimally affected by THERAFLEX.[71] Viscolelastic parameters require appropriate levels of fibrinogen and platelets in the test samples. Some of the cited studies used PCs stored in PAS that affect fibrinogen levels. Other studies have found alterations in viscoelastic parameters when storage time was extended beyond reasonable storage limits (14 days).[68] Moreover, investigations using thromboelastography on buffy-coat PCs found that this methodology may lack sensitivity to detect normal storage-related quality changes.[78]

3.3 | Comparative studies among PRTs

Picker et al.[48] compared changes in quality parameters of PCs exposed to MIRASOL with those induced by gamma-irradiation and found the results with MIRASOL slightly better than their historical data with INTERCEPT.[30] They concluded that PRT-treated apheresis PCs remained comparable to untreated ones in terms of integrity and morphology. Few studies have objectively compared INTERCEPT and MIRASOL technologies.[73–77] MIRASOL was slightly superior to INTERCEPT for HSR and aggregation with TRAP-6.[73] Studies on shear-induced adhesion found significant differences in favor of MIRASOL versus INTERCEPT.[75] In contrast, platelet storage lesion was increased in MIRASOL-treated PCs versus untreated ones in another study.[76] Interestingly, the latter study included a UV only arm as a control. The authors concluded that UV irradiation could be more accountable for the damaging actions of PRT than the riboflavin photosensitizer. In another study,[77] exposure to MIRASOL or INTERCEPT caused differential impairments in platelet aggregating responses, although both treatments caused a reduction of platelet thrombus formation under flow conditions. The authors hypothesized that MIRASOL mainly accelerated platelet storage lesion, while INTERCEPT interfered more directly with mechanisms of platelet activation.[77] Feys et al. have also suggested that INTERCEPT or MIRASOL may impair platelet functions through different biochemical mechanisms.[79] Although different mechanisms of action for the various PRTs, UV lengths, and photosensitizers are very likely,[40,67] the hypothesis of selective changes by one or another PRT does not seem widely substantiated. Extensive evidence from numerous studies (Supplemental Table) indicates that different PRTs result in a similar pattern of modifications in the in vitro parameters of treated PCs.

4 | CHANGES IN THE PLATELET PROTEOME

Proteomic studies on standard PCs indicate that 97% of the proteins remain unchanged during storage but proteins related to the cytoskeletal and apoptotic functions show some changes.[80] Schubert et al. identified 12 proteins,[81] involved in cytoskeletal reorganization either as binding proteins to the actin filaments or as regulatory proteins for actin polymerization. Other studies reported alterations in signaling pathways involving ROS and post-translational modifications on phosphorylation mechanisms.[82]

Study of proteomic changes induced by INTERCEPT in buffy-coat PCs found alterations of 23 and 58 proteins at days 1 and 5, respectively.[83] Only three proteins showed consistent changes after treatment and storage: platelet endothelial aggregation receptor 1 precursor, protein tyrosine sulfotransferase 2 and CLIC4, another protein associated with cytoskeletal reorganization, apoptotic mechanisms, and oxidative stress. Prudent et al.[84] reported a low impact on the proteome of INTERCEPT-treated platelets, affecting mainly proteins related to mitochondrial activity and oxidative stress. INTERCEPT PRT caused potential functional lesions involving the ADP receptor, cAMP synthesis, and PI_3K, all crucial for platelet activation and aggregation.

With MIRASOL technology, Schubert et al. identified 26 proteins differentially expressed at day 6 of storage versus day of production and treatment.[85] Proteins affected were also associated with the structure and

regulation of the cytoskeleton and with phosphorylation, of proteins linked to actin dynamics and regulation of GPIIb-IIIa activation. In treated apheresis PCs, Marrocco et al. investigated variations in protein profiles with gamma-irradiation or MIRASOL treatment.[86] According to this proteomic analysis, gamma-irradiation results in the acceleration of the PLT storage lesions and MIRASOL treatment only moderately exacerbated these phenomena. Salunkhe et al. found significant changes at the proteome level after MIRASOL that were essentially related to the functional aspects described to affect current PCs during storage.[87] In treated apheresis PCs, MIRASOL altered 26 unique proteins.[88] Interestingly, this study demonstrated for the first time that platelets can synthesize proteins despite riboflavin and UV treatment and suggested that platelets may possess a mechanism to protect their mRNA from damage by the PRT. Further studies on day 2 of storage in PCs prepared from buffy-coats in PAS exposed to MIRASOL found a high proportion of oxidations in platelet proteins with additional interference on several cytoskeletal proteins involved in platelet aggregation.[89]

Mohr et al. evaluated the impact of THERAFLEX UVC on the platelet proteome in comparison with UVB alone or gamma-irradiation.[19] The study found 67 proteins modified by UVB treatment, 48 by UVC, and 87 by gamma-irradiation, in the treated samples compared to controls. Proteome analysis revealed a common set of 92 protein spots affected by all three types of irradiation. Specific alterations were most pronounced for gamma-irradiation, followed by UVB and UVC.

In a comparative study, Prudent et al. investigated the oxidative damages produced by INTERCEPT and MIRASOL on model peptides.[90] MIRASOL was found to generate more oxidation than INTERCEPT, and triggered dysregulation of cell signaling, alteration of the cytoskeleton, and the redox metabolism.[82] Similar modifications had been reported in previous studies on INTERCEPT-treated PCs.[84] In another comparative review, the authors merged the key findings of the proteomic analyses of INTERCEPT-, MIRASOL-, and THERAFLEX-treated PCs.[91] The study concluded that all PRTs had a relatively weak impact on the overall proteome of platelets.

5 | A CRITICAL APPRAISAL OF THE IN VITRO DATA AND ITS SIGNIFICANCE

A bibliometric analysis of the proportion of studies evaluating different aspects of the in vitro quality of PCs exposed to PRTs reveals more abundant information on MIRASOL, with studies on qualitative aspects (glycoprotein alterations or thrombolelastometry) that are lacking for INTERCEPT or THERAFLEX (Figure 1). It should be noted that the extent of information available for a particular PRT technology does not correlate with its impact on the in vitro quality of treated platelet product. The bibliometric evaluation also reveals that the majority of studies have utilized indirect platelet quality surrogates, and few have used direct functional parameters, thus indicating that functional studies are more complex to perform.

Modifications of metabolic, functional, and proteomic parameters in PRT-exposed PCs are consistent with an acceleration of the classically described storage lesion. Despite the metabolic alterations, final pH and platelet number in PCs after PRTs still meet the criteria of regulatory authorities. Moreover, pO_2 and pCO_2 levels confirm proper gas exchange in the stored PCs, both control and PRT-treated.

Moderate quantitative modifications in the GPs detected by flow cytometry, despite significant, should not have dramatic impact on the hemostatic response of platelets. It is well established in heterozygotic forms of Bernard-Soulier's or Glanzmann's thrombasthenia that platelets that possess half the amount of GPIb or GPIIb-IIIa have normal hemostatic performance[92,93] It is possible that receptor-mediated signaling mechanisms affected by the storage and PRTs may have an additional impact on functional responses.[82,94] Increase in platelet activation markers in pathogen-reduced platelets is an indicator of the development of apoptotic mechanism. However, if these changes only represent natural apoptosis, they should not necessarily indicate a critical reduction in platelet function. Partially activated platelets can still be effective in the treatment of active bleeding.[95]

Overall, patterns of metabolic and functional alterations observed with different PRTs were indistinguishable. The impact of PRTs on the overall proteome of platelets is relatively low, with various studies indicating that PRTs accelerate the common storage lesion. Despite particular interpretations, a distinctive proteomic fingerprint has not been reported for any of the PRTs investigated until now. Interestingly, alterations of the proteomic and metabolic profiles in platelets exposed to PRTs are comparable or less than the ones observed in currently gamma-irradiated PCs.

6 | CLINICAL STUDIES

Preliminary studies with radio-labeled platelets given as autologous transfusions to healthy volunteers indicated that platelets treated with INTERCEPT, MIRASOL, or THERAFLEX had a slightly decreased recovery and

survival..[46,69,96] Pathogen-reduced PCs have been studied for their clinical effectiveness in 11 randomized controlled clinical trials, seven with INTERCEPT,[97–103] three with MIRASOL,[102,104,105] and one with THERAFLEX-treated platelets.[106] The trials involved more than 2900 patients—~1900 patients in RCT with INTERCEPT, 860 patients with MIRASOL, and 87 with THERAFLEX. Both buffy-coat and apheresis platelets have been used for the different PRTs with platelets suspended in plasma or PAS. A tabular review from all RCTs published by December 2018 is available.[107]

The corrected count increments (CCIs) in patients receiving PRT-treated platelets were consistently lower than in control patients at both 1 and 24 h following transfusion (Table 2). CCIs seemed slightly better in the more recent clinical study with THERAFLEX although a higher dose of platelets (>25% vs. control platelets) was used. The total dose of treated platelets needed was in general larger than the dose required of control platelets and the transfusion intervals shorter for treated PCs. With the exception of one smaller study[100] in which patients receiving PCs treated with INTERCEPT experienced more bleeds, the overall results of larger studies showed no significant differences in the rates of higher bleeding among patients receiving platelets subjected to PRTs vs. conventional platelets. The number of red blood cells received by patients was similar between treated and untreated platelet recipients in all RCTs, confirming the absence of differences in excessive bleeding. In either case, the important point is no relative difference in bleeding results from transfusion of all kinds of PR platelets. Thus, in this large number of RCTs, PCs exposed to PRTs showed as hemostatically effective as conventional ones.

The rates of transfusion reactions were similar in patients receiving PCs exposed to PRTs or control platelets. In all RCTs, there were no statistically significant differences in the overall rate of transfusion reactions. A Cochrane meta-analysis published in 2017 reported findings from 2075 patients randomized in 12 trials to receive untreated platelets or exposed to PRTs.[108] The analysis concluded that there were no differences between PRT-treated platelets and standard platelets in the incidence of all-cause mortality at 4–12 weeks. No differences in the incidence of serious adverse events were observed. There is clear evidence that patients receiving pathogen-reduced platelet transfusions required more frequent platelet transfusion and were at a higher risk of developing platelet refractoriness. Remarkably, no transfusion-transmitted bacterial infections occurred in the trials that reported this outcome. For long-term safety, manufacturers carry out extensive hemovigilance studies to continuously document and characterize the safety profile of INTERCEPT and MIRASOL platelets. More than 875,000 INTERCEPT PCs have been transfused to patients in various countries, with no reported transfusion-transmitted infections or sepsis-related fatalities. More than 700,000 MIRASOL units have been transfused. No serious adverse events have been reported with the use of MIRASOL-treated platelets or plasma. Thus, the clinical efficacy and safety profile of PR platelets prepared with both INTERCEPT and MIRASOL appear to be satisfactory and similar.

7 | FUTURE PROSPECTS

It would be desirable that PRTs could be adapted not only to platelets, but also to other blood products including whole blood. MIRASOL, the alkylating agent S-303 and THERAFLEX are being investigated for pathogen reduction in red blood cell concentrates and whole blood. INTERCEPT and MIRASOL are being evaluated in phase III clinical trials,[109] while some experimental approaches are underway with THERAFLEX.[110] In a landmark study, MIRASOL PRT whole blood has been successfully used to prevent transmission of malaria in endemic regions.[111] This is the only trial that has shown prevention of actual transfusion-transmitted infection.

New platelet products such as cold stored, cryopreserved, or substitutive will become increasingly available. PRTs use is being explored with these new products.[112] The combined implementation of cold- or cryopreservation methodologies with PRTs would help optimize different platelet products for specific clinical purposes. New pathogen reduction strategies are being investigated using novel photosensitizers[113] and illuminations with wavelengths in the blue (400–450 nm) or red light 600–737 nm) spectrum.[114]

There is a lack of studies evaluating a possible synergistic detrimental action of PRTs in combination with gamma-irradiation. Although several in vitro studies referred in this review have evaluated the impact of gamma-irradiation or PRT comparatively with INTERCEPT[48,51] or MIRASOL,[19,64] none of them has investigated a possible negative impact of combining PRT plus gamma-irradiation. A measurable adverse effect of irradiation on ex vivo platelet aggregation was reported earlier.[115] Although it is generally accepted not to cause critical modifications on the in vitro quality of platelets, gamma-irradiation of PCs produces similar metabolic changes as have been observed after PRTs.[116–118] Remarkably, molecular studies suggest that gamma-irradiation causes more pronounced changes in the platelet proteome than INTERCEPT,[83] MIRASOL,[86] or THERAFLEX.[119] Gamma-irradiated PCs have been

TABLE 2 Descriptive information for the different clinical trials using platelet concentrates treated with different PRTs

Technology acronym	Description/type of study	1-h CCI reference treatment		Reduction %	24-h CCI reference treatment		Reduction %
INTERCEPT EuroSPRITE[97]	Controlled, randomized, double-blinded trial 103 patients PRT (311 transfusions) vs. control (256 transfusions)	14,900	13,100	−12%	10,600	7400	−30%
INTERCEPT SPRINT[98]	Patients randomly assigned, 645 patients (318 PCT and 327 control)-PRT 280 versus control 294-	16,000	11,100	−31%	10,100	6700	−33%
INTERCEPT Janetzko[99]	Multicenter, randomized, controlled, double-blind 43 patients PRT 86 versus control 107	15,100	11,600	−23%			
INTERCEPT HOVON 82[100] Plasma	Randomized open-label non-inferiority 278 patients 99 plasma, 85 PRTPAS-III 357 Plasma, 257 PRT PAS-III	17,100	10,600	−38%	12,500	6800	−46%
INTERCEPT HOVON 82[100] PAS-III	Randomized open-label non-inferiority 278 patients 94 PAS-III, 85 PRTPAS-III 278 PAS-III 257 PRT PAS-III	15,300	10,600	−31%	11,700	6800	−42%
INTERCEPT TESSI[101]	Randomized, controlled, double-blinded 201 patients 101 PRT versus 100 controls	9383	8163	−13%	6549	4588	−30%
INTERCEPT IPTAS[102]	Randomized, non-inferiority, controlled 228 patients 113 treated versus 115 controls 667 PRT-PLTs versus 441 reference	11,391	9387	−18%	9153	6087	−34%
INTERCEPT Effipap[103]	Randomized, non-inferiority, 3-arm 126 PRT PAS versus 262 Controls plasma	—	—	—	10,200	5000	−51%
INTERCEPT Effipap[103]	Randomized, non-inferiority, 3-arm 126 PRT versus 120 Controls PAS	—	—	—	8200	5000	−39%
Average values		14,167 ± 2746	10,647 ± 1575	−24.8%	9875 ± 1901	6047 ± 1050	−38.1%
Technology acronym	**Description**	**1-h CCI reference treatment**		**Reduction %**	**24-hour CCI referenc treatment**		**Reduction %**
MIRASOL MIRACLE 1[104]	Multicenter, randomized controlled trial. 541 on-protocol PLT transfusions (303 PRT-PLTs; 238 reference)	16,939	11,725	−31%	9886	6676	−32%
MIRASOL IPTAS[102]	Randomized, non-inferiority, controlled 196 patients 99 treated versus 97 controls 457 PRT-PLTs versus 457 reference	17,639	12,357	−30%	8605	6051	−30%
MIRASOL PREPAReS[105]	Randomized, multicenter non-inferiority, parallel arm design 469 patients 284 PRT-PLTs, 283 reference transfusions)	13,000	8000	−39%	7000	4000	−43%
Average value		15,859 ± 2501	10,694 ± 2354	−33.3%	8497 ± 1446	5576 ± 1400	−35%
THERAFLEX CAPTURE[106]	Randomized, controlled, double-blind, non-inferiority, multicenter −87 treated versus 84 controls 320 PRT-PLTS, 248 control transfusions	15,530 ± 6.090	12,700 ± 5.98	−18.2%	10,850 ± 6160.	8770 ± 5.520	−19.2%

sporadically used in the different RCTs with PRTs. Unfortunately, the results and numbers of patients who received irradiated and non-irradiated blood have not been homogeneously reported or segregated in the different RCTs so it is not possible to determine whether gamma-irradiation had any clinical effect. The possible synergistically detrimental action of PRT plus gamma irradiation should be further investigated. Presently, PCS are gamma irradiated to prevent transfusion-associated graft versus host disease (TA-GVHD). A recognized additional benefit of PRT would be in the prevention of this unwanted complication. Early experimental studies demonstrated that MIRASOL inactivated the immunologic responses mediated by leukocytes and prevented the development of GVHD in a mouse model.[120] Further observations have shown that non-irradiated PRT-blood components do not cause TA-GVHD.[121] No case of transfusion-related acute lung injury or TA-GVHD has been attributed to the transfusion of PCs exposed to PRT.[107,122] Thus, the need for both treatments should be reconsidered since the implementation of PRTs alone precludes the necessity for irradiating cellular components to prevent TA-GVHD.

8 | CONCLUSIONS

The large number of in vitro studies examined confirms that PRT technologies have a homogeneous and interchangeable detrimental action on the in vitro quality parameters of treated PCs when they are compared with non-treated products. PRTs have a relatively low impact on the overall proteome of platelets with results from different studies confirming that these technologies accelerate the classic storage lesion. Surprisingly, gamma-irradiation seems to have a more profound impact on proteomic modifications than current PRTs.

RCTs with platelets subjected to PRTs indicate a moderate deterioration of platelet quality and reduced survival in the transfused patients. Post-transfusion count increments are lower and the transfusion interval shorter for patients receiving PCs treated with either kind of PRTs. However, by far the most important issue is that the trials establish that the ability of treated platelets to control bleeding is equal to control platelets in routine use.

In summary, PRTs add a supplementary level of safety to current donor screening and regulated testing for known pathogens. These technologies increase patient safety at the expense of some platelet functional and survival losses in clinical trials. It has been claimed that researchers and health organizations have been crying wolf on possible infectious threats based on false alarms and patient safety.[123] Limitations in the extent of previous infectious outbreaks and their specific geographical localization may have given a misinterpretation of their real threat. COVID-19 is a closer call, a deadly infectious disease sweeping across the world. COVID-19 does not seem to be transmitted through blood components, but is warning our health systems that global expansion of emerging infections is real. The current approach of donor screening and blood testing for known pathogens has dramatically improved the safety of transfused blood products. With increasing globalization, climate change, and the unpredictability of emerging pathogens, the proactive implementation of PRTs that could be adapted to treat platelets, red blood cells or whole blood should be considered. PRTs will be valuable for virtually all infectious emerging agents and would certainly increase safety against blood-transmissible future threats.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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