Therapeutic efficacy of platelet components treated with amotosalen and ultraviolet A pathogen inactivation method: results of a meta-analysis of randomized controlled trials

J. Cid, G. Escolar & M. Lozano
Department of Hemotherapy and Hemostasis, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Hospital Clínic, University of Barcelona, Barcelona, Spain

Background and Objectives There are conflicting data regarding the therapeutic efficacy of platelets inactivated using amotosalen and ultraviolet A light. We have performed a meta-analysis to summarize the results of different randomized controlled trials (RCT).

Materials and Methods Five RCTs reported through March 2011 met the criteria for meta-analysis. Weighted mean difference (WMD) in corrected count increment (CCI) at 1 h, CCI-24 h, and transfusion interval (days) and summary odds ratio (OR) of bleeding in inactivated platelet (I-P) group vs. noninactivated platelet (C-P) group were calculated across studies.

Results Randomized controlled trials were statistically homogeneous when we analysed CCI-24 h, and the transfusion of C-P was associated with a higher CCI-24 h when compared with the transfusion of I-P (WMD, 3 × 10^3; 95% CI, 2.32 × 10^3–3.69 × 10^3; P < 0.00001). RCTs were statistically heterogeneous when we analysed CCI-1 h, transfusion interval and OR of bleeding. Regarding the OR of bleeding in the I-P and C-P groups, it varied by as much as a multiple of four among the trials, from 0.66 to 2.66. When we combined double-blinded and high methodologic quality score RCTs, the use of I-P was not statistically associated with an increase in the OR of bleeding when compared with the use of C-P (OR, 0.97; 95% CI, 0.75–1.27; P = 0.84).

Conclusion Although the transfusion of I-P was associated with lower CCI-24 h when compared with the transfusion of C-P, this was not associated with differences in the OR of bleeding between I-P and C-P.

Key words: meta-analysis, pathogen inactivation, platelet transfusion.

Introduction Despite continued improvements in pretransfusion donor screening and testing to detect viruses associated with transfusion-transmitted infections, blood components continue to carry risk of infectious diseases [1]. The transmission of some infections still occurs because the present reactive approach to avoid them is limited to specific known pathogens, is not effective against bacterial contamination [2], does not test for all pathogens [3], fails to prevent transmission of CMV despite testing [4] and tests for new pathogens, such as West Nile virus [5] or Chikungunya virus [6], can only be implemented after the new agent is identified. And unfortunately, the list of infectious agents causing life threatening infections is continuously increasing [7]. Moreover, with increasing globalization combined with climate changes, previously localized transfusion-transmitted infections are now becoming more widespread or appearing in places where they did not exist before [8]. To reduce the risk of bacterial contamination of platelet concentrates (PC), different strategies have been implemented, including sensitive bacterial
screening of PCs. However, transfusion-related sepsis continues to occur and the US Food and Drug Administration determined that in spite of performing bacterial screening, 5 days should be the maximum shelf life of PCs due to residual bacterial septic risk [9, 10]. For all these reasons, proactive strategies have been developed to treat the blood components in a way that will inactivate viruses, bacteria, protozoa and contaminating leucocytes but retain therapeutic efficacy of blood components [11, 12].

One method for inactivating PCs (I-P) uses a novel psoralen, amotosalen and ultraviolet A (UVA) light (A-UVA, Intercept Blood System; Cerus Co, Concord, CA, USA) to inactivate a broad spectrum of viruses, bacteria, protozoa and leucocytes in PCs and plasma [13]. Amotosalen intercalates into helical regions of DNA and RNA and is cross-linked to pyrimidine bases upon activation with UVA light (320–400 nm), thereby preventing replication of susceptible pathogens and leucocytes. PCs treated with A-UVA demonstrated acceptable viability in healthy volunteers [14], corrected prolonged bleeding times in thrombocytopenic patients [15] and exhibit adhesive and aggregating capacities similar to noninactivated platelets (C-P) in vitro [16]. To our knowledge, there are five published randomized controlled trials [RCT] [17–21] and two meta-analyses that examined the therapeutic efficacy and safety of I-P, one of the meta-analysis combining amotosalen and riboflavin RCTs [22] and another one limited to amotosalen and UVA RCTs [23]. One of the RCT [20] and the two meta-analyses [22, 23] reported data suggesting that the clinical efficacy of I-P was inferior to C-P resulting in an increase in bleeding.

We report here another meta-analysis of amotosalen and UVA published RCTs, where, using a different approach from that applied in the meta-analyses published so far, we have looked at the therapeutic efficacy of I-P in patients who had thrombocytopenia due to hypoproliferative marrow requiring platelet transfusion support.

Materials and methods

Randomized controlled trials reported through March 2011 in which the intervention was transfusion of I-P with A-UVA and were identified from MEDLINE (1966–2011), EMBASE (1980–2011) and the Cochrane Library. Sensitive RCT search strategies based on those published before [24, 25] were used on MEDLINE and EMBASE, combined with text and index terms to capture the topic of interest. In the Cochrane Library, only topic-specific index search terms were employed. The reference lists of the identified RCTs and relevant narrative reviews were checked for additional RCTs. To be eligible for inclusion in the meta-analysis, a study had to have enrolled a treatment group of patients receiving I-P treated with A-UVA and a group of patients receiving C-P. (2) had to have reported (or presented data for the calculation of) the following outcome measures:

(a) the mean difference in the corrected count increment at 1 h (CCI-1 h), at 24 h (CCI-24 h) and the transfusion interval
(b) the odds ratio (OR) of bleeding in the I-P group vs. the C-P group

The quality of the design of the clinical trials was assessed by instrument of Jadad et al. [26]. Briefly, the maximum quality score that can be given to a study by this instrument is 5: up to two points given for random assignment of patients to comparison groups; up to two points given for blinding investigators and patients and one point given if all enrolled patients are accounted for at the inclusion of the study with reasons for all dropouts and withdrawals.

The authors extracted the following information from all RCTs eligible for analysis:

(1) the mean and standard deviation (SD) of the post-transfusion platelet CCI and of the transfusion interval of the I-P group, the mean and SD of the post-transfusion platelet CCI and of the transfusion interval of the C-P group, and the number of patients included in the I-P and C-P groups;

(2) 2 × 2 contingency table counts for the calculation of the OR of bleeding in the I-P vs. the C-P group.

It is important to point out that we collected the previous data as reported in the original RCTs. Of note, regarding the OR of bleeding, we did not recategorize the bleeding events because of the following reasons: (1) bleeding is a complex outcome because it is composite [27], (2) the five RCTs included in the present meta-analysis used three different bleeding scales and (3) measuring and grading bleeding is difficult [28], and observers often disagree [29]. Taking into account these previous caveats, we considered that recategorization of the bleeding events might introduce another potential variable that might affect the results of the meta-analysis.

If we did not find the necessary data in the published RCTs, we contacted with authors and/or sponsors of the trials to obtain them [30, 31].

Statistical analysis

An OR of bleeding in the I-P group vs. the C-P group and a 95% confidence interval (CI) of the OR were calculated for each study. The OR compares the odds of bleeding among the I-P group with the odds of bleeding among the C-P group. The odds of bleeding among the patients in one
group equal the probability that those patients will present a bleeding event divided by the probability that those patients will not present a bleeding event. Summary of OR of bleeding in the I-P group (compared with the C-P group) was calculated across the combined studies by the random-effects method. A weighted mean difference (WMD) and a 95% CI of post-transfusion platelet CCI or transfusion interval were calculated for each study. To combine the mean differences in the post-transfusion platelet CCI or the transfusion interval across the studies, we used the random-effects method. In both cases, we used the random-effects meta-analysis because we assumed that the treatment effects for the individual studies vary around some overall average treatment effect, although there is no consensus about whether to use fixed or random-effects models [32].

Because of controversy in providing a meta-analytical estimate when statistical heterogeneity is present, the results of separate studies were integrated in this meta-analysis only if the variation in reported findings was sufficiently modest to be attributed to chance. This condition is met if the hypothesis of homogeneity of effects is not rejected across the studies that are eligible for inclusion in the meta-analysis. Therefore, prior to any integration of studies results, the magnitude of variation in reported findings was evaluated in this analysis using a $Q$ test statistic. The $P$-value calculated by the $Q$ test statistic represents the probability that the variation in reported results might have arisen by chance. The hypothesis of homogeneity is rejected if $P < 0.20$, that is, if there is a smaller than 20% probability that the differences among the studies might have arisen by the chance. We chose $P < 0.20$ as the cut-off point because it is known that the power of the $Q$ test statistic becomes unacceptably low when the number of eligible studies is small [31], as in the current meta-analysis. Moreover, we also used the quantity $I^2$ to measure the consistency between trials and to know the percentage of total variation across studies that is a result of heterogeneity rather than chance [34, 35]. We considered inconsistency between trials when the mean of the quantity $I^2$ was $>40\%$.

When the studies eligible for meta-analysis were not homogeneous according to the results of the $Q$ test statistic and $I^2$, we prespecified and evaluated the following seven variables as possible sources of variation in the reported efficacy of the transfusion of I-P (Table 1): (1) design of the study (double blinded vs. open label), (2) number of days of platelet transfusion support (1 day vs. $>1$ day), (3) platelet transfusion trigger ($\leq10 \times 10^9/l$ vs. $>10 \times 10^9/l$), (4) ABO compatibility of platelets transfused (all vs. variable vs. not stated), (5) maximum storage duration of transfused platelets (5 days vs. 7 days), (6) methodologic quality score (0–2 vs. 3–5) and (7) grading of bleeding (WHO scale vs. other scales).

Each of these seven study descriptors had two or three levels. Studies were stratified according to the levels of each individual descriptor, to allow examination of whether the hypothesis of homogeneity would still be rejected if the analysis was limited to studies that were similar in that descriptor. Altogether, the seven study descriptors had a total of 15 possible levels. So, we conducted as many as 15 analyses for each of the outcome measures.

Analysis was carried out with software (Review Manager (REVMAN) (Computer program). Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

**Results**

We electronically retrieved 31 studies, but we excluded 26 because of the following reasons: 21 were not RCTs, three were further analyses of the SPRINT trial, and two were cross-over studies. Indeed, we identified five RCTs that compared the transfusion of I-P and C-P, met all the three criteria listed earlier and were, thus, eligible for the

### Table 1 Randomized controlled trials that compare inactivated vs. noninactivated platelet transfusion: study descriptors

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Design of the study</td>
<td>Double blinded</td>
<td>Double blinded</td>
<td>Double blinded</td>
<td>Open label</td>
<td>Double blinded</td>
</tr>
<tr>
<td>Number of days of platelet transfusion support</td>
<td>Up to 56</td>
<td>Up to 28</td>
<td>Up to 28</td>
<td>Up to 42</td>
<td>1</td>
</tr>
<tr>
<td>Platelet transfusion trigger ($\times 10^9/l$)</td>
<td>$&lt;20$</td>
<td>$&lt;10$</td>
<td>$&lt;20$</td>
<td>10–40–60</td>
<td>10–20</td>
</tr>
<tr>
<td>ABO compatibility</td>
<td>All ABO compatible</td>
<td>Variable</td>
<td>Not stated</td>
<td>Not stated</td>
<td>All ABO compatible</td>
</tr>
<tr>
<td>Maximum storage duration of transfused platelets (days)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Methodologic quality score$^a$</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Grading of bleeding</td>
<td>Own scale</td>
<td>WHO$^b$ scale</td>
<td>WHO scale</td>
<td>CTCAE$^c$ criteria</td>
<td>WHO scale</td>
</tr>
</tbody>
</table>

$^a$ According to the scale of Jadad et al. [26].
$^b$ World Health Organization.
$^c$ Common terminology criteria for adverse events.
inclusion in the meta-analysis [17–21]. The study descriptors of the RCTs analysed are outlined in Table 1. It is important to point out that all trials except one [20] were double-blinded RCTs. All trials included patients who suffered from chemotherapy-induced thrombocytopenia: three trials included patients with haematologic and oncologic diseases, and patients who underwent stem cell transplantation (SCT) [17, 18, 20]; one trial included only patients who underwent SCT [19]; and one trial included patients with haematologic diseases and patients who underwent SCT [21].

The quality of the studies is shown in Table 2. No trial presented a high quality according to the scale by Jadad et al. [26] because of the following reasons: first, all trials were randomized, but four trials did not describe the method to generate the sequence of randomization [17–20]; second, one study was not double blinded [20]; third, only two trials described the number and the reasons for withdrawal in each group [18, 20].

**Mean difference in the post-transfusion CCI-1 h**

This outcome was available in all five RCTs included in this meta-analysis (Fig. 1). The published SPRINT trial reported only the mean CCI-1 h and authors kindly provided the SD after our request [18]. In two trials [18, 20], there was a significant increase ($P < 0.01$) in the CCI-1 h in the C-P group when compared with the I-P group. The mean difference in the CCI-1 h between C-P group and I-P group varied by as much as a multiple of four among the five trials, with a range from $1.2 \times 10^3$ in the trial by Lozano et al. [21] to $4.9 \times 10^3$ in the SPRINT trial [18].

Because of the variation among the findings of the RCTs, the hypothesis of homogeneity was rejected ($P = 0.002$ for the $Q$ test statistic) when all five trials were combined. Moreover, the $I^2$ showed high inconsistency among the results ($I^2 = 77\%$; 95% CI, 43–90%). Thus, we performed eight subgroup analyses according to the levels of the seven study descriptors (Table 3). The hypothesis of homogeneity was still rejected in all but one of the subgroup analyses (Table 3 in bold). The $Q$ test showed a $P = 0.67$ and the $I^2 = 0\%$ when the trials that guaranteed the ABO compatibility of the platelet transfusions were combined. In such case, the use of C-P was statistically associated with an increase in the CCI-1 h when compared with the use of I-P (WMD, $1.4 \times 10^3$; 95% CI, $0.11 \times 10^3$–2.69 $\times 10^3$; $P = 0.03$).

**Mean difference in the post-transfusion CCI-24 h**

This outcome was available in all five RCTs included in this meta-analysis (Fig. 2). The published SPRINT trial reported only the mean CCI-24 h, and authors kindly provided the SD after our request [18]. The hypothesis of homogeneity was not rejected by the $Q$ test ($P = 0.39$), and the statistic $I^2$ showed no inconsistency among results ($I^2 = 3\%$; 95% CI, 0–80%). The transfusion of C-P was associated with a higher CCI-24 h when compared with the transfusion of I-P (WMD, $3 \times 10^3$; 95% CI, $2.32 \times 10^3$–$3.69 \times 10^3$; $P < 0.00001$).

**Mean difference in the transfusion interval**

This outcome was available in all five RCTs included in this meta-analysis (Fig. 3). The published SPRINT trial reported only the mean transfusion interval, and authors kindly provided the SD after our request [18]. In two trials [18, 20], there was a significant increase ($P < 0.05$) in the transfusion interval in the C-P group when compared with the I-P group. The mean difference in the transfusion interval between C-P group and I-P group had a range from 0 days in the trial by Lozano et al. [21], to 0.67 days in the trial by Kerkhoffs et al. [20].

Because of the variation among the findings of the RCTs, the hypothesis of homogeneity was rejected ($P = 0.15$ for the $Q$ test statistic) when all five trials were combined. Moreover, the $I^2$ showed high inconsistency among the results ($I^2 = 41\%$; 95% CI, 0–78%). Thus, we performed eight subgroup analyses according to the levels of the seven study descriptors (Table 3). The hypothesis of homogeneity was still rejected in all but three of the subgroup analyses (Table 3 in bold). The $Q$ test showed a $P = 0.89$ and the $I^2 = 0\%$ when all the trials that performed a platelet transfusion support >1 day were combined. In such case, the use of C-P was statistically associated with an increase in the transfusion interval when compared with the use of I-P (WMD, 0.5 days; 95% CI, 0.35–0.65; $P < 0.00001$). The $Q$ test also showed a $P = 0.21$ and the $I^2 = 34\%$ when the trials that had a platelet transfusion trigger $>10 \times 10^9/\lambda$ were combined. In such case, the use of C-P was statistically associated with an increase in the transfusion interval.

---

**Table 2** Assessment of the quality of randomized controlled trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Blinding</th>
<th>Patient attrition</th>
<th>Total quality score$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum score</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Study</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>EuroSPRITE [17]</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>SPRINT [18]</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Janetzko [19]</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Kerkhoffs [20]</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lozano [21]</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$According to the scale by Jadad et al. [26].
when compared with the use of I-P (WMD, 0.28 days; 95% CI, 0.04–0.51; P = 0.02). The Q test also showed a P = 0.9 and the $I^2 = 0\%$ when the trials that stored platelets for up to 5 days were combined. In such case, the use of C-P was statistically associated with an increase in the transfusion interval when compared with the use of I-P (WMD, 0.48 days; 95% CI, 0.33–0.64; P < 0.0001).

**OR of bleeding**

This outcome was available in all five RCTs included in this meta-analysis (Table 4, Fig. 4). All but one study [20] did not detect a significant difference in the OR of bleeding in the I-P and C-P groups. The OR of bleeding varied by as much as a multiple of four among the trials, from 0.66 in the trial by Kerkhoffs et al. [21] to 2.66 in the trial by Lozano et al. [21] to 2.66 in the trial by Kerkhoffs et al. [20].

Because of the variation among the findings of the RCTs, the hypothesis of homogeneity was rejected ($P = 0.08$ for the $Q$ test statistic) when all five trials were combined. Moreover, the $I^2$ showed high inconsistency among the results ($I^2 = 53\%$; 95% CI, 0% to 83%). Thus, we performed eight subgroup analyses according to the levels of the seven study descriptors (Table 3). The hypothesis of homogeneity was rejected ($P = 0.04$ for the $Q$ test statistic) when the trials that stored platelets for up to 5 days were combined. In such case, the use of C-P was statistically associated with an increase in the transfusion interval when compared with the use of I-P (WMD, 0.48 days; 95% CI, 0.33–0.64; P < 0.0001).
was not rejected in five subgroup analyses (Table 3 in bold). All these five subgroup analysis showed no statistically significant increase in the OR of bleeding of I-P when compared with C-P. The \( Q \) test showed a \( P = 0.58 \) and the \( I^2 = 0\% \) when double-blinded trials and high methodologic quality trials were combined. In such case, the use of I-P was not statistically associated with an increase in the OR of bleeding when compared with the use of C-P (OR, 0·97; 95% CI, 0·75–1·27; \( P = 0·52 \); Fig. 5). The \( Q \) test also showed a \( P = 0·44 \) and the \( I^2 = 0\% \) when the trials that used the WHO scale for grading bleeding were combined. In such case, the use of I-P was not statistically associated with an increase in the OR of bleeding when compared with the use of C-P (OR, 0·95; 95% CI, 0·72–1·25; \( P = 0·71 \)).

Discussion

We present here the results of a meta-analysis of RCTs studying the effect of transfusing C-P and I-P, treated with A-UVA. We have focused the meta-analysis in four outcome measures: the CCI-1 h, the CCI-24 h, the interval between transfusions and the appearance of bleeding. The main conclusion of the present meta-analysis is that there was a high variation among the findings of the RCTs and the hypothesis of homogeneity was rejected when all five RCTs were combined in the case of three outcomes: the CCI-1 h, the CCI-24 h, and the OR of bleeding.

We therefore evaluated the seven variables described before as possible sources of the reported variation. In all these cases, the meta-analysis served us to investigate the reasons for disagreements among studies that differed markedly in size although they all pointed at the same

---

**Table 4** Reported odds of bleeding in the included randomized controlled trials (RCT)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV, Random</td>
<td>IV, Random</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>Weight</td>
</tr>
<tr>
<td><strong>Study or Subgroup</strong></td>
<td>Mean Difference</td>
<td>Mean Difference</td>
</tr>
<tr>
<td></td>
<td>IV, Random</td>
<td>IV, Random</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>Weight</td>
</tr>
<tr>
<td><strong>RCTs</strong></td>
<td>I-P group(^a)</td>
<td>C-P group(^b)</td>
</tr>
<tr>
<td>EuroSPRITE [17]</td>
<td>0·90 [0·75, 1·05]</td>
<td>0·90 [0·75, 1·05]</td>
</tr>
<tr>
<td>SPRINT [18]</td>
<td>0·91 [0·76, 1·08]</td>
<td>0·91 [0·76, 1·08]</td>
</tr>
<tr>
<td>Janetzko [19]</td>
<td>0·92 [0·77, 1·10]</td>
<td>0·92 [0·77, 1·10]</td>
</tr>
<tr>
<td>Kerkhoffs [20]</td>
<td>0·93 [0·78, 1·11]</td>
<td>0·93 [0·78, 1·11]</td>
</tr>
<tr>
<td>Lozano [21]</td>
<td>0·94 [0·79, 1·11]</td>
<td>0·94 [0·79, 1·11]</td>
</tr>
</tbody>
</table>

* C-P, noninactivated platelets; I-P, inactivated platelet.
\(^a\)Inactivated platelet group.
\(^b\)Noninactivated platelet group.

© 2012 The Author(s)
Vox Sanguinis © 2012 International Society of Blood Transfusion
Vox Sanguinis (2012) 103, 322–330
We have included data from the SPRINT trial [18], because authors provided us with the necessary data. We deemed essential to request the missing data of the authors because the exclusion of the SPRINT trial would have decreased the power of the meta-analysis [30] due to the fact that this RCT included the highest number of patients and, following the guidelines to perform meta-analysis [31], one can contact with authors to ask missing data in the published RCT. Fourth, regarding the OR of bleeding, in the present meta-analysis, we extracted data from the original published RCTs and not from the expanded safety report of that study. Moreover, we extracted data as reported in the RCTs, and we did not perform any recategorization of this outcome, such as severe haemorrhage or clinically significant bleeding, as Dr Vamvakas did.

In the latest meta-analysis published by Dr Vamvakas [23], he discussed some of the previous issues. However, regarding the OR of bleeding, he continued using a recategorization of bleeding events. We think that with that approach, he introduces another source of variation that might explain the differences observed in the results of his meta-analyses and ours. To resolve this discrepancy, we would propose to perform an individual patient data (IPD) review [31]. IPD review means to work with original data in two meta-analyses about the same topic. In contrast with the results published recently by Vamvakas the ABO compatibility was guaranteed. This was an expected finding because it is well-known that either major or minor ABO incompatibility is associated with a decrease in the response to a platelet transfusion [36]. Moreover, in a previous meta-analysis of studies looking at the effect of platelet transfusion dose in several parameters, it was found that when the studies that guaranteed the ABO compatibility of the platelet transfusions were combined, the use of high doses of platelets was statistically associated with an increase in the post-transfusion platelet count increment when compared with the use of low doses of platelets (WMD, 23.6 × 10^9/l; 95% CI, 18.28 × 10^9/l to 28.92 × 10^9/l; P = 0.00001) [37].

The results we found in the present meta-analysis are in contrast with the results published recently by Vamvakas [22, 23] in two meta-analyses about the same topic. In comparison with the first one [22], several methodological differences can be outlined. First, we have included only RCTs that inactivate platelets with A-UVA, whereas Vamvakas included RCTs that inactivate platelets with different methodologies, such as amotosalen and riboflavin [38]. Second, we have included data from Lozano et al. [21], a recent published RCT that was not available before the publication of the first meta-analysis by Vamvakas. Third, in contrast to the first meta-analysis performed by Vamvakas, we have included data from the SPRINT trial [18], because authors provided us with the necessary data.

direction [33]. In this sense, regarding the CCI-1 h, we found that the hypothesis of homogeneity was not rejected when the ABO compatibility was guaranteed. This was an expected finding because it is well-known that either major or minor ABO incompatibility is associated with a decrease in the response to a platelet transfusion [36]. Moreover, in a previous meta-analysis of studies looking at the effect of platelet transfusion dose in several parameters, it was found that when the studies that guaranteed the ABO compatibility of the platelet transfusions were combined, the use of high doses of platelets was statistically associated with an increase in the post-transfusion platelet count increment when compared with the use of low doses of platelets (WMD, 23.6 × 10^9/l; 95% CI, 18.28 × 10^9/l to 28.92 × 10^9/l; P = 0.00001) [37].

The results we found in the present meta-analysis are in contrast with the results published recently by Vamvakas [22, 23] in two meta-analyses about the same topic. In comparison with the first one [22], several methodological differences can be outlined. First, we have included only RCTs that inactivate platelets with A-UVA, whereas Vamvakas included RCTs that inactivate platelets with different methodologies, such as amotosalen and riboflavin [38]. Second, we have included data from Lozano et al. [21], a recent published RCT that was not available before the publication of the first meta-analysis by Vamvakas. Third, in contrast to the first meta-analysis performed by Vamvakas, we have included data from the SPRINT trial [18], because authors provided us with the necessary data. We deemed essential to request the missing data of the authors because the exclusion of the SPRINT trial would have decreased the power of the meta-analysis [30] due to the fact that this RCT included the highest number of patients and, following the guidelines to perform meta-analysis [31], one can contact with authors to ask missing data in the published RCT. Fourth, regarding the OR of bleeding, in the present meta-analysis, we extracted data from the original published RCTs and not from the expanded safety report of that study. Moreover, we extracted data as reported in the RCTs, and we did not perform any recategorization of this outcome, such as severe haemorrhage or clinically significant bleeding, as Dr Vamvakas did.

In the latest meta-analysis published by Dr Vamvakas [23], he discussed some of the previous issues. However, regarding the OR of bleeding, he continued using a recategorization of bleeding events. We think that with that approach, he introduces another source of variation that might explain the differences observed in the results of his meta-analyses and ours. To resolve this discrepancy, we would propose to perform an individual patient data (IPD) review [31]. IPD review means to work with original data from original included and not included patients in all the previous RCTs and to re-analyse again together. The central
collection of IPD is perhaps the most resource intensive and time-consuming approach for systematic reviews.

In the present study, in contrast to the findings in the meta-analyses by Vamvakas [22, 23], bleeding complications across the four double-blinded and high methodologic quality score RCTs were not statistically significant (as shown in Fig. 5) [17–19, 21]. This important aspect of the design of the trial should be taken into account, as Kerkhof et al. [20] suggested, because the open-label aspect of their study cannot completely exclude bias with regard to evaluation of bleeding. Moreover, the evaluation of bleeding was done with different scales selecting different levels of severity in trials, and when only RCTs that used the WHO scale were combined, the hypothesis of homogeneity was not rejected, and we can conclude that the OR of bleeding was not statistically different in the C-P and I-P groups. However, several caveats arise when analysing platelet transfusion trials and the use of bleeding as a surrogate or composite outcome is one of them. As other authors have recently published [27], perhaps it is time for transfusion researchers to broaden the scope of clinical trials and tackle clinically relevant questions that explore the impact of the platelet interventions long term.

In conclusion, according to our results, the transfusion of C-P was associated with statistically significant higher CCI-24 h when compared with the transfusion of I-P. Regarding the CCI-1 h, transfusion interval and OR of bleeding, there was a high variation among the findings of the RCTs, and the hypothesis of homogeneity was rejected when all five RCTs were combined. However, we did not find statistically significant differences in the OR of bleeding between I-P and C-P, when double-blinded and high methodologic quality trials were combined.

Acknowledgements
Joan Cid designed the study; performed the literature search; and acquired, analysed and interpreted data. Gines Escolar and Miguel Lozano revised the paper critically. Miguel Lozano approved the submitted and final versions of the paper.

Conflict of interest
Joan Cid received lecture fees in the past from CaridianBCT and Cerus Co. Ginés Escolar has received research grants from CaridianBCT and Cerus Co and consultant fees from CaridianBCT. Miguel Lozano has received research grants from CaridianBCT and Cerus Co and lecture fees from Cerus Co.

References
5 Biggerstaff BJ, Petersen LR: Estimated risk of West Nile virus transmission during an epidemic in Queens, New York City. Transfusion 2002; 42:1019–1026
6 Bianco C: Dengue and Chikungunya viruses in blood donations: risks to the blood supply? Transfusion 2008; 48:1279–1281
8 Perkins HA, Busch MF: Transfusion-associated infections: 50 years of relentless challenges and remarkable progress. Transfusion 2010; 50:2080–2099
static efficacy and capacity of pathogen-reduced platelets. *Transfusion* 2011; 51:1058–1071


33 Vamvakas EC: Applications of meta-analysis in transfusion medicine; in Vamvakas EC (ed): Evidence-Based Practice of Transfusion Medicine, 1st edn. Bethesda, MD, AABB Press, 2001:221–258


