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Original Article

METHODS AIMED AT REDUCING THE RESIDUAL RISK OF PATHOGEN TRANSMISSION DURING PLATELET TRANSFUSION: A LITERATURE REVIEW

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ABSTRACT

Objective: In the Brazilian public health system, sterile filtration is often used to prevent infections associated with platelet transfusion. The literature addressing this issue indicates that pathogen inactivation could be incorporated as an alternative to the development of individual tests and blood donor selection. The objective was to assess whether the use of platelets submitted to pathogen inactivation by photochemical methods could decrease the incidence of post-transfusion infections by viruses, bacteria or other pathogens compared to the use of platelet concentrate or platelets extracted by apheresis without photochemical treatment.

Methods: A literature review from 1998 to 2015 was conducted. The scientific literature was surveyed using six electronic databases, two Internet search tools and a manual search of references, using specific search strategies for each database. The selected studies were assessed for quality according to a specific methodology. Data analysis was performed by observations made from the efficacy of the methods.

Results: From a detailed analysis of 426 articles retrieved, 10 articles were selected for this review. Among the selected studies, seven studies were clinical trials, and three studies were systematic reviews in combination with meta-analysis. The outcomes analyzed included the reduction of the residual risk in pathogen transmission, mortality, occurrence of hemorrhagic events, corrected count increment (CCI) after 1 h, CCI after 24 h, and transfusion reactions.

Conclusion: Differences were found in the quality of the included studies. Systematic reviews conducted on this topic, in alliance with political, social and administrative factors, will aid decision makers regarding its incorporation into the Brazilian Health System.

Keywords: Blood Platelets, Platelet Transfusion, Platelet Transfusion/methods*, Riboflavin, Ultraviolet Rays, Photosensitizing Agents, Platelet Transfusion/adverse effects

INTRODUCTION

Blood and blood component transfusions are important procedures in modern therapeutics; however, like most treatments, they may cause acute and late complications. Moreover, such procedures may also serve as vehicles for infectious agents. According to the World Health Organization (WHO) [1] the transmission of infectious agents through blood or blood components represents a focal point for transfusion risk. In the Brazilian public health system, transfusion is a high-cost practice associated with voluntary donation and cutting-edge technology. These features necessitate the rational use of blood components, always considering the safety of the donor and the recipient, and the availability of access [2].

In Brazil, besides donor selection, screening tests for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), syphilis, human T-lymphotropic viruses I and II (HTLV I-II), antibody against hepatitis B virus (HBV) core antigen (Anti-HBc) and *Trypanosoma cruzi* are performed on 100% of the blood bags [3]. In addition to the disposal of blood bags with the direct or indirect identification of pathogens, technological developments in chemotherapy have incorporated novel techniques that aim to increase transfusion safety, once immunology is a medical biotechnology area in constantly development [4].

Regarding the prevention of infections associated with platelet transfusion, sterile filtration to avoid clots and microaggregates is a prominent standard practice in the Brazilian public health system [3]. However, this technique does not a goal to eliminate pathogens and the literature addressing this issue highlights the need for identification and/or removal of emerging pathogens and zoonotic viruses [5]. Thus, pathogen inactivation has been proposed as a complementary approach to reduce residual risk of infection by a widely knowed microorganism and mainly when individual tests and blood donor selection are not enough [6, 7].

The techniques for pathogen inactivation can be used on several blood products. The methods applied in platelet concentrates are based on the assumption that the photochemical inactivation of pathogens nucleic acids may ensure safer transfusions.

These techniques were initially developed in the 1990s and, according to Kaiser-Guignard and colleagues [8], the three most commonly used technologies are the amotosalen/ultraviolet A (amotosalen/UVA) (Intercept® Blood System–Cerus, Europe, BV, Amersfoort, The Netherlands), riboflavin/ultraviolet A and ultraviolet B (riboflavin/UVA-UVB) (Mirasol® PRT) and ultraviolet C (UVC) (Theraflex-UVC®).

The present study aimed to identify and classify the available evidence on the efficacy of methods that aim to reduce the residual risk of pathogen transmission in platelet transfusions.

MATERIALS AND METHODS

The literature review sought to answer the following question: Compared to platelet concentrate or platelets extracted through apheresis without photochemical treatment, does the use of platelets inactivated by photochemical methods such as Intercept®, Mirasol® or Theraflex® decrease the incidence of post-transfusion infections by viruses, bacteria or other pathogens?

Additionally, the effects of the pathogen inactivation methods on the preservation of the blood components were assessed regarding the maintenance of transfusion efficacy compared to components that did not undergo photochemical treatment and with respect to ensuring the safety of the transfusion recipients.

The database searches were guided by questions according to a PICO question, which considered patients requiring platelet transfusion and intervention as treatment of platelets using amotosalen-HCl in combination with UVA radiation (Intercept® Blood System) or riboflavin in combination with UVA+UVB (Mirasol® PRT) or UVC radiation (Theraflex®). The comparison was between platelet concentrate and platelets extracted by apheresis without photochemical treatment. The observed outcomes were a reduction of the residual risk of pathogen transmission, mortality, occurrence of hemorrhagic events, duration of the hemorrhagic event, platelet count before transfusion, corrected count increment (CCI) after 1 h, CCI after 24 h, transfusion reactions. Randomized clinical trials and systematic literature reviews were selected and assessed.

Studies excluded from this review were those that concerned a matrix other than the one of interest (platelets), studies that used the technology during the blood product production process, experimental *in vitro* studies, studies that lacked an abstract and/or that used a technology different from the ones of interest, single-arm and/or open clinical trials, and studies that used a limited population or that did not evaluate any of the outcomes of interest.

The research was performed from August to December 2015. No temporal limits were set, thus all studies found in the investigated databases at the time of data collection were considered. Randomized controlled clinical trials that assessed pathogen inactivation methods regarding the outcomes of interest, as well as systematic reviews and meta-analyses, were selected to gather scientific evidence on the proposed technologies.

Descriptors, keywords and Medical Subject Headings (MeSH) terms were used to define the searches in the following electronic databases: Medline (via PubMed), Cochrane Library (via Bireme), Centre for Reviews and Dissemination (CRD), LILACS (via BVS) and Science Direct. Searches were performed with a combination of the terms for platelets and the terms of one of the technologies, according to the corresponding database. An additional search was performed in the reference list of the selected articles to find studies that were not identified in the electronic databases. A comparison of the search results in the different databases was performed to eliminate duplicates.

Regarding data collection and data mining, the initial stage, consisting of study selection, was performed through title and abstract reading by two reviewers (P. M. V. and R. R. A. F.). Next, the selected texts were read in full, and those that met the selection criteria were included. When the first two reviewers disagreed, a third reviewer (G. B. G. M.) made the final decision. All studies were subjected to the Oxford Centre for Evidence-Based Medicine (CEBM) Evidence Level [9].

After a full reading, the articles included were detailed in tables wherein the outcomes and the main findings were highlighted. The methodological limitations that might have compromised the strength of the results and conclusions were assessed. The CEBM recommendations were used as parameters. All studies were classified according to their methodological design. The associated recommendation level considered the quality and reliability of the information provided.

RESULTS

In the analyzed literature, the amount of evidence varied according to the type of pathogen inactivation technology and the blood component. No evidence was found for Theraflex UVC®. Among the technologies available for the microbial treatment of platelets, Intercept® (Amotosalen) was the most extensively studied, followed by Mirasol®.

Fig. 1 shows the selection process of the eligible studies. Out of 426 citations, six studies were included. Additionally, four studies identified from cross-references were included, totaling 10 studies that comprised this review. Among the included studies, seven were clinical trials (one associated with Mirasol® and six with Intercept®) and three were systematic reviews in combination with meta-analysis associated with Intercept®, totaling nine studies on Intercept® and one on Mirasol®.

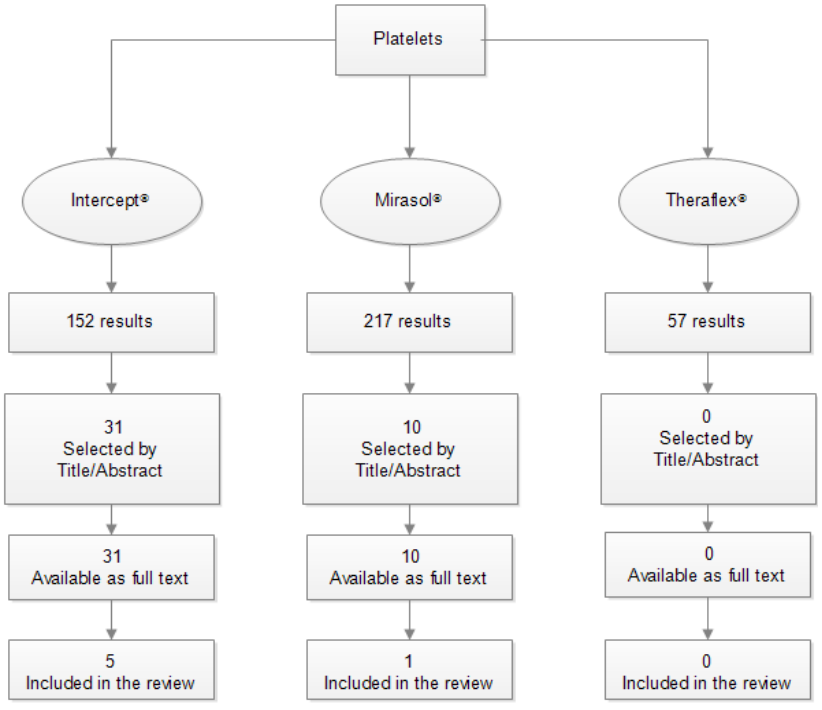

Fig. 1: Flowchart of results search and selection

For the Intercept® technology, which was applied when platelets were therapeutically recommended, three meta-analyses and six randomized clinical trials were obtained from the literature. table 1 shows the main features of the clinical trials.

Table 1: Outcomes of the selected clinical trials

Study	Outcome (Intervention vs. control)										Source
	Reduction of the residual risk of pathogen transmission	Mortality (%)	Occurrence of hemorrhagic events (%)	Duration of hemorrhagic events (days)	Amount of transfused blood components (mean dose) x 10[11]/l	Platelet count prior to transfusion (mean) x 10^9/l	Corrected count increment (CCI) after 1 h (mean) x 10^3/l	Corrected count increment (CCI) after 24 h (mean) x 10^3/l	Transfusion reactions	Interval between transfusions (days)	
Janetzko, 2005	No patient developed transfusion-associated sepsis or bacteremia	NA	45 vs. 62	NA	15.8±10.2 vs. 19.8±16.5	18.5 ±6.0 vs. 17.1±9.6	11.6±7.3 vs. 15.1±6.4	7.3±6.2 vs. 10.4± 6.5	23% vs. 29%	2.4±1.0 vs. 2.8±1.0	[10]
Lozano, 2011	NA	4.7 vs. 1.0	<25 in both groups	NA	NA	9.8±4.24 vs. 9.6±5.38	8.16±5.3 vs. 9.3±5.9	4.5±3.5 vs. 6.5±5.2	NA	No differences	[11]
McCullough, 2004	NA	3.5 vs. 5.2	58.5 vs. 57.5*	3.2 vs. 2.5*	3.7 vs. 4.0	15.1 vs. 15.2	11.1 vs. 16.0	6.7 vs. 10.1	3.0% vs. 4.4%	1.9 vs. 2.4	[12]
Simonsen, 2006	No patient developed transfusion-associated sepsis or bacteremia	NA	NA	NA	2.8±0.38 vs. 3.0±0.43	NA	6.58±4.53 vs. 8.93±13.14	NA	17.4% vs. 8.3%	27.1±24.0 vs. 30.0±18.5	[13]
Slitcher, 2006	NA	NA	NA	1-2 h later (19.3±9.5) 18-24 h later (18.3±9.3)	NA	29.2±1.6	10.4±4.9	6.6±3.8	13% acute reactions	NA	[14]
van Rhenen, 2003	No patient developed transfusion-associated sepsis or bacteremia	0 vs. 0	54 vs. 49	NA	22.3 vs. 21.2	19.1±13.3 vs. 16.7±13.1	27.5±13.5 vs. 35.8±23.3	16.4±9.5 vs. 24.7±17.6	1.6 vs. 5.0	NA	[15]

Source: Developed by the authors; NA: Not available

The outcomes evaluated in the clinical trials were heterogeneous. Janetzko and colleagues [10] and Lozano and colleagues [11] observed differences in the platelet corrected count increment (CCI) among the groups; however, according to the authors, these differences were not significant and thus were not clinically relevant. Alternatively, van Rhenen [15] and Simonsen [13] found that the 1-h CCI levels were significantly lower in patients who received platelets subjected to the intervention compared to patients who received control platelets (P=0.03).

Janetzko and colleagues [10] reported that the most common adverse events included fever, diarrhea, vomiting, and epistaxis, with at least one adverse event noted by each participant. The differences in the occurrence of severe adverse events between the intervention and control groups were not statistically significant. In contrast, Lozano [11] considered a positive blood culture as an adverse event and noted that 6.7% of the intervention group exhibited this event, compared with 1.9% in the control group. The other adverse events observed were fever, chills, nausea and cutaneous rash. In the study by van Rhenen [15], the most frequent adverse events were epistaxis, gingival bleeding, bleeding at the injection site and purpura; no significant differences were observed in the frequency of severe adverse events between the intervention and control groups.

The clinical trial performed by McCullough and colleagues [12] evaluated the percentage of patients with different bleeding levels according to the scale used by the WHO, which ranges from 0 to 5. The frequency of grade 2 hemorrhage was the primary outcome of the study; however, other bleeding levels were also assessed (grade 3 or 4 bleeding occurred in 4.1% of the intervention group and in 6.1% of the control group, with no statistical significance).

Moreover, patients in the intervention group were observed to have decreased the 1-h and 24-h CCIs and exhibited a shorter interval between transfusions. According to the authors, these differences would be minimized in clinical practice as the methodology performed for pathogen inactivation in this study resulted in platelet loss. A lower rate of platelet viability was also reported in the intervention group and thus, the frequency of platelet refractoriness was higher in this group.

In the study of van Rhenen [15], the need for a greater number of transfusions in the intervention group patients compared to the control group was reported (mean: 7.5±5.8 and 5.6±5.5, respectively). The authors suggested that this phenomenon was caused by the loss of platelet content in the samples subjected to the pathogen reduction technology, which occurred in two ways: (a) the need for samples used to verify the amotosalen concentration and (b) the loss of platelets during transfusion through the use of the technology. The crossover design was adopted in the clinical trial performed by Simonsen [13]. In this study, the authors did not observe the non-inferiority of the pathogen inactivation method in comparison to the platelet concentrate that was not subjected to the technology. In addition to the outcomes depicted in table 2, this study also evaluated changes in the level of bleeding events according to the WHO scale and observed no significant differences.

Our search revealed that the studies with the highest level of evidence were systematic reviews with a meta-analysis. Due to the heterogeneity of the outcomes addressed, it was not possible to synthesize the information into a single-table format. Only the outcomes of the 1-h CCI and the 24-h CCI were addressed by all studies and are thus depicted in table 3.

Table 2: Description of features in the selected studies

Study	Study population	Method of platelet collection	Outcomes	Observed results	Source
Butler, 2013 Level of Evidence: 1A	Systematic review/NA	NA	Number, type and severity of bleeding, mortality from all causes, adverse events, corrected count increment, need for and interval of red blood cell and platelet transfusion	Nine clinical trials evaluated the effectiveness of Intercept®. No evidence was reported of differences in mortality, "clinical significance", "severe bleeding", transfusion reactions or adverse events. Some benefits of the standard platelets were observed with respect to those subjected to Intercept®.	[16]
Cid, 2012 Level of Evidence: 1A	Meta-analysis/NA	NA	Corrected count increment after 1 hour and 24 h, interval between transfusions, bleeding odds ratio	Five clinical trials found. High variation of results among the randomized clinical trials. Inactivated blood showed lower corrected increment count (24-h CCI); however, this finding was not associated with differences in the bleeding odds ratio. A higher interval between transfusions was observed in patients who received platelets that were not subjected to pathogen inactivation.	[17]
Janetzko, 2005 Level of Evidence: 2B	Randomized, controlled clinical trials, double-blind, multicenter, phase III/43 patients affected by transfusion-dependent thrombocytopenia	Apheresis	Count increment after 1 hour and 24 h, acute transfusion reactions, adverse events, occurrence of bacteremia associated with transfusion, antibody formation against amotosalen	Photo chemically treated platelets and standard platelets were safe and effective.	[10]
Lozano, 2011 Level of Evidence: 1B	Non-inferiority, randomized, controlled, multi-center clinical trial, double-blind/242 blood cancer patients with thrombocytopenia	Apheresis/leukoreduced platelet concentrate	Proportion of patients with grade 2, 3 or 4 bleeding, number of days with grade 2 bleeding, 1-h and 24-h CIs and CCIs, number of days until new platelet transfusion, number of platelet transfusions, number of red blood cell transfusions, adverse events, development of antibodies against the neoantigen amotosalen	The 24-h CCI was significantly lower in patients who received blood subjected to pathogen inactivation; however, no significant changes were observed with regard to bleeding events. An episode of alloimmunization was observed in the intervention group, which led to one of the deaths.	[11]
McCullough, 2004 Level of Evidence: 1B	Randomized controlled, double-blind, multicenter clinical trial, phase III/671 blood cancer pediatric	Apheresis	Primary outcome: proportion of patients with grade 2 bleeding according to the scale used by the World Health Organization (WHO);	Patients who received platelets treated with Intercept® exhibited lower CCI levels and shorter intervals between transfusions.	[12]

	and adult patients with thrombocytopenia		secondary outcomes: proportion of patients with grade 3 or 4 bleeding, duration of grade 2 bleeding, 1-h and 24-h CIs and CCIs, interval between transfusions, number of platelet transfusions, incidence of platelet refractoriness, and number of red blood cell transfusions. Safety outcomes: number of transfusion reactions and development of antibodies to amotosalen		
Simonsen, 2006 Level of Evidence: 2B	Randomized, controlled clinical trial, non-inferiority/28 blood cancer patients with thrombocytopenia (or suspected thrombocytopenia)	Platelet concentrates leukoreduced by filtration	CCI at 1 h, CI at 1 h, interval between transfusions, frequency of acute transfusion reactions, changes in bleeding severity according to the WHO scale	CCI at 1 h, CI at 1 h and interval between transfusions were significantly lower in the intervention group. Transfusion reactions occurred at a significantly higher frequency in this group.	[13]
Slichter, 2006 Level of evidence: 2B	Randomized, controlled clinical trial, multicenter/60 blood cancer patients with thrombocytopenia	Collected with CS-3000 and leukoreduced by filtration	Hemostasis evaluated by duration of percutaneous bleeding, platelet count, increments, CCIs, interval between transfusions, clinical hemostasis	Patients with thrombocytopenia: Average bleeding time in PCT (29.2 min) and reference (28.7 min) groups. Mean 1-h CCI was 41.9 $X10^9$ and 52.3 $X10^9$for PCT and reference groups, respectively. Time to the next transfusion was 2.9 d and 3.4 d for PCT and reference groups, respectively. Clinical hemostasis did not differ.	[14]
Vamvakas, 2011 Level of Evidence: 1A	Meta-analysis/NA	NA	Hemostatic Efficacy	Four clinical trials were analyzed. Pathogen reduction led to a reduction in the 1-hour CCI; significant reduction in the 24-h CCI; increase in platelet transfusions, reduced interval among transfusions.	[18]
van Rhenen, 2003 Level of Evidence: 2B	Controlled, randomized, multicenter clinical trial, double-blind/103 patients with thrombocytopenia or receiving treatment that causes thrombocytopenia	Leukoreduced platelet concentrate	CCI at 1 h, CCI at 24 h, number of transfusions, interval between transfusions, clinical hemostasis before and after transfusions, amount of red blood cell transfusions, refractoriness, alloimmunization, adverse events, occurrence and severity of bleeding	Patients in the intervention group had significantly lower 1-h CCI and needed more platelet transfusions. Hemostatic scores, cases of refractoriness and number of red blood cell transfusions were similar among groups. No patient developed antibodies to amotosalen.	[15]

Source: [9-17]. NA: Not available

The other outcomes of lesser importance are briefly described in the following paragraphs.

Butler *et al.*, 2013 [16]

This study evaluated the efficacy of platelet concentrates subjected to pathogen reduction by both Intercept® and Mirasol® in preventing hemorrhages. Only clinical trials with any type of patient who required transfusion were considered. The studies comparing the use of Intercept® with the standard intervention were evaluated.

Eight clinical trials were found that examined the outcome of "any bleeding event"– regardless of the time or intensity. A meta-analysis was performed with a subgroup of studies that evaluated a single transfusion with a 48-hour follow-up (3 studies) and studies that evaluated multiple transfusions with a 7-day follow-up (5 studies). The pooled results for the first group showed no increased risk of bleeding associated with the intervention (RR 0.86 [0.63–1.19]; CI 95%; P=0.48 and I^2=0%). Regarding the arm that received the intervention, more bleeding was found (RR 1.07 [1.01–1.13]; CI 95%; P=0.007 and I^2=59%).

For the outcome of the clinically significant bleeding event, 6 clinical trials were found: 2 trials addressed single transfusions, and 4 trials addressed multiple transfusions. The meta-analysis performed only for the latter group that had a 7-day follow-up, showed no significant difference between the study arms (RR 1.04 [0.91–1.18]; CI 95%; P=0.58 and I^2=0%).

Regarding the outcome of severe bleeding, a meta-analysis was performed only for the subgroup of multiple transfusions with a 7-day follow-up. In the pooled results, no differences between the study arms were observed (RR 1.18 [0.67–2.06]; CI 95%; P=0.57 and I^2=60%).

Table 3: Outcomes of the selected clinical trials

Study	Outcomes (I vs. C)										Source
	Reduction of the residual risk of pathogen transmission	**Mortality (%)**	**Occurrence of bleeding events (%)**	**Duration of bleeding events (days)**	**Amount of transfused blood components (mean dose)) x 10[11]/l**	**Platelet count prior to transfusion (mean) x 10^9/l**	**Corrected count increment (CCI) after 1 h (mean) x 10^3/l**	**Corrected count increment (CCI) after 24 h (mean) x 10^3/l**	**Transfusion reactions**	**Interval between transfusions (days)**	
Janetzko, 2005	No patient developed transfusion-associated sepsis or bacteremia	NA	45 vs. 62	NA	15.8±10.2 vs. 19.8±16.5	18.5 ±6.0 vs. 17.1±9.6	11.6±7.3 vs. 15.1±6.4	7.3±6.2 vs. 10.4± 6.5	23% vs. 29%	2.4±1.0 vs. 2.8±1.0	[10]
Lozano, 2011	NA	4.7 vs. 1.0	<25 in both groups	NA	NA	9.8±4.24 vs. 9.6±5.38	8.16±5.3 vs. 9.3±5.9	4.5±3.5 vs. 6.5±5.2	NA	No differences	[11]
McCullough, 2004	NA	3.5 vs. 5.2	58.5 vs. 57.5*	3.2 vs. 2.5*	3.7 vs. 4.0	15.1 vs. 15.2	11.1 vs. 16.0	6.7 vs. 10.1	3.0% vs. 4.4%	1.9 vs. 2.4	[12]
Simonsen, 2006	No patient developed transfusion-associated sepsis or bacteremia	NA	NA	NA	2.8±0.38 vs. 3.0±0.43	NA	6.58±4.53 vs. 8.93±13.14	NA	17.4% vs. 8.3%	27.1±24.0 vs. 30.0±18.5	[13]
Slichter, 2006	NA	NA	NA	1-2 h later (19.3±9.5) 18-24 h later (18.3±9.3)	NA	29.2±1.6	10.4±4.9	6.6±3.8	13% of acute reactions	NA	[14]
van Rhenen, 2003	No patient developed transfusion-associated sepsis or bacteremia	0 vs. 0	54 vs. 49	NA	22.3 vs. 21.2	19.1±13.3 vs. 16.7±13.1	27.5±13.5 vs. 35.8±23.3	16.4±9.5 vs. 24.7±17.6	1.6 vs. 5.0	NA	[15]

Source: [9-14] (I vs. C): Intervention vs. Control. NA: not available. *Results of grade 2 or higher bleeding (according to the World Health Organization classification, 2003)

Concerning mortality from all causes, a meta-analysis was performed only for studies with a 12-week follow-up (6 clinical trials). In this case, no difference was observed between the intervention arms (RR 0.73 [0.41–1.29]; CI 95%; P=0.28 and I^2=0%). For mortality caused by hemorrhage and by infection, meta-analysis was performed with the same studies, and no differences between the arms were observed in any case, with the following results: (RR 1.03 [0.28–3.72]; CI 95%; P=0.97 and I^2=0%) and (RR 0.58 [0.25–1.39]; CI 95%; P=0.22 and I^2=0%), respectively.

Cid *et al.*, 2012 [17]

This study aimed to evaluate the use of Intercept® as a method of pathogen inactivation, with a focus on the following outcomes: 1-h and 24-h CCI, in addition to the odds ratio (OR) for bleeding events.

A meta-analysis of 4 clinical trials was performed for bleeding events. Due to differences among the findings, the hypothesis of homogeneity was rejected. Moreover, I^2 showed moderate discrepancy among the results (I^2=53%; CI 95%, 0%-83%).

Thus, the study examined 8 subgroups of constructed studies wherein the assumption of homogeneity was not rejected in the following 5 results: double-blind studies with ABO compatibility, studies with 5-day storage period for platelets, studies with high-quality Jadad scores [19] and studies that used the WHO bleeding scale.

The use of Intercept® was not statistically associated with an increase in the OR associated with bleeding events compared to the non-intervention in any the subgroup analyses. The results of these five subgroups are shown in table 4.

Table 4: Results of bleeding events with Intercept® for the study subgroups

Study subgroup	Number of studies	OR [CI 95%]	P-value for Q test	I^2 (%)	Source
Double blind	4 [1-4]	0.97 [0.75–1.27]	0.58	0	[10–12,15]
ABO compatibility	2 [1,4]	0.84 [0.48–1.45]	0.76	0	[10–12,15]
5-day storage	3[1-3]	1.04 [0.78–1.39]	0.26	21	[10,12,15]
High Jadad quality (3-5)	4 [1-4]	0.97 [0.75–1.27]	0.58	0	[10–12,15]
WHO scale	3 [2-4]	0.95 [0.72–1.25]	0.44	0	[10–12]

Vamvakas, 2011 [18]

This systematic review with a meta-analysis of 4 clinical trials used the main outcomes of the 1-h and 24-h CCIs. These outcomes were also reported by all other systematic reviews and are depicted in table 5.

Regarding the Mirasol® technology, only one clinical trial was obtained from the literature on the use of this technology as recommended for platelets. The study evaluated a group of 118 patients (60 in the intervention group and 58 in the control group) that received a total of 541 transfusions during 28 d. The outcomes measured are presented in table 5.

The study of Cazenave [20] did not report non-inferiority of platelets treated by Mirasol® compared to platelets that were not subjected to this method with regard to the primary outcome analyzed, the 1-h CCI. The result was similar for the secondary outcomes. One hour after the transfusions, 71.3% of transfusions were successful in the intervention group compared with 84.1% in the control group. After 24 h, this result was 58.9% and 68.1%, respectively.

Table 5: Description of the outcomes found in the meta-analyses

Study	1-h CCI ($x10^3$) [CI 95%] Difference among the means	24-h CCI ($x10^3$) [CI 95%] Difference among the means	Source
Butler, 2013	-0.89 [-2.35; 0.58]	-1.96 [-3.24;-0.68]	[16]
Cid, 2012	1.4 [-2.69; 0.11]	3 [-3.69; 2.32]	[17]
Vamvakas, 2011	3.15 [1.85; 4.45]	3.5 [2.06; 5.0]	[18]

Source: Developed by the authors

To evaluate the method's safety, the occurrence of infections as adverse events was assessed. Through this analysis, no significant differences were observed in the proportion of patients with one or more infections when the intervention and control groups were compared. Mortality was included as a severe adverse event; however, mortality data were not presented separately. In the intervention group, 13 patients (23.2%), compared to 11 patients (20.4%) in the control group, had at least one severe adverse event.

The results showed that the patients who received platelets subjected to this technology exhibited inferior evaluations in regard to the analyzed outcomes; however, this finding was not clinically significant. Regardless, no riboflavin reference concentration was found to be recommended for this use, thus it is not possible to conclude whether the concentration that was able to maintain platelet viability is the same concentration that should be used for pathogen inactivation.

DISCUSSION

The studies showed several types of heterogeneity in their methodologies, traversing the domains of clinical, methodological and statistical diversity.

Some of the observed heterogeneity was associated with the population included in the study, the variety of the observed outcomes and differences in the methodology and parameters used to measure the outcomes.

Moreover, it was possible to observe that no gold standard existed for the outcomes or for measuring the outcomes, with no gold standard to determine the efficacy and safety, creating obstacles for the comparison of the data collected and generating considerable heterogeneity among the studies.

Limitations were also found in the analyzed studies. Among these limitations, the following may be highlighted: (a) inadequate amotosalen concentration use, with some studies using the technology component solution at concentrations below those recommended by the Food and Drug Administration (FDA); (b) inaccuracy or omission of the method for obtaining the blood component, without any specification of whether it was through apheresis or buffy-coat and/or the amotosalen dose used; and (c) a lack of outcome standardization, wherein each study evaluated efficacy and safety in a specific manner instead of using a common manner.

Studies by Simonsen [13], Janetzko [10], McCullough [12] and van Rhenen [15] reported the use of amotosalen in a concentration significantly lower than that recommended by the FDA (150 µM vs. 3 mM). In the study of Lozano [11], the concentration used was not described. Notably, the main aim of that study was to test the safety of the pathogen inactivation method and thus it would have been germane to discuss the differences between the concentrations tested and the one that was approved. This observation may represent an important confounding variable because it is not possible to assure that the low occurrence of adverse events and platelet quality would be maintained had the approved concentration been used instead, which is 20 times the concentration tested.

CONCLUSION

The present study aimed to evaluate, from a comprehensive review of the scientific literature, the evidence demonstrating the potential benefits and risks of the large-scale use of platelets subjected to pathogen inactivation methods. The scope of the literature was distinctive. Evidence for employing the amotosalen (Intercept®) technology was more robust and was supported by a higher number of studies. Overall, the studies aimed to assess the efficacy and safety of the transfusions of platelets previously treated with pathogen inactivation methods in comparison to untreated platelets. The outcomes in reference to platelet efficacy were associated, directly or indirectly, with the ability of the method to maintain the viability of this blood component. Concerning the safety aspect, the observations were similar to those regarding the efficacy, always referring to the blood component attributes.

The results of the studies predominantly found no significant differences of the transfusion efficacy between the intervention and control arms, particularly in the case of outcomes associated with hemorrhagic events.

Notably, the use of Intercept® resulted in a reduction in the number of platelets and the volume to be transfused. Moreover, it is currently unclear whether the relationship between the amotosalen concentration and platelet reduction is dose-dependent. Amotosalen was found to have been used at concentrations significantly lower than the dose approved for clinical practice by the FDA; thus, if a dose-dependent relationship is eventually detected, it is possible that the use of amotosalen at the recommended concentration may cause a significant reduction in the number of platelets, capable of interfering with the efficacy of the clinical procedure and with the need for more donations.

Ultimately, the studies showed supportive results concerning efficacy; however, results addressing the inactivation of pathogens were lacking. Thus, the data are insufficient to conclude that such methods exhibit clinical superiority in regard to their primary purpose: to prevent post-transfusion infections.

The currently available evidence supports the conclusion that the methods that actually inactivate pathogens in blood components are based on *in vitro* studies only. However, even if the evidence exists from *in vitro* studies, the epidemiological data showing the efficacy of a particular method against a specific pathogen are the most important type of evidence in clinical practice [8].

Most of the clinical trials assessed were non-inferiority trials, i.e., they sought to show that the quality of platelet concentrates that were subjected to pathogen inactivation was not inferior to the control. In contrast, the few studies that assessed bacteremia and sepsis after transfusion as adverse events found no such events in

both the intervention and control arms. These findings do not permit us to conclude that the technologies herewith are effective for pathogen inactivation; thus, based on this weak evidence, our recommendation is that these technologies not be incorporated into the Brazilian Unified Health System.

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest regarding the content of this article.

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