Is platelet transfusion efficient to restore platelet reactivity in patients who are responders to aspirin and/or clopidogrel before emergency surgery?

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PURPOSE:	The aim of this study was to confirm that emergency platelet transfusion effectively restores platelet function to patients receiving antiplatelet therapy (APT) with aspirin and/or clopidogrel.
PATIENTS AND METHODS:	This was a prospective observational case report series conducted between January 1, 2009, and January 1, 2012. All responder patients according to the Verify Now device requiring emergency platelet transfusion because of a potentially life-threatening hemorrhage or before emergency neurosurgery were included. Aspirin or P2Y12-specific tests were used as appropriate for patients under aspirin or clopidogrel. Patients who were responders to aspirin had an aspirin reaction unit of less than 550, and patients who were responders to clopidogrel had an inhibition percentage of more than 20%. The Verify Now test was performed again after platelet transfusion. Pretransfusion and posttransfusion test results were compared.
RESULTS:	During the 36-month period, 25 patients met the inclusion criteria. Of these patients, 4 were receiving dual APT, 8 were receiving clopidogrel only, and 13 were receiving aspirin only. The average platelet transfusion dose was 0.12 UI/kg (range, 0.10–0.14 UI/kg). For patients under clopidogrel, the inhibition percentage lowered significantly after transfusion (median 54 [range, 31–69] before and 25 [range, 18–50] after transfusion; $p < 0.005$) but remained above the 20% threshold. Our patients were still responsive to clopidogrel after platelet transfusion. This result is conflicting with the existing literature. The median aspirin reaction unit of aspirin users before and after transfusion were 420 (range, 400–470) and 630 (range, 610–640), respectively ($p = 0.001$). The efficacy of platelet transfusion to restore aspirin-mediated disaggregation is confirmed by our case series.
CONCLUSION:	Platelet transfusion does not restore platelet function in patients under clopidogrel, but it is efficient for patients under aspirin. This sheds new light on previous large-scale studies that have been unable to show any effectiveness of emergency platelet transfusion in patients under APT. Emergency platelet transfusion may only be indicated in aspirin users who are responders and not in all patients under APT as is actually recommended. (*J Trauma Acute Care Surg*. 2013;74: 1367–1369. Copyright © 2013 by Lippincott Williams & Wilkins)
LEVEL OF EVIDENCE:	Therapeutic study, level IV.
KEY WORDS:	Platelet transfusion; Verify Now; clopidogrel; aspirin; emergency surgery.

BACKGROUND

Acute hemorrhage can be particularly life threatening in patients receiving antiplatelet therapy (APT). It seems likely that restoring normal platelet function would prevent further bleeding and improve outcome. To achieve this goal, emergency platelet transfusion is routinely performed in case of previous APT during hemorrhagic shock or intracranial hemorrhage or to prepare for emergency high-risk surgery such as neurosurgery.[1,2] Platelet-rich plasma from untreated volunteers has been shown to restore normal aggregation when mixed in vitro to platelets from volunteers pretreated by aspirin or a loading dose of clopidogrel.[3] However, platelet transfusion is now being questioned in patients with previous APT as no clinical trial has yet proven its effectiveness in vivo.[4,5] Our aim was to confirm that in vivo platelet transfusion effectively restores platelet function to patients receiving previous APT with aspirin and/or clopidogrel.

PATIENTS AND METHODS

This was a prospective monocenter observational case report series. As platelet infusion therapy is still considered standard of care for patients with previous APT and a potentially life-threatening hemorrhage or before emergency neurosurgery, this work induced no change from usual practice and was part of a quality insurance policy. These consecutive cases took place between January 1, 2009, and January 1, 2012, in the ICU at the Fondation Ophtalmologique A. de Rothschild (Paris, France).

Inclusion Criteria

The participants of this study were all adult patients under aspirin, clopidogrel or a combination and were identified as responders by the Verify Now device (Accumetrics, San Diego, CA). Responders were defined by the following thresholds: for aspirin an asprin reaction unit (ARU) less than 550; for

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clopidogrel an inhibition percentage (IP) above 20%. All patients required emergency platelet transfusion because of hemorrhagic shock, intracranial hemorrhage or emergency neurosurgery. Platelet count was superior to 100,000/mL. Our protocol was as follows: when a patient previously receiving APT required platelet transfusion, Verify Now™ (Accumetrics, San Diego, CA), testing was performed using the aspirin-specific test for patients receiving aspirin or the P2Y12-specific test for patients receiving clopidogrel. Both tests were performed for patients under dual APT. In every case, a 0.1-U/kg platelet transfusion was prescribed regardless of the Verify Now™ test results. Posttransfusion Verify Now™ testing was performed between 30 min and 4 hours after the end of the platelet transfusion. Only patient responders before platelet transfusion were subsequently included in this study. The validity of the Verify Now™ has been extensively studied by others.[6]

STATISTICAL ANALYSIS

Data are expressed as mean (25th–75th percentile interquartile range) as appropriate. A Wilcoxon-matched pairs test was performed to compare numerical data. $p < 0.05$ was considered significant. Statistical analysis was performed using statistical software (Prism 4, Version 4.0b; GraphPad Software, La Jolla, CA).

RESULTS

During the 36-month period, 25 patients met the inclusion criteria. Of these patients, 4 were receiving dual APT, 8 were receiving clopidogrel only, and 13 were receiving aspirin only. Seventeen patients were included in the aspirin group, and 18 aspirin tests were performed before and after platelet transfusion because one patient required two distinct surgical procedures between which aspirin treatment was resumed. All aspirin tests before transfusion were less than 550 ARU, all but one tests after transfusion were more than 550 ARU (Fig. 1). The median ARU values before and after transfusion were 420 (400–470) and 630 (610–640) ($p = 0.001$). The average platelet transfusion dose was 0.13 UI/kg (0.10–0.15 UI/kg).

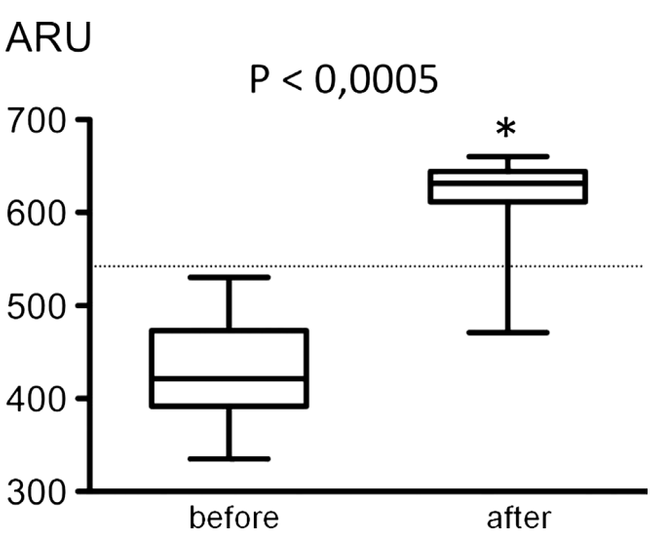

Figure 1. ARU before and after platelet transfusion.

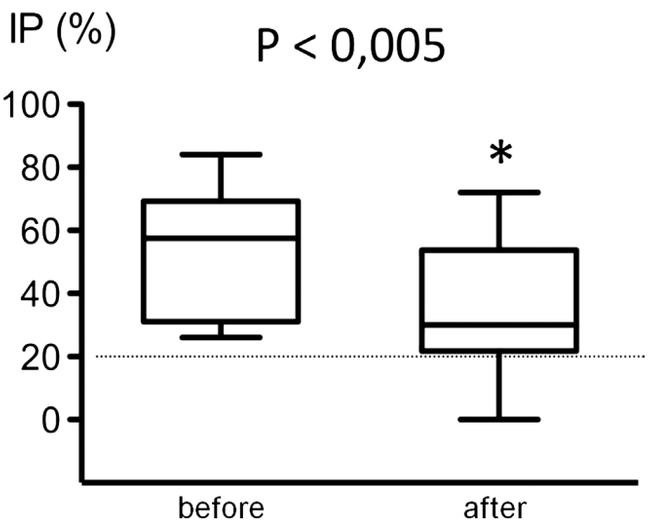

Figure 2. IP of platelet aggregation before and after platelet transfusion.

Twelve patients were included in the clopidogrel group, 14 P2Y12 tests were performed before and after platelet transfusion as 2 patients required two distinct surgical procedures between which clopidogrel treatment was resumed. The median IP before and after transfusion were 54 [31;69] and 25 [18–50] $p < 0.005$ (Fig. 2). The IP was significantly lowered after transfusion but it remained above the 20% threshold. Average platelet transfusion dose was 0.10 UI/kg (0.10–0.13 UI/kg).

DISCUSSION

The results of this case series indicate that platelet transfusion effectively restores normal aggregation to patients previously responsive to aspirin. Surprisingly, our results do not show that emergency in vivo platelet transfusion is effective to restore normal aggregation to patients previously responsive to clopidogrel. To study the effectiveness of platelet transfusion to restore normal aggregation, we have used the Verify Now™ point-of-care assay. The result of the aspirin test, ARU, became superior to the 550 threshold after platelet transfusion in patients under aspirin therapy (Fig. 1). However, although P2Y12 IP significantly decreased after platelet transfusion, it remained superior to the 20% threshold in patients receiving clopidogrel (Fig. 2). We were unable to confirm that emergency platele transfusion is effective to patients currently treated by clopidogrel.

The efficacy of platelet transfusion to restore aspirin-mediated disaggregation is confirmed by our case series and is consistent with the existing literature. Vilahur et al.[3] showed that in vitro platelet-rich plasma from untreated volunteers normalized light transmittance aggregometry challenged by arachidonic acid to platelet-rich plasma from volunteers pretreated by aspirin. In vivo homologous platelet transfusion has also been found to be effective in a small subpopulation of eight patients who had received a platelet transfusion after

intracranial hemorrhage.[7] In this latter study, as in ours, platelet transfusion led to an increase of ARU above the 550 threshold in patients who had previously been responsive to aspirin.

Our results are conflicting with the existing literature concerning the recovery from clopidogrel-mediated disaggregation. This is surprising because convincing data show that ADP-mediated aggregation can be restored by fresh platelets whether in vitro by adding platelet-rich plasma from untreated volunteers to clopidogrel pretreated platelets[3] or in vivo by production of fresh platelets.[8] Weber et al.[8] have shown that spontaneous recovery after the discontinuation of clopidogrel treatment is gradual as new platelets are produced. In that study, ADP-mediated platelet aggregation returned to baseline after a 7-day period during which two distinct pools of platelets coexisted. However, we have found no data on the steady-state concentration of the active metabolite of clopidogrel and on the aggregation process during the first 48 hours after discontinuation in patients receiving a daily dose of 75 mg of clopidogrel. The pharmacokinetics of the active metabolite of clopidogrel is still poorly understood. We know the cytochrome P450 2C19 to be important, but only recently, paraoxonase 1 has also been identified as a major determinant of clopidogrel activity.[9] Our results lead us to assume that the active metabolite of clopidogrel could still be produced and circulating several hours after the last oral dose, thus blocking the freshly transfused platelets and impairing their efficacy in patients who have not discontinued treatment such as our emergency cases. Another possible explanation could be the loss of potency of preserved platelets. Our small sample size did not enable us to explore the notion that younger platelets are more prone to normalize the aggregation process of patients treated by clopidogrel. Finally, one must bear in mind that although our patient population was mostly neurosurgical patients, our results may not be extended to other populations such as trauma patients in whom a complex coagulopathy is known to exist and who could well benefit from platelet transfusion.

Despite these limitations, our results shed new light on previous studies that have been unable to show any effectiveness of emergency platelet transfusion in patients under APT.[1,5] These studies have been designed to assess the efficacy of platelet transfusion considering all patients under APT as a homogenous population with induced thrombopathy. However, this is clearly not the case. Bansal et al.[10] have shown that 37% of patients taking clopidogrel on admission to a trauma center are nonresponders. We should consider that four populations of patients are included in the general qualification "under APT": clopidogrel responders, aspirin responders, dual responders to both clopidogrel and aspirin, and patients who are not responders to either drug. It seems that only a fraction of these patients, those responders to aspirin, would really benefit from platelet infusion. We believe that the availability of the Verify Now device in an emergency room would prove useful to screen patients under APT and guide management such as international normalized ratio for Coumadin.

In conclusion, our in vivo study does not confirm the results of others regarding the efficacy of platelet transfusion to restore platelet function in patients treated by a daily dose of clopidogrel. On the basis of these results, we are questioning the effectiveness of transfusion of platelets in case of chronic use of clopidogrel to treat life-threatening hemorrhage or before high-risk surgery such as neurosurgery. On the other hand, this study confirms that emergency homologous platelet transfusion is effective to restore aspirin-induced disaggregation, and we advise that it should be used as stated by existing guidelines. Our work raises some questions as to the pharmacokinetics of the active metabolite of clopidogrel. A future study on the steady-state concentrations of the active metabolite of clopidogrel during treatment and in the first 48 hours after discontinuation would help better understand our results. Any future large-scale study on the effectiveness of emergency platelet transfusion in patients under APT should precisely distinguish patients under clopidogrel from those under aspirin as well as responders from nonresponders because they do not face the same risks and do not require the same treatment.

AUTHORSHIP

G.T. performed literature search, data collection, data analysis, data interpretation, and writing of the article. A.T. performed statistical analysis and contributed the figures. D.O. performed literature search and data collection. J.-M.D. performed study design and overall supervision.

DISCLOSURE

The authors declare no conflicts of interest.

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