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REVIEW

The clinical and biological impact of new pathogen inactivation technologies on platelet concentrates

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ABSTRACT

Since 1990, several techniques have been developed to photochemically inactivate pathogens in platelet concentrates, potentially leading to safer transfusion therapy. The three most common methods are amotosalen/UVA (INTERCEPT Blood System), riboflavin/UVA–UVB (MIRASOL PRT), and UVC (Theraflex-UV). We review the biology of pathogen inactivation methods, present their efficacy in reducing pathogens, discuss their impact on the functional aspects of treated platelets, and review clinical studies showing the clinical efficiency of the pathogen inactivation methods and their possible toxicity.

1. Introduction

Platelets play an essential role in hemostasis; when a transfusion is necessary, clinicians require platelets of reliable quality to treat their patients. Advances in surgical techniques and oncological treatments have led to an ever-increasing need for platelets. On average, an annual increase of around 10% in the amount of platelets used has been reported in Switzerland since 2000 [1]. In Europe, platelet concentrates (PC) are obtained either by apheresis (single-donor platelets) or prepared through buffy-coat extraction from several units of whole blood (pooled platelets). Platelets have to be stored at room temperature (22 °C). Cold temperatures induce aggregation of von Willebrand factor receptors, exposing a β-GlcNac residue that leads to capture and elimination of the platelets by liver macrophages [2,3]. Storage at room temperature increases the risk of bacterial contamination, assessed as one out of 12,000 PC, which has provided motivation for the development of pathogen inactivation (PI) methods (although some authors prefer to use the term pathogen reduction, we have chosen to use pathogen inactivation, since it is predominantly used in the literature) [4,5]. More generally, PI methods for blood components are an important safety issue within the context of globalization and newly emerging pathogens, not all of which can be detected by current screening methods [6–8]. This was one of the major points in the Toronto Consensus Conference recommendation for the implementation of new technologies [9,10]. Two other possible advantages of PI are the inactivation of lymphocytes, obviating the need for γ-irradiation for graft-versus-host disease (GvHD) prophylaxis [11,12], and the extension of shelf life from 5 to 7 days, allowing for better inventory management. However, there are still controversies about the position this type of product holds in the therapeutic arsenal.

2. Pathogen inactivation methods

The INTERCEPT Blood System (Cerus Corporation, Concord CA, USA) uses a combination of the psoralen amotosalen and UVA light. Amotosalen penetrates through cellular and nuclear membranes and establishes a noncovalent link between pyrimidic base residues in DNA and RNA chains. Exposition to UVA light (320–400 nm) induces a photochemical reaction that transforms the preexisting link into an irreversible covalent bond, preventing DNA replication and RNA transcription. Although all of the toxicological studies of amotosalen have shown that there is no toxicity at the concentration used [13], the manufacturer decided that this compound should not be administered needlessly to patients. Therefore, this PI method terminates with a recapture step, during which a compound adsorption device (CAD)

Abbreviations: CAD, compound adsorbing device; CCI, corrected count increment; GvHD, graft-versus-host disease; HSR, hypotonic shock response; LTA, light transmission aggregometry; PC, platelet concentrates; PI, pathogen inactivation; RCT, randomized controlled trial; RBC, red blood cell; TR, transfusion reaction.

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containing a resin chelates the excess amotosalen. Recapture takes between 6 and 16 h and leaves a minimal residual quantity of amotosalen (<2 μM) [14,15]. Both the spectrum of organisms inactivated by the INTERCEPT Blood System and the efficacy of this PI method have been published: there was a 4- to 6-fold log reduction in infectivity for most pathogens tested [8,16–18]. According to a July 2013 AABB report, about 20 countries have adopted and are currently using the INTERCEPT Blood System [19].

MIRASOL PRT (Terumo BCT, Lakewood, CO, USA) uses vitamin B2 (riboflavin) as the photosensitizing agent. After broad-spectrum UVA/UVB (270–360 nm) illumination of the PC, free oxygen radicals are formed, causing irreversible damage to guanidic nucleic bases. Because riboflavin is a natural vitamin, the riboflavin is not captured at the end of the procedure [20,21].

Theraflex-UV (Macopharma, Tourcoing, France) is still under development. This method uses UVC, which acts directly on nucleic acids to induce pyrimidine dimers and block DNA replication [22,23]. All three techniques have also been developed for plasma treatment.

3. Pathogen reduction

The different inactivation methods introduced above have been tested against varying numbers of pathogens. Both the spectrum of microorganisms for which documented evidence of inactivation is available in the scientific literature and the degree of inactivating efficiency vary among the existing techniques. Results obtained with one method cannot automatically be transposed to another. Excellent reviews of the subjects have been published [24–26]. The efficacy of the three methods on various pathogens is summarized in Table 1. In general, the available methods are more efficient against enveloped viruses than against small, nonenveloped viruses. There is more documented evidence of inactivation with amotosalen/UVA compared to the competing methods, and the level of log reduction in infectivity is also generally greater with this method. However, it is important to consult the available scientific evidence before drawing conclusions about the efficacy of a particular method against a specific pathogen. Even if there is evidence derived from laboratory studies, epidemiological data showing the efficacy of a particular method against a specific pathogen are the most important type of proof in clinical practice. This was the case in La Réunion, where a Chikungunya outbreak occurred [27]. Occasional case reports, even if they appear to provide interesting epidemiological data, should be interpreted with caution. For example, a report stated that the INTERCEPT Blood System was apparently inefficient against hepatitis E [28]; however, the company did not claim that inactivation of this virus was efficient.

Table 1
Degree of reduction of pathogens in log (adapted from [24] with Permission).

	Amotosalen/UVA	Riboflavin/UV	UVC
Enveloped virus			
HBV	>5.5	2.3	na*
HCV	>4.5	3.2	na
HIV (cell free)	>6.2	>5.9	1.4
HIV (cell-associated)	>6.1	>4.5	na
HTLV-I	4.7	na	na
CMV (cell-associated)	>5.9	na	na
West Nile virus	>6.0	>5.1	5.4
Chikungunya	>6.4	2.1	na
Influenza A virus	>5.9	>5	na
Nonenveloped virus			
HAV	0	1.8	na
Parvovirus B19	3.5 to 5.0	>5	5.46
Bacteria			
S. aureus	≥6.6	≥4	>4.8
S. epidermidis	≥6.6	4.2	4.8
P. aeruginosa	4.5	4.6	4.9
E. coli	≥6.4	4.4	>4
Spirochaete bacteria			
T. pallidum	>6.8	na	na
B. burgdorferi	>6.8	na	na
Parasite			
T. cruzi	>5.3	6	na
P. falciparum	>6	>3.2	na

* Information not available.

4. Functional and biochemical studies

Although PI techniques aim at targeting nucleic acids, it has been demonstrated that peptides [29] and platelet proteins are also affected (reviewed elsewhere [30]). The proteomic profile of PI-treated platelets has been analyzed by several groups, and the results have been summarized: PI had a relatively weak impact on the overall proteome of platelets, but some data showed that different PI treatments led to an acceleration of storage lesions. Even though a variety of proteins were affected (i.e., degraded, oxidized, or phosphorylated), the number of altered proteins was low (relative to the whole proteome) and the majority of proteins remained intact. Platelets are anucleated, yet they contain mRNA and the ribosomal equipment required for de novo protein synthesis in case of activation [31]. Thus, platelets are capable of de novo synthesis of proteins, such as of the $\alpha_{2b}\beta_3$ integrin [32]. The potential impact of PI techniques targeted toward nucleic acids on this protein synthesis capacity is largely unknown, as is the relevance of the protein synthesis capacity for platelet function [33].

Unfortunately, no global test for platelet function is currently available; however, a number of approaches have been developed to test platelet function, and some of them are used routinely in the laboratory to detect functional platelet defects [34–36]. These techniques have also been used to detect the potential effect of PI on the metabolic, biochemical, and biological characteristics of platelets. Basic tests may cover platelet metabolic activity, such as pH, glucose, and lactate measurements, or lactate dehydrogase (LDH) dosage, platelet count, and mean platelet volume (MPV), or they may check for swirling (a light diffusion phenomenon used to confirm that the discoid shape of platelets is maintained) [37]. Platelet function tests can be divided into two categories: tests with and without shear forces. The former category includes platelet aggregation tests featuring by light transmission or impedance, flow cytometry, and thromboelastography. The latter category comprises PFA 100 and Cone and Plate(let) analyzer (R-Impact) [38]. However, it remains difficult to study platelets in vitro, given that their manipulation can induce activation [39]. Platelets are stored in a mixture of plasma and additive solution with citrate as anticoagulant, which is quite different from their physiological environment. Certain methods require preliminary reconstitution of whole blood, or the addition of electrolytes (i.e., $Ca^{++}$and Mg^{++}) [40,41]. More importantly, in vitro test results are often unable to predict platelet function after transfusion, because a certain degree of functional recovery may occur [42,43]. Finally, study results should be analyzed while keeping in mind the possible lack of correlation between the results and clinical efficacy [38,39,43,44].

In 2000, Van Rhenen et al. published the first results of a functional assessment of buffy-coat PCs treated with amotosalen/UVA [45]. Platelets have a predominantly oxidative metabolism and store ATP in their dense granules. If necessary, they can switch to anaerobic glycolysis with formation of lactate and H^+ ions, leading to a decrease in efficacy due to lowered pH. In Van Rhenen et al.'s study, the values for pH, pO_2, pCO_2, HCO_3, glucose, ATP, and lactate were similar to those observed in untreated platelets after 7 days of storage. Hypotonic shock response, which allows for the assessment of platelet integrity and shows decent correlation with platelet function in vivo, was maintained; this indicates preservation of platelet metabolism [46,47]. However, expression of P-selectin (also known as CD62P), a marker of platelet activation [48], was increased during storage in PI-treated platelets, as was the number of lysed platelets visualized by electron

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microscopy. In a similar study, Picker et al. had significantly different results regarding platelet metabolism (a greater decrease in pH in the PI-treated platelets, with increased lactate production and glucose consumption); however, the values never decreased below the viability level for platelets (pH < 6.2) during the 7 days of storage [49]. This could reflect a decrease in mitochondrial oxidative metabolism due to damage to mitochondrial nucleic acids, leading to preferential energy production through anaerobic glycolysis [50]. These data were confirmed in studies with apheresis PCs [51–53].

To check whether amotosalen/UVA treatment induces apoptosis and premature platelet lysis, Jansen et al. measured caspase 3 activation [54]. This enzyme is implicated in a signaling pathway that leads to platelet apoptosis; its consequence is the expression of phosphatidylserine on the membrane surface. Although these markers increase during storage, no significant differences were found in PI-treated PCs.

In a trial using platelets radiolabeled with indium-111, Snyder et al. showed a decrease of 7.8% in the recirculation of INTERCEPT-treated platelets after transfusion in healthy volunteers [55]. The mean survival of the platelets decreased from 6.0 to 4.8 days. However, these values are still compatible with an acceptable efficacy and are consistent with the reduction in recirculation of PI-treated platelets after transfusion observed in clinical studies.

Compared to untreated platelets, INTERCEPT-treated platelets express more activation markers on their surface, such as P-selectin (contained in alpha granules and expressed on the platelet surface after activation) and CD42b (also known as Gp1b, the linkage site for thrombin and von Willebrand factor) [56]. Previous studies have shown that the degree of platelet activation, such as the activation measured by flow cytometry for specific markers, could have an impact on the functional capacity of platelets, leading to a decreased response in aggregation tests with different agonists [57–59].

To assess the capacity of induction of clot formation in PI-treated platelets, Tynngard et al. compared amotosalen/UVA-treated platelets (stored in a mixture of 38% plasma and 62% InterSol) with standard platelets stored in 100% plasma. Using free oscillation rheometry (Rheorox, an equivalent of ROTEM), they observed a significantly shorter coagulation time in PI-treated platelets [60].

Lozano et al. showed on rabbit aorta fragments under flow conditions (low shear rates of 800/s) that there was no difference in adhesion between amotosalen/UVA-treated and untreated platelets until day 7, when adhesion of PI-treated platelets was better [61]. Another study used the Impact-R cone and plate(let) analyzer to compare standard PCs with amotosalen/UVA- and riboflavin/UV-treated platelets under high shear stress conditions (2000/s) [62]. Adhesion of the untreated PCs was lower, and during storage, the adhesion of riboflavin/UV-treated platelets was significantly less diminished than that of untreated or amotosalen/UVA-treated platelets. The correlation of this finding with clinical findings has been documented in several trials [63,64]. The discordance with the results produced by Lozano et al. may be explained by differences in test conditions. In the same study, in PI-treated PCs, the authors discovered a storage-induced increase in the expression of CD41 and CD61 (GPIIb/IIIa, a fibrinogen receptor), increased expression of P-selectin, and a decrease in the aggregatory response after stimulation with TRAP6 (an agonist of the thrombin receptor PAR-1). This decrease was significantly lower in riboflavin/UV-treated platelets.

To better assess intrinsic platelet characteristics, Hechler et al. washed platelets [65] to remove the storage medium. They suspended the platelets in neutral Tyrode's buffer containing glucose [66]. Expression of P-selectin and GPIIb/IIIa was not modified after amotosalen/UVA treatment, nor was aggregation after stimulation with different agonists (i.e., ADP, collagen, and thrombin). These results differ significantly from previously published data and suggest that the storage medium may have an inhibitory-yet-reversible effect on platelets. Similarly their study of mitochondrial transmembrane potential did not show any modifications, indicating that there was no mitochondrial damage. These findings were confirmed by another trial on mitochondrial DNA [50].

In our laboratory, a fibrinogen adhesion test under static conditions did not detect differences in adhesion between untreated and amotosalen/UVA-treated platelets (submitted manuscript). However, after 4–7 days of storage, adhesion was increased in PI-treated platelets. These data were supported by increased expression of GPIIb/IIIa, as measured by PAC-1 levels in PI-treated PCs after 7 days of storage; this measure was correlated with energy metabolism and membrane integrity.

In summary, functional and biochemical studies have revealed that PI has a moderate impact on platelet function, sometimes with discordant results, illustrating the difficulties of assessing platelet function in vitro. Data suggestive of damage to mitochondrial metabolism have not been clearly confirmed. Storage lesions may be more pronounced, since increased P-selectin expression and decreased agonist-induced aggregation was observed [67]. PI-treated platelets seemingly present a higher basic activation state, with higher surface expression of GPIIb/IIIa; this could explain the faster clearance, leading to lower recirculation rates, observed in some clinical trials. The influence of the storage medium (i.e., plasma, InterSol, or Tyrode buffer) is obviously substantial and could explain some of the discordant study results. However, hemostatic function appears to be preserved in PI-treated PCs compared to standard PCs, under both static and flow conditions, in concordance with clinical observations that did not detect an increase in the bleeding risk.

5. Adverse effects and hemovigilance

Some of the reactions following PC transfusion can be explained by the presence of cytokines and chemokines that are released during storage. The occurrence of undesirable reactions has notably been linked to the presence of sCD40L. According to a study by Cognasse et al., treatment of PC with amotosalen/UVA does not increase the production of detrimental cytokines [68].

Published hemovigilance data predominantly concern INTERCEPT. This technique was approved in France in 2002 (AFSSAPS) and in Germany (PEI) and Switzerland (Swissmedic) in 2009. Switzerland was the first country to implement INTERCEPT nationwide from 2011. Swiss hemovigilance data on the transfusion of 551 PCs revealed a transfusion reaction (TR) rate of 2% and a corrected count increment (CCI) of 10,000 after 1–4 h [69]. French hemovigilance data showed no increase in the number of platelet transfusions before and after the introduction of INTERCEPT and confirmed the decrease in the TR rate [70]. A decrease in the TR rate linked to the use of additive solutions has been described previously [71], but the French data appears to show a specific PI effect that is independent of plasma substitution. In Belgium, a retrospective study on transfusion data compared a 3-year period before and after the introduction of INTERCEPT; there were no differences in the number of PC transfusions per day of thrombocytopenia, in the total dose of platelets administered to patients, or in the number of red blood cell (RBC) transfusions given to thrombocytopenic patients [72]. Finally, a prospective hemovigilance program conducted in France, Belgium, and Spain that included 7437 PC transfusions, mostly in hemato-oncological patients, revealed an undesirable event rate of 0.9% after transfusion without any bacterial contamination [73]. These hemovigilance reports all confirm both the safety and efficacy of INTERCEPT-treated PCs in a huge number of platelet transfusions.

6. Clinical studies

The results of six phase III randomized controlled trials (RCTs) with INTERCEPT-treated PCs have been published since 2003, as well as one with MIRASOL-treated PCs [74–79]. All of the studies had at least two study arms in which one group of patients received PI PCs, while the

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other received standard PCs. The participants in these trials were predominantly hemato-oncology patients who were receiving prophylactic transfusion protocols in a setting of post-chemotherapy thrombocytopenia; the study periods ranged from 28 to 56 days. One of the principal stakes of these studies rested on the definition of the primary outcome. The more common outcome used was the change in CCI. The CCI indicates the increase in platelet count after transfusion, corrected for the number of platelets transfused and the body surface area of the recipient. This formula was originally used to define refractory state to platelet transfusion; as such, it is not an intrinsic quality parameter for platelet products [80]. CCI has the advantage of easy measurement and allows for quantitative comparisons. However, it has not been established that this measure is of clinical relevance. For example, in the PLADO study, although the CCIs were different in three groups of patients who received 1.1×10^{11}, 2.2×10^{11}, and 4.4×10^{11} platelets/m^2, respectively, the clinical outcomes were similar [81].

The SPRINT trial was the only trial to use the bleeding score, as defined by the World Health Organization (WHO), as the primary outcome measure [77]. Other clinical criteria, such as the number of PC and RBC transfusions and the time interval between two transfusions, have been used as secondary outcomes, together with the TR rate, the appearance of neoantigens, and the risk of platelet alloimmunization.

In addition to how clinically relevant outcomes are defined, numerous other biases may arise in association with the methods used in the aforementioned studies. Possible pitfalls were described by Cook and Heddle in their review of the methodology of clinical trials with patients transfused with PI-treated PCs [82]. The very characteristics of the PCs varied among the studies, making it difficult to compare the study results: platelets were obtained through apheresis or prepared from buffy coats (in Europe) or platelet-rich plasma (in the USA), the number of platelets per bag and the composition of the additive solution differed, the shelf life was variable, and the presence or absence of γ-irradiation and the transfusion threshold was substantially different from one study to another. Part of the variability may also be patient linked, although the exclusion criteria generally contained risk factors for platelet refractoriness, such as splenomegaly, HLA or HPA alloimmunization, and the presence of disseminated intravascular coagulopathy. To avoid the possible impact of a variable number of transfusions per patient, only the first eight transfusions were assessed in both the euroSPRITE and the MIRACLE study [82]. Interpatient variability was further complicated by the variability of the response to transfusions in a single patient; interpretation of a study becomes more complex when randomization occurs at the patient level and not at the transfusion level. Lozano et al. limited their assessment to one transfusion in order to reduce this effect [76]. It is also noteworthy that only the Janetzko study [74] formally defined the incidence of bacterial contamination as a secondary outcome, although the frequency of this complication was at an order of magnitude beyond the predictive power of these studies.

The first RCT of PI-treated PCs, published in 2003, was the euroSPRITE trial [79], which compared 103 patients who received PC prepared from buffy coats. The PCs were either treated or untreated with amotosalen/UVA (311 and 256 transfusions, respectively), and the transfusion results were monitored over a time period of 56 days. The CCI was not significantly different between the two groups (13.100 ± 5.400 vs. 14.900 ± 6.200, respectively). Secondary outcomes (i.e., number of platelet transfusions per patient, occurrence of bleeding, number of RBCs transfused, development of a refractory state, and TR rate) also did not differ between the two groups.

The SPRINT trial [77] included 645 patients and was published in 2004. The primary outcome was the occurrence of grade 2 bleeding (WHO classification) during a follow-up period of 28 days; platelets were obtained through apheresis. The occurrence of grade 2 bleeding in the amotosalen/UVA-treatment arm was 58.5%, versus 57.5% in the control group. The occurrence of grade 3 or 4 bleeding was 4.1% and 6.1% in the amotosalen/UVA-treated and control groups, respectively. No statistically significant difference was observed. In contrast with the results of the euroSPRITE trial, CCIs were lower in the recipients of PI-treated PCs compared to controls (11.1 versus 16.0), and the former group received more transfusions (8.4 vs. 6.2 per patient). It should, however, be noted that the platelet content was lower in the treatment group than in the control group (3.7×10^{11} vs. 4.0×10^{11}/unit).

In Janetzko et al.'s study [74], a commercially available kit for amotosalen/UVA treatment was used, which reduced the number of preparation steps and limited the platelet loss. Their RCT of 43 patients revealed a decrease (although not statistically significant) in CCI after the transfusion of apheresis platelets treated with amotosalen/UVA (11.600 ± 7.300 vs. 15.100 ± 6.400), confirming the results of the SPRINT trial. However, the standard platelets were stored in 100% plasma, whereas the amotosalen/UVA-treated platelets were resuspended in a mixture of plasma and platelet additive solution III (PAS III) [74]. Since there was no difference in the number of transfusions or in the occurrence rate of bleeding and adverse effects, the authors concluded that both types of PC were equivalent in terms of efficacy and safety.

In contrast with the results of the other studies, the HOVON trial [75] included three arms: PCs stored in full plasma, in PAS III without INTERCEPT, and in PAS III with INTERCEPT. Although the primary outcome of this study was CCI and not bleeding, even prior to publication major concerns arose about a possible reduction in clinical efficacy for PCs treated with amotosalen/UVA: 32% of patients in the INTERCEPT arm presented a bleeding episode compared to 19% in the plasma arm, and CCIs in the INTERCEPT arm were lower by 31% compared to the plasma arm. However, this study had serious flaws, including a lack of blinding, the absence of bleeding assessment by independent and trained observers, and the use of a bleeding grading system different from the WHO scale. Furthermore, the only statistically significant differences were found between the plasma arm and the PAS III + INTERCEPT arm, leaving some doubts about the specific effects of additive solution and INTERCEPT treatment [83].

One of the advantages of PI-treated PCs is that shelf life can be extended from 5 to 6 or 7 days, since the 5-day limitation was based on the risk of bacterial contamination [84]. In the TESSI trial (Efficacy and Safety Study of Platelets Treated for Pathogen Inactivation and Stored for Up to Seven Days), Lozano et al. [76] opted for an innovative study design: they compared the therapeutic efficacy of amotosalen/UVA-treated vs. standard platelets that had been stored for 6 or 7 days. Every patient was included for only a single transfusion. The authors confirmed the noninferiority of PCs treated with INTERCEPT and stored for 6 or 7 days: the mean CCIs (after 1 h) were 8.163 and 9.383, respectively, for amotosalen/UVA-treated and standard platelets.

To minimize confounding variables, a Swiss team from Basel performed an open prospective study that compared a group of 44 patients who received amotosalen/UVA-treated apheresis platelets with a group of 72 patients who received γ-irradiated standard platelets in PAS III over a period of 28 days. The platelet content of the bags was identical (around 2.8×10^{11}/unit) between the two groups. There was no difference in the CCI (after 1 h) between the two study arms (11.400 ± 4.900 vs. 11.000 ± 4.900, respectively, for amotosalen/UVA-treated apheresis platelets and γ-irradiated standard platelets) [78]. Due to a lack of availability of INTERCEPT-treated PCs, 38% of the transfusions in the INTERCEPT arm were given with standard platelets. A per-protocol analysis (including only transfusions with INTERCEPT-treated platelets) revealed a CCI (after 1 h) of 10.700 ± 5.600.

The MIRACLE study is the only published RCT thus far of PCs treated with riboflavin/UV (MIRASOL). It was published in 2010 and included 118 patients. The CCI (after 1 h) was significantly lower in the riboflavin/UV arm than in the control arm (11.725 ± 1.14 vs. 16.939 ± 1.15, respectively). Thus, the study did not meet the previously defined noninferiority limit of 30% loss. However, the number of PCs and RBCs transfused was similar in the two study arms, and the authors raised the question of whether the CCI is a reliable surrogate marker for bleeding risk assessment.

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As shown by the studies discussed above, the results of the published clinical studies should be interpreted with caution, and their characteristics and possible biases should be taken into account. Results obtained with one method cannot be extrapolated to those obtained by other methods. In the first published meta-analysis that included the HOVON trial, Vamvkas concluded that there was a clinically significant increase in mild and moderate bleeding complications in the arm receiving treated-platelets [85]. However, this meta-analysis contained a serious methodological bias: it combined the results of clinical studies of amotosalem/UVA with the results of a clinical study of riboflavin/broad spectrum UV. In a second meta-analysis, which was recently published by Cid et al., although the CCIs were lower after INTERCEPT, the hemostatic efficacy of INTERCEPT-treated PCs was maintained. These findings support the results of previously published hemovigilance data, which did not show an increase in the number of PC transfusions after INTERCEPT [86].

7. Conclusions

The beneficial effects of INTERCEPT-treated platelets have been clearly demonstrated. Indeed, they reach beyond the original scope: in addition to the reduction in infectious risk, INTERCEPT-treated platelets obviate the need for γ-inactivation for GvHD prophylaxis and extend the maximum shelf life of platelets from 5 to 7 days. Furthermore, a reduction in the transfusion reaction rate has been observed, due either to partial plasma substitution by additive solution or to a specific PI effect. Although platelet recovery, as measured by CCI or survival studies with radiolabeled platelets, is lower after PI treatment, the hemostatic efficacy, as measured by clinical outcomes, is maintained. The results of prospective clinical trials have been confirmed by retrospective hemovigilance data. However, the heterogeneity of these clinical trials complicates their comparison.

At the laboratory level, PI-treated platelets seem to present an increased activation status, and moderate changes at the level of mitochondrial metabolism are expressed in increased metabolic parameters; however, the results are discordant among studies. These modifications might explain the reduced survival and decreased recirculation level of PI-treated platelets, although the increased activation status of PI-treated platelets does not lead to a decrease in hemostatic efficacy. Activated fibrinogen receptor expression appears to be increased after PI, perhaps through a direct effect of PI on this integrin. These data relate mainly to the amotosalen/UVA technique and, to a lesser extent, to the riboflavin/UV method.

The data available thus far in the literature allow us to conclude that the hemostatic efficacy of PI-treated platelets is satisfactory. In addition to a sharp decrease in the transmitted infection risk, PI also provides GvHD prophylaxis and extension of the maximum platelet shelf life from 5 to 7 days.

Practice points

- PI represents of an important change of paradigms in transfusion medicine: testing and exclusion of blood donors according to specific risks are not the sole pillars of security of blood transfusion.
- PI methods are particularly efficient to prevent transfusion-related bacterial infections.
- PI methods of PC globally reduce the risk of transfusion transmitted diseases and replace γ-irradiation for the prevention of GvHD.
- Hemostatic efficacy of PI-treated PC appears to be maintained, although the CCI is lower when compared to untreated PC.

Research agenda

- The future of PI in transfusion medicine will be determined according to the results of well conducted, double blind, clinical trials.
- The storage lesions have to be deciphered according to time of storage as well as to the particular and specific PI methods that are used.
- Inactivation of all blood products will be a challenge for the future: fundamental, translational and clinical studies are needed to better characterize the molecular mechanisms involved by PI methods.

Conflict of interest

NL and JCO received conference honorarium from Cerus, manufacturer of the INTERCEPT Blood System. The other authors declare that they have no competing interests.

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