Platelet concentrates: Balancing between efficacy and safety?

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Summary

Platelet transfusions continue to be the mainstream to treat patients with quantitative and qualitative platelet disorders. Each year, about 10 millions of platelet transfusions are administered to patients worldwide with marked differences in usage between regions depending on socioeconomic development of the countries. Unfortunately, its use is associated to immune and non-immune side effects. Among the non-immune, bacterial contamination is still the major infectious risk. When bacterial culture methods are introduced for preventing bacterial septicaemia it has been found that this strategy reduce to one half the septic reactions, but do not eliminate completely that risk. To remove completely the risk, a new bacteria detection test at the time of issuance in the case of platelets stored for four or five days would be needed. Pathogen inactivation (PI) methods already in the market (based in the addition of amotosalen (A-L) or riboflavin (R-L) and the illumination with ultraviolet light) or under development (ultraviolet light C and agitation) have shown to be efficacious in the inactivation of bacteria and no cases of septic reactions associated to a pathogen-reduced product has been identified. However, it has been shown that PI technologies have measurable effects on platelet in vitro parameters and reduce the recovery and survival of treated platelets in vivo. Although these effects do not hamper the hemostatic capacity of treated platelets, an increased usage associated with PI technologies has been reported. This increase in utilization seems to be the toll to be paid if we want to completely eliminate the risk of bacterial sepsis in the recipients of platelet transfusion.

Introduction

Platelet transfusions continue to be the mainstream to treat patients with quantitative and qualitative platelet disorders. Each year, about 10 millions of platelet transfusions are administered to patients worldwide with marked differences in usage between regions depending on socioeconomic development of the countries [1]. After years of research and development, current platelet concentrates represent the highest quality possible but unfortunately, they are not perfect. And, the main reasons for that are the particular characteristics of platelets. Due to its specific role in the
physiology of the organisms, i.e. mainly to detect lesions in the vessel walls and rapidly adhere and aggregate at the site of injury to form an hemostatic plug, they are extremely sensitive to a wide variety of stimulus that provoke its activation. Depending on the stimulus and its intensity the activation can be reversible, i.e. the platelet recovers its resting disc form, or irreversible, when the platelet changes from a disc shape to an spiky and sticky sphere that adhere to each other. Both types of activation if occurring during the preparation or storage of platelet concentrates have a deleterious effect on the efficacy of platelet transfusion.

The current platelet concentrates are probably the safest that we have ever had. However, there are still adverse effects associated to its use that can be grouped in immune and non-immune mediated. Among the non-immune the infectious risks, particularly the bacteria, are the more severe and dreadful for the recipient of a platelet transfusion. In this paper, we will discuss the current infectious risks of platelet transfusion, the strategies current available to prevent them and the impact that this measures might have in the platelet function. The interested reader is referred to other recent papers that review the immune mediated adverse effects of platelet transfusions [2,3].

Infectious complications of platelet transfusion

That infectious diseases are potential complications of blood transfusion was very early recognized and already in 1939, it was suggested to add sulfanilamide to the blood to prevent bacteria growth [4]. But in the case of platelet concentrates, the situation was worsened by the discovery that the optimal storage conditions for platelet were at 22 °C under continuous agitation [5] since those conditions were also optimal for the growth of bacterial. Actually, an increase in the number of reported cases of posttransfusion sepsis (from 3 in 1984 to 11 in 1985) after increasing the maximum storage time of platelet from 5 to 7 days in 1984, provoked that in 1986, the Food and Drug Administration (FDA) of USA reduced again to 5 the maximum storage time of platelet concentrates [6].

Thanks to the measure implemented in the Blood Establishments to prevent transfusion-transmitted viral infections, mainly strict criteria for donor selection and the screening of all blood donations using very sensitive techniques, the risk of transmitting viral infections nowadays is very low. However, due to differences in donor selection criteria and in the epidemiology, the residual risk between countries varies widely. For instance, the estimated residual risk of transfusion-transmitted infections by donations screened by nucleic acid testing for hepatitis B virus (HBV) varies from 1 in 71,942 in Italy to 1 in 620,000 in Germany, for hepatitis C virus (HCV) from 1 in 1,149,000 in USA to 5,000,000 in Italy. For human immunodeficiency virus (HIV), the risk varies between 1 in 550,000 in Spain and 1 in 7,800,000 in Canada [7].

But it must be taken into account that risk in calculated per every donation but when the platelet concentrates are prepared from whole blood donation from 4 to 6 units are pooled, the risk of a platelet transfusion should be multiplied by the number of units pooled. Assuming that 5 donations are pooled, for instance the residual risk of HBV for a recipient in Italy would be 1 in 14,388 and the risk of HIV for a recipient in Spain would be 1 in 110,000. And those risks are considering just one platelet transfusion, when the usual recipient of platelet transfusions, a patient with a malignant hematologic disease might receives dozens of platelet transfusions. For instance, in the TRAP study the mean (± standard deviation) number of platelet transfusions received by the patients in the different arms of the study ranged from 13 ± 8 to 16 ± 13 [8].

Currently the main infectious thread for the recipient of a platelet transfusion is the bacterial sepsis. The reported risk of bacterial contamination of platelet concentrates differs by testing and manufacturing procedures, however recent studies report a confirmed-positive contaminated platelet concentrates at a rate between, 1:1036 to 1:7194 platelet products [9]. However, the rate of septic reactions to platelets is smaller and has been estimated to be 1:20,000 and related fatality in about 1:60,000 transfusions [10]. Several reasons might explain the discrepancy. One is that about 60 % of the contaminated platelet components are transfused without causing any significant reaction. Second is that patients who are on antibiotics or are neutropenic may show few immediate signs after bacterial exposure although delayed reactions have been reported when the attending physician will not recognized it as related to the platelet transfusion [11].

The hemovigilance systems have recorded the morbidity and mortality of bacterial sepsis associated to platelet transfusions. In France, the only European country with a mandatory hemovigilance system where all the reactions to transfusion have to be reported, found between 2000 and 2008 with 1,940,000 platelet concentrates transfused a rate of bacterial septic reactions of 1:40,485 with a fatality rate of 1:200,000 [12].

Unfortunately, the transmission of infectious agents by platelet transfusion is not limited to the classical viruses and bacteria. Protozoa diseases as Chagas disease has been shown to be transmitted by platelet concentrates prepared from infected donors [13]. In addition, emergent pathogens such as Ebola, dengue, chikungunya, West Nile virus, hepatitis E or Zika virus represent a potential thread not only to platelet concentrates but to the whole blood supply [14,15].

Strategies to prevent infectious complications of platelet transfusion

Currently two strategies are available for preventing the transmission of infectious agents by platelet concentrates transfusion. One strategy is using the screening of the concentrates for potential pathogens. Unfortunately, this strategy can be only
applied to bacterial contamination since no other one of the known pathogen can be currently screened. The second strategy that can be used is to apply a pathogen inactivation technology to the platelet concentrate. Following we will review both strategies.

**Bacterial screening of platelet concentrates**

Currently there are several methods available for the screening of bacterial contamination of platelet concentrates, although the based on the microbiological culture of a sample of the platelet product (BacT/ALERT, bioMérieux, Marcy-l’Étoile, France) is by far the most used around the world [16]. It is that method the one we are going to discuss.

A wide variability exists regarding the performance of the tests [17] but the practice of most of the centers consists on the removal of a sample of between 4 to 8 mL of the platelet product (whole blood-derived or apheresis) between 3 to 30 hours after preparation or collection. The sample is then inoculated into an aerobic culture bottle although some centers also use an anaerobic culture bottle [16]. Positive initial results are confirmed by re-culturing of the platelet product. If the same bacterial species growth in the initial and confirmatory culture, then the term “true-positive” is used [17].

After the introduction of bacterial screening several centers have reported their experience. It has been identified that several factors affects the reported rate of true-positive cultures of platelet concentrates including: skin preparation method, the diversion of the first milliliters of blood during phlebotomy procedure or apheresis, the performance of aerobic and anaerobic cultures, delay before sampling and volume of product cultured [9]. The reported rate of confirmed-positive using the BacT/Alert System varies from 1:1036 to 1:7194 [9], as mentioned earlier.

However, it has been found that, unfortunately, a negative result in the culture result does not mean that the platelet product is not contaminated, due to the fact that initially, the number of the bacteria in the platelet product is very low and might not be present in the sample that it is removed from the product for culture. In 2007, the American Red Cross reported its experience with the introduction of BacT/Alert for screening the platelet concentrates prepared by apheresis. In 1,004,206 donations screened between 2004 and 2006, they found 186 (1:5399) confirmed-positive culture results. During the same period, 20 septic transfusion reaction were reported, including 3 fatalities (1:498,711 fatalities per distributed component), which implicated screened-negative apheresis platelet concentrates [18]. Similar finding has been reported by other authors [19-21] confirming the fact that the implementation of bacterial screening using culture does not prevent the occurrence of bacterial sepsis at the time of transfusion.

Due to this fact, it has been suggested that it would be needed another method of bacterial contamination detection at the time of issue [22-24]. However, doubts about the sensitivity of the tests and the cost associated to its use and to discarding 1 in 292 platelet products due to false positive results [23], has severely limited its implementation in routine. However in USA, FDA is considering to issue a request for a secondary bacterial testing at the time of issue, particularly for platelet concentrates that have been stored for four or five days.

**Pathogen inactivation methods**

Fortunately, since the early 2000s technologies are available that allows the inactivation of pathogens potentially present in platelet concentrates. It represented a significant breakthrough in the field of transfusion medicine, because until then inactivation technologies were only available for plasma derivatives in the 1980s such as coagulation factor concentrates or intravenous immunoglobulins and plasma in the early 1990. And it has to be emphasized that since the introduction of effective virus inactivation technologies for treating coagulation factor concentrates there has been no transmission of HBV, HCV or HIV by United States licensed plasma derivatives since 1987 with the exception of intravenous immunoglobulins that transmitted HCV in only one outbreak involving the product of one manufacturer in 1994 [25].

The first method available for inactivating pathogens in platelet concentrates was based on the use of a synthetic psoralen, amotosalen, and the illumination with ultraviolet A (UVA) light. The combination of 150 μM amotosalen and 3 Joules per cm² of UVA light (A-L, Intercept® Blood system, Cerus Co) was shown to inactivate high levels of enveloped and nonenveloped viruses, bacteria and protozoa in platelet concentrates resuspended in platelet additive solution [26-29]. Some of the nonenveloped viruses evaluated in vitro, such as hepatitis A virus, porcine parvovirus and feline conjunctivitis virus have shown resistance of poor inactivation response to inactivation by A-L [27,30,31].

The recent publication of the transmission of two cases of hepatitis E by two plasmas coming from the same donation suggests that also hepatitis E is resistant the inactivation by A-L [32]. Leucocytes are also inactivated and their cytokine production inhibited [30], and the treatment with A-L is considered as an alternative to gamma irradiation for preventing graft-versus-host disease associated to transfusion.

In 2000, Goodrich reported the use of vitamin B₂ (riboflavin) and light (R-L) for inactivating pathogens in platelet concentrates and plasma (Mirasol PRT System, TerumoBCT, Lakewood CO) [33]. The pathogen inactivation method currently available consists in the addition of 35 mL of riboflavin (500 μmol/L in 0.9 % saline) to the platelet product, in plasma or platelet additive solution, and the illumination with UV light (phosphor 265-370 nm, dose of 6.2 J/ml) [34]. The system has been tested with a wide variety of enveloped and nonenveloped viruses, gram-negative and gram-positive bacteria as well as a parasites [35-38]. Prevention of GVHD due to leucocyte...
inactivation has been studied both in vitro and in vivo [39,40] and is considered as an alternative to gamma irradiation for preventing graft-versus-host disease associated to platelet transfusion. The results of these studies have demonstrated a broad inactivation capacity of bacteria, viruses, parasites, and leucocytes in platelet concentrates. For nonenveloped viruses there are contradictory results. For porcine parvovirus Ruane et al. reported a virus reduction after treatment with R-L of \( \geq 5.03 \) logs while Kwon et al. reported a reduction of \(< 1 \) logs. As the same strain of model virus was used, difference in viral strains is not the cause of the large difference for susceptibility to inactivation [31].

To note that a recent comparison of A-L versus R-L in the inactivation capacity of gram-positive and negative bacteria found that in the platelet products spiked with high titer of bacteria the log reduction factor in bacteria ranged from 4.26 to 5.45 for R-L and \( \geq 7.74 \) to \( \geq 10.11 \) for A-L. In the experiments performed, spiking platelet concentrates with low titer of bacteria for reproducing the conditions usually found in every day practice when initially the bacterial contamination levels of the products are low, postinactivation bacterial growth was detected in the products spiked with Staphylococcus aureus and Bacillus subtilis in the products treated with R-L while no bacterial growth was observed in the products treated with A-L [31].

Currently, another inactivation method for platelet concentrates based on the illumination with short-wave ultraviolet light (UVC) and agitation is being developed in Europe (Theraflex UVC-Platelets, MacoPharma International) [41]. The system does not use any photosensitizer and relies only in the inactivation capacity C (wave length 254 nm). To overcome the low penetration of UVC, the illumination system is combined to an agitator. It is essential for the efficacy of the system that the platelet concentrate is suspended in platelet additive solution and that the bags are loosely placed during agitation since it allows for an increased mixing rate and wave movement of the bag during agitation. The wave movement causes the formation of areas of layers within the platelet unit that becomes thin enough to be UVC permeable. Other parameters such as the cell concentration and the protein content of the irradiated fluid have a great influence on pathogen inactivation efficiency as they critically determine the UVC transparency of the solution to be treated [42].

UVC under agitation has proven to be effective inactivating a broad number of gram-negative and positive bacteria, viruses and protozoa. It has been also shown that residual leukocytes of the platelet concentrates are also inactivated at a level that might be at least equivalent to gamma irradiation preventing graft-versus-host disease associated to transfusion [43]. Unfortunately, studies have shown that HIV is resistant to the inactivation using UVC and agitation. The diploid nature of the virus genome and the HIV-associated reverse transcriptase, which may be unaffected by UVC, may provide the basis for an effective repair mechanism of the virus [41]. UVC-light and agitation was at least as effective as gamma irradiation in preventing GVHD in a mouse model and was more effective in suppressing T-cell proliferation, cytokine secretion, and antigen presentation than gamma irradiation [44].

**Effect of pathogen inactivation technologies on platelet function**

Several studies have looked at the effect of the different pathogen inactivation technologies on platelet function. Let’s start reviewing the data available for A-L, the first one introduced in the market. In one of the studies, after applying A-L to Buffy coat-derived platelets and stored them up to 7 days, of the several in vitro parameters tested statistically significant higher values were observed only in glucose consumption, lactate production, and CD62P expression of A-L platelet units compared to platelet units kept as a control, and differences were relatively small in most cases. The treatment also caused a loss in platelet concentration of approximately 6.5 % [45,46]. In vitro studies performed under flow conditions suggested that platelets treated with A-L preserved adhesive and aggregating properties up to 7 days, similar to non-treated platelets [47].

The effect of A-L treatment on the recovery and survival of transfused platelets has been studied in healthy subjects using radio-labelling techniques. Such studies showed that A-L units, compared to control units, showed statistically significant lower rates of in vivo recovery (42.5 % vs. 50.3 %) and survival (4.8 days vs. 6.0 days) [48]. In vivo studies have shown that in spite of statistically significant lower posttransfusion corrected count increments (CCI) the correction of the prolonged bleeding time in thrombocytopenic patients observed with A-L inactivated platelets was similar to that observed with the unmanipulated product [49].

Studies have also looked at the effect of treating platelet concentrates with R-L. Ruane et al. looked at the *in vitro* platelet performance after R-L treatment and after 5 days of storage using a panel of 10 platelet quality assays. The results showed that platelet quality was adequately maintained after treatment and during storage. Although P-selectin expression (41.7 % vs. 17.9 %), glucose consumption (0.033 vs. 0.019 mmol/10^{12} cells/h), and lactate production increased relative to controls at day 5 (0.032 vs. 0.056), this was not beyond accepted levels. The pH of treated PCs also decreased slightly relative to control PCs on days 5 (7.13 vs. 7.48) [35]. Other authors have also reported similarly an increase in platelet activation and changes in biochemical parameters when platelets were suspended in plasma but those changes were mitigate when instead of plasma, a platelet additive solution (PAS) E was used to suspend the platelets [50,51].

When evaluated under flow conditions, apheresis platelets treated with R-L showed adhesive and aggregating properties similar to the control when stored up to 5 days [34].
Interestingly, when platelets were suspended in PAS E the functionality under flow conditions was similar to the untreated platelets when stored up to 7 days. However a significant reduction in swirling pattern was observed with respect to the control when stored up to 7 days [52]. R-L treated apheresis platelets were studied also in vivo in healthy volunteers using radiolabeling techniques. Recovery of treated platelets (50.0 ± 18.9 %) was reduced from that of controls (66.5 ± 13.4 %); survival was similarly shortened (104 ± 26 h vs. 142 ± 26 h; \( P < 0.001 \)) [53]. The treatment of platelet concentrates with UVC is associated to a higher metabolic activity (glucose consumption and lactate accumulation) during storage. Also increased levels of activation such as P-selectin surface expression and increase binding of annexin V has been reported. The most UVC sensitive in vitro parameter was identified to be the hypotonic shock reaction showing a decrease of 20–30 % immediately after UVC irradiation [54]. When the recovery and survival of UVC-treated platelets stored for 5 days were studied in vivo using radiolabelling techniques, a reduction in recovery of 17 % and in survival of 20 % compared to non-treated platelets, was found [55].

**Effects of pathogen inactivation technologies treated platelets in patients**

Unfortunately, none of the in vitro tests available has shown a correlation with the clinical response to a platelet concentrate transfusion. Thus, the gold standard for definitively establishing the effect of a new technology on platelet concentrates continues to be a clinical trial with clinically relevant endpoints and a sufficient number of patients. Several clinical studies have looked at the effect of A-L treatment on platelet concentrates in patients. The first clinical study published was the euroSPRITe study, a multicenter, randomized, controlled, double-blinded trial in thrombocytopenic patients requiring repeated platelet transfusions conducted in Europe to evaluate the therapeutic efficacy and safety of platelet concentrates prepared using the buffy coat method and treated with A-L. For euroSPRITe, 103 patients were randomized to receive A-L platelets (311 transfusions) or control platelets (256 transfusions). The mean 1-hour posttransfusion count increment for up to the first eight transfusions was lower in the patients receiving the A-L platelets compared to controls (27.5 vs. 35.8; \( P = 0.03 \)). When the 1-hour count increment was adjusted for differences in platelet dose using the CCI, the mean 1-hour CCI was not statistically significantly different between treatment groups (13,100 vs. 14,900; \( P = 0.11 \)). The mean 24-hour posttransfusion CCI was less \( (P = 0.02) \) for the test group (7400 ± 5500) than for the control group (10,600 ± 7100). Clinical hemostasis, hemorrhagic AE, and overall AE were not different between treatment groups [56].

One year later, the results of SPRINT trial were published. In this case, the primary endpoint was the proportion of patients with World Health Organization (WHO) grade 2-or-higher bleeding during the period of platelet support. A total of 645 patients (318 in the A-L arm and 327 patient in the control arm) were evaluated after receiving 4719 platelet transfusions (2678 A-L; 2041 control). The primary endpoint, the incidence of grade 2-or-higher bleeding (58.5 % A-L platelets vs. 57.5 % controls), and the secondary endpoint, the incidence of grade 3-or-4 bleeding (4.1 % A-L vs. 6.1 % controls), were equivalent between the two groups \( (P = 0.001 \) by non-inferiority). The mean 1-hour posttransfusion platelet CCI (11,100 A-L vs. 16,000 controls), average number of days to next platelet transfusion (1.9 A-L vs. 2.4 controls), and number of platelet transfusions (8.4 A-L vs. 6.2 controls) were statistically significant different \( (P < 0.001) \). Transfusion reactions were fewer following A-L platelets \( (3.0 \% \) vs. 4.4 %; \( P = 0.02 \)) [57]. Later, a publication reported and extended analysis of the adverse events found during the SPRINT trial [58]. The study found that petechiae were more frequently reported in the group of patients receiving A-L treated platelet components \( (39 \% \) than in the group receiving control platelets \( (29 \% \), \( P < 0.01 \)). Also fecal occult blood positive test was more frequently reported in the group transfused with A-L platelets \( (33 \% \) than in the control \( (25 \% \), \( P = 0.03 \). There were no differences between the two groups regarding epistaxis, hematuria or oral mucosal petechiae [58]. Interestingly, a randomized controlled trial with 43 patients performed with an optimized integrated set for the treatment of platelet concentrates for A-L which minimized the loss of platelets during treatment in Europe, the 1- and 24-hour CCI was not statistically significant different between the A-L and the control group. Number, frequency and dose of platelet transfusions, acute transfusion reactions and adverse effects were similar between the two groups [59].

A Dutch–Belgian HOVON cooperative group has reported the results of a study where they looked at the clinical effectiveness ofuffy coat-derived leucoreduced platelet concentrates stored up to 7 days in plasma, in platelet additive solution with or without A-L treatment [60]. The authors reported that the primary endpoint of the study, 1-hour CCI was reduced a 31 % for A-L treated group in comparison to platelet concentrates in plasma \( (P < 0.0001) \). In addition, 32 % of patients had bleeding events \( (59 \% \) of them grade 1, i.e. petechiae, minimal or microscopic bleeding not requiring intervention) in the A-L arm, as compared to 19 % \( (63 \% \) grade 1, \( P = 0.045 \)) in the plasma arm. It is worthy of notice that the patients in the A-L arm had a mean pre transfusion platelet count significantly lower in comparison to patients receiving platelet products in plasma \( (16 \pm 11 \) vs. \( 18 \pm 13 \), \( P = 0.04 \)) and that the mean platelet content per transfused product was also significantly lower \( (3.9 \pm 1.0 \times 1011 \) vs. \( 3.4 \pm 0.8 \times 1011 \), \( P < 0.0001 \)). In theory, CCI calculation controls for the platelet dose administered and the posttransfusion platelet count increment, but data suggests that lower pre transfusion counts and lower platelet
content in the product produce lower CCI. In the PLADO study the group of patient receiving higher platelet dose had a posttransfusion CCI significantly higher (11 vs. 10, P = 0.03) in comparison to the group receiving medium dose [61].

The authors admitted that the number of off-protocol transfusions in the A-L arm (34 %) was an important limitation of the study and that the open label aspect of the study might have biased the evaluation of bleeding [60]. Actually, in PLADO, where the bleeding was evaluated by specifically trained blinded personnel, WHO grade 2 bleeding (gross, symptomatic bleeding and oropharyngeal bleeding or epistaxis for more than 30 minutes during a 24-hour period) was of 60 % [61] as compared to HOVON where the incidence was 6 % in the plasma arm.

A multicenter, randomized, controlled, double-blinded clinical trial looked at the effect of storing A-L treated buffy coat-derived platelets stored during 6 or 7 days compared versus control (TESSI study). The primary endpoint was the 1-hour CCI evaluated with a non-inferiority margin ratio of A-L treated/control > 0.70. The A-L:control platelet concentrates ratio of 1-hour CCI was 0.87 (95 % confidence interval: 0.73-1.03), demonstrating non-inferiority of A-L platelets. The mean 1-hour CCI for A-L and control platelets were 8163 and 9383, respectively. The 24-hour CCI was significantly lower for A-L platelets (4589 vs. 6549). However, the median time to the next platelet transfusion after study platelet concentrates was not significantly different between groups: (2.2-2.3 days; P = 0.72). The number of red blood cell concentrates (RBC) transfused 24 hours after study platelet concentrates and the maximal posttransfusion hemostatic scores were also not significantly different between groups. Acute transfusion reactions, hemorrhagic AE, overall AE, and serious AE were not significantly different between the A-L and non-treated groups [62].

Meta-analysis is a useful statistical tool, which allows the combination of different studies, in the hope of identifying among different study results patterns, source of disagreements or other relationship. So far, there are three meta-analysis published dealing with the results of clinical studies related to pathogen inactivation technologies [63-65]. Depending on the clinical studies included, and the methodology applied, mainly if recategorization of the bleeding grade reported in the studies is applied, the conclusions varies, from finding an increase in bleeding risk [64] or not [65].

There is also indirect evidence that suggest that the transfusion of A-L treated platelet concentrates is not associated to an increase in bleeding and is from the data of the use of RBC. In the SPRINT trial [57] and in the HOVON trial [60], the mean number of RBC transfusions was similar in patients receiving A-L treated platelet concentrates and in patients receiving control platelet components. In the Janetzko et al. study, the number of RBC transfusions per day at risk was the same in both groups [59]. Another source of interesting data are from those center, which implemented pathogen inactivation technology.

Osselaer et al. published their experience before and after implementing A-L in their University Hospital in Belgium. They analyzed the consumption of RBC units 3 years before and 3 years after implementing pathogen inactivated platelet concentrates. They considered the units of RBC that the patients undergoing platelet transfusion support received during the whole period and only during the period that the patients were actually receiving platelet transfusions. In all the periods analyzed, the number of RBC units received was similar in the two groups, 15.1 RBC units per patients before implementing A-L platelets and 15.0 RBC units per patients after implementation of A-L (P = 0.90) [66]. A similar experience has been reported by Cazenave et al. in Alsace [67].

In summary, evidence exist indicating that the inactivation of platelet concentrates with A-L provokes measurable effects on platelet in vitro tests although their adhering and aggregating capacities to damaged endothelium under flow conditions are preserved up to 7 days of storage. Data from in vivo studies using radiolabelling have shown that the recovery and survival of A-L inactivated platelets are decreased a 15.5 % and a 20 %, respectively, as compared to control. Data from randomized controlled trials suggest that 24-hour CCI is significantly reduced as compared to patients receiving non-inactivated products. However, data from randomized controlled trials, meta-analysis and from its use in routine in some center suggest that hemostatic capacity of A-L treated platelets is maintained and bleeding is not increased.

Regarding R-L treated platelet products, there is only one randomized controlled trial published. In that study, 118 patients were randomly assigned to received apheresis or buffy coat-derived platelets in plasma treated with R-L or without treatment and stored up to 5 days. The study patients received 678 platelet transfusions, 368 in the R-L group and 310 transfusion in the control group. The primary outcome was 1-hour CCI analyzed in the first eight platelet transfusion. The study failed to show non-inferiority of R-L treated platelet concentrates compared to controls. The least square mean 1-h CCI was 11,725 for R-L treated platelets and 16,939 for controls. The authors conclude that further studies are required to determine if the lower CCI observed in the study translated into an increased risk of bleeding [68]. Currently there are two clinical trials trying to clarify that point. One is PREPARES a multicenter international randomized controlled trial currently enrolling patients and the other one is the Italian Platelet Technology Assessment Study (IPTAS) a multicenter randomized controlled trial closed in June 30th 2014 due to financial restriction after enrolling 424 evaluable patients (the initial calculated size of the study was 828) whose results were presented at the AABB Annual Meeting in Anaheim, in October 2015 [69]. The study was actually two multicenter parallel studies. In one group A-L treated platelets were compared with controls in three centers and in the other group AB-L treated platelet (leukoreduced

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apheresis or buffy coat-derived whole blood platelets in additive solution), were compared with controls in three other centers. The results showed and increased proportion of patients transfused with treated platelets had grade 2 or higher bleedings (+5.5% A-L, 95% CI: −6.4 to 19.4; +3.8% R-L, 95% CI: −10.7 to 17.5) although the increase was not statistically significant. The mean number of platelet concentrates transfused per patient was 48% higher for A-L and 35% higher in the case of R-L. However, due to the reduce size and subsequent low power, the conclusions on non-inferiority were not possible [69].

Regarding UVC, only a phase I clinical study of apheresis platelet concentrates treated with UVC under agitation has been published. The results showed that repeated transfusions of autologous UVC-treated PCs were well tolerated and did not induce antibody responses in all volunteers studied [70].

The balance between safety and efficacy

From the evidence that we have reviewed, it is clear that bacterial infections are currently the main infectious complication for a recipient of a platelet transfusion. At a risk over 1000 times higher in comparison to the current residual risk for the usually screened viruses. However, there is a striking difference between the frequency of bacterial contamination in platelet concentrates is found and the development of clinical manifestations in the recipient of the contaminated unit. As discussed before several reasons explain that difference, from the fact that very often the main population receiving platelet transfusion, the hematologic-oncology patients, are receiving broad antibiotic coverage to the under-recognition and under reporting that the transfusion reaction that the recipient of the platelet transfusion is suffering is due to the presence of bacteria in the platelet product that the patient is or has just received. In contrast to viruses, where the screening strategy has shown to be highly successful reducing significantly the risk of transmission of infections via transfusion, that is not the case for bacteria. After implementing bacteria screening, i.e., the removal of a sample of the platelet concentrate in the first 24 hours of preparation and the microbiological culture of the sample, it has been shown that this strategy could only reduce the risk of bacteria sepsis in the recipient by 50%. Thus, data from the American Red Cross showed that the risk of dying after implementing bacterial screening of the concentrates remained at 1:498,711 per distributed component [18]. As presented, a very low number of bacterial present at the beginning of the storage are not sampled and thus, not detected by the culture method, although are able of growing exponentially at day 4 and 5 provoking then the fatal transfusion reaction in the recipient of the contaminated unit.

So far, the only strategy that has been able to eliminate completely the risk of bacterial contamination of platelet concentrates has been pathogen inactivation technologies. For instance, as Cazenave et al. has reported in Alsace between 2006 to 2012, that after implementing A-L for treating platelet concentrates, no case of bacterial septic reaction in recipients of platelet transfusions was reported to the hemovigilance system [67]. In contrast, in the same period 37 septic reactions (1:43,283) and 7 fatalities (1:240,211) were reported in regions where pathogen inactivation had not been implemented.

As discussed earlier, in vitro data have shown that pathogen inactivation technologies currently available in the market have measurable effects on platelets after storage. Meanly an increase in metabolic activity and also an increase in the activation markers of platelets. When the impact of pathogen inactivation technologies is studied in vivo, measuring the recovery and survival of treated platelets a decrease in was observed. The reduction in recovery ranges between 16 to 24% and in survival is between 20 to 26% [48,53]. However, when the impact of pathogen inactivation technologies on platelets is measured in patients for instance as the development of bleeding complications, one randomized controlled trial in the case of A-L treated platelets has shown that the incidence of WHO grade II bleeding was not statistically significant from that observed with the control platelets [57]. The IPTAS study reported a similar finding with no statistical significance in the incidence of WHO grade 2 bleeding in patients receiving A-L or R-L treated platelets with respect to the control.

However, what has been reported in two randomized controlled trials is that the patients receiving pathogen-reduced platelet is associated with an increase in the number of product transfused. For instance, SPRINT trial reported an increased usage of 35.4% of A-L treated apheresis platelets compared with control (8.4 A-L vs. 6.2 controls) [57]. The IPTAS study also reported an increase in utilization for A-L group (48%) and for R-L group 35%. This increase in utilization seems to be the toll to be paid if we want to completely eliminate the risk of bacterial sepsis in the recipients of a platelet transfusion introducing just a single measure in contrast to bacterial detection that we would need to perform two tests, one at the start of storage and another one at the time of transfusion, particularly in the concentrates stored for 4 to 5 days.

Conclusion

Bacterial contamination continues to be the major infectious risk for the recipient of a platelet transfusion at a level over 1000 times higher compared to virus infectious risks. The introduction of bacterial culture for preventing bacterial septic reactions has shown that this strategy reduces to one half the septic reactions, but does not eliminate completely that risk. To remove completely the risk, a new bacteria detection test at the time of issuance in the case of platelets stored for four or five days would be needed. Pathogen inactivation has shown to be efficacious in the inactivation of bacteria and no cases of septic reactions associated to a pathogen-reduced product have been identified. However, it has been shown that PI technologies
have measurable effects on platelet in vitro parameters and reduce the recovery and survival of treated platelets in vivo. Although these effects are not associated to and increase risk of bleeding of treated platelets, an increased usage associated with pathogen inactivation technologies has been reported. This increase in utilization seems to be the toll to be paid if we want to completely eliminate the risk of bacterial sepsis in the recipients of a platelet transfusion introducing just a single measure.

References


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