Thrombosis & Haemostasis Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

CD40(L) = co-stimulatory CD40 (ligand); **CI** = confidence interval; **CLEC-2** = C-type lectin-like receptor-2; **COVID-19** = coronavirus disease 2019; **CVT** = cerebral venous thrombosis; **H2Ra** = histamine-2 receptor antagonist; **IMPROVE** = International Medical Prevention Registry on Venous Thromboembolism; **ITP** = immune thrombocytopenia; **NOAC** = non-vitamin K oral anticoagulants; **PPI** = proton-pump inhibitor; **PPN** = platelet-mimicking procoagulant nanoparticles; **PV** = polycythaemia vera; **T-regs** = regulatory T cells; **VTE** = venous thromboembolism.

Welcome to the latest issue of Thrombosis & Haemostasis Research Review.

Results from the AURORA systematic review and meta-analysis published in *The Lancet* by lead stroke neurologist Professor Tudor Jovin and colleagues suggest that endovascular thrombectomy for anterior circulation stroke with reversible cerebral ischaemia provides a clinical benefit over medical intervention beyond the generally accepted six-hour period with the caveat that patients with large infarcts, higher National Institutes of Health Stroke Scale scores or disability were not included in the analysis. One-month of post-hospitalisation thromboprophylaxis with low-dose rivaroxaban should be considered for patients at high-risk of venous thromboembolism (VTE) after hospitalisation for coronavirus disease 2019 (COVID-19) according to results from the Brazilian MICHELLE trial and data from larger trials such as ACTIV-4c are eagerly awaited to confirm this strategy. A German interdisciplinary collaborative group have elucidated the molecular aetiology of cerebral venous thrombosis (CVT), finding that activation of two platelet receptors caused brain-specific clots and death in rodents and paving the way for new therapeutic approaches. This research is especially relevant in the era of COVID-19, with CVT reported to be a risk after COVID-19 as well as a rare complication from COVID vector-based vaccines.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Professor Harshal Nandurkar
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Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA)

Authors: Jovin T et al.

Summary: This systematic review and individual patient data meta-analysis (AURORA - Analysis of Pooled Data from Randomized Studies of Thrombectomy More Than 6 Hours After Last Known Well) was funded by Stryker Neurovascular to elucidate the benefit of endovascular thrombectomy when administered between six and 24 hours after anterior circulation proximal large vessel occlusion stroke. Six randomised trials, including DAWN and DEFUSE 3 (NCT02142283 & NCT02586415), with a total of 505 individuals (mean age 68.6 years; 51.3% female), that published results of endovascular stroke therapy were included in the analysis. Ordinal logistic regression analysis found that the primary outcome measure of functional independence at 90-days, assessed using the modified Rankin Scale, was more than twice as frequently achieved after thrombectomy versus the control of best medical therapy only (45.9% vs 19.3%; unadjusted odds ratio 2.42, 95% confidence interval [CI], 1.76–3.33, $p<0.0001$). Efficacy did not come at the expense of reduced safety with comparable rates of 90-day mortality and symptomatic intracerebral haemorrhage found between groups (16.5% vs 19.3% and 5.3% vs 3.3%, respectively). The magnitude of treatment effect was consistent across subgroups defined by age, gender and baseline stroke severity, amongst others. A benefit was reported in patients randomised between six- and 12-hours and in those randomised between 12- and 24-hours.

Comment: There is an unmet need to extend the period of intervention for thromboembolic stroke beyond the currently accepted six-seven hours from the onset of symptoms. This is because, unlike in acute myocardial infarction, a patient with a stroke may not be aware of the event if asleep and if there is no obviously recognisable neurological deficit. This is a meta-analysis of individual patient data published in randomised trials of endovascular thrombectomy versus no thrombectomy against a background of usual care in patients with ischaemic stroke, randomly assigned from six to 24 hours from the recognisable onset of symptoms or time last seen well. 505 patients with moderate-to-severe stroke were included. The primary outcome was the score on the modified Rankin scale at 90 days. Intervention with thrombectomy resulted in 45.9% of patients reaching a modified Rankin Score of 0–2, indicating higher rates of independence in activities of daily living, than those given best medical therapy alone. In comparison, in those who did not receive thrombectomy, only 19.3% achieved a modified Rankin score of 0-2. This data demonstrates that delayed intervention beyond the customary six hours of recognised stroke results in an improved functional outcome. A caveat to the above broad brush stroke interpretation is that the original trials had differing thresholds of ischaemic core volume for inclusion in that particular study. This highlights the need for better techniques to estimate core and reversible ischemia volumes for decision making.

Reference: Lancet 2022;399(10321):249-58
Abstract

Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial

Authors: Ramacciotti E et al., on behalf of the MICHELLE investigators

Summary: The Brazilian multicentre phase 3 MICHELLE (Medically Ill Hospitalized Patients for COVID-19 THrombosis Extended ProphyLaxis with Rivaroxaban ThErapy; NCT04662684) trial evaluated the safety and efficacy of extended post-hospitalisation VTE prophylaxis in high-risk patients hospitalised for COVID-19. A total of 320 patients hospitalised (50% in intensive care unit) with PCR-confirmed SARS-CoV-2 infection and pneumonia deemed at risk for VTE by virtue of a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score of ≥ 4 (38%) or IMPROVE score of 2-3 plus a D-dimer >500 ng/mL (62%) were enrolled and randomised 1:1 to a one-month (35-day) post-hospitalisation thromboprophylaxis regimen with 10 mg/day rivaroxaban or no anticoagulation (n=160 each). All patients received in-hospital pharmacological thromboprophylaxis with standard doses of heparin. The prevalence of a composite outcome measure comprised of symptomatic, fatal or asymptomatic VTE, symptomatic arterial thromboembolism or cardiovascular death at day 35 was three-fold lower in the rivaroxaban arm compared to the no anticoagulation arm (3% vs 9%; relative risk 0.33; 95% CI, 0.12-0.90; *p*=0.0293). There were no incidences of major bleeding in either trial arm. One case of rivaroxaban-associated allergy was reported.

Comment: COVID-19 leads to higher rates of thrombotic events. There is acceptance for standardised in-hospital thromboprophylaxis but there is no consensus on extended thromboprophylaxis on discharge. This trial investigated the utility of thromboprophylaxis in COVID-19 patients after discharge with rivaroxaban 10 mg versus no anticoagulation. The inclusion criteria required IMPROVE VTE score of ≥4, or 2–3 with a D-dimer >500 ng/mL. Apart from symptomatic or fatal VTE, the study included bilateral lower-limb venous ultrasound and CT pulmonary angiogram to document asymptomatic VTE. The primary outcome was consistent across prespecified subgroups with no signs of heterogeneity. The benefit of anticoagulation with rivaroxaban was present in subgroups of patients with advanced age, obesity, moderate renal failure (creatinine clearance <50 mL/min), elevated IMPROVE VTE score (≥4), increased D-dimer, and those on concomitant antiplatelet therapy. Thus, post discharge anticoagulation with rivaroxaban 10 mg daily has considerable merit.

Reference: Lancet 2022;399(10319):50-9
Abstract

Effect of anticoagulant therapy for 6 weeks vs 3 months on recurrence and bleeding events in patients younger than 21 years of age with provoked venous thromboembolism

Authors: Goldenberg N et al., for the Kids-DOTT Trial Investigators and the ATLAS Group

Summary: The Kids-DOTT randomised clinical trial (NCT00687882) has published the primary per-protocol population analysis in *Journal of the American Medical Association*. The international trial, sponsored by Johns Hopkins All Children's Hospital, enrolled 417 paediatric patients (< 21 years) with first-episode acute provoked VTE (non-spontaneous events caused by central vein catheterisation, infection, dehydration, surgery, trauma amongst others) from sites in the US, Canada, Israel, Australia and the Netherlands between 2008 and 2021 to assess the hypothesis that a shorter duration anticoagulation therapy is non-inferior to conventional duration. Patients received either six-weeks (n=207) or standard three-month duration (n=210) anticoagulant therapy. The trial met the prespecified absolute risk differences in efficacy and safety in a primary population analysis (n=297) to demonstrate non-inferiority of the reduced-duration regimen (Kaplan-Meier estimate of cumulative symptomatic recurrent VTE, 0.66% vs 0.70%; rate of one-year clinically relevant bleeding events, 0.65% vs 0.70%).

Comment: This multinational randomised clinical trial (conducted at 42 centres in five countries) demonstrates that for patients younger than 21 years with first-episode acute provoked VTE, the net clinical benefit (as measured by the one-year risks of symptomatic recurrent VTE and clinically relevant bleeding events) of a shortened duration of anticoagulant therapy (six weeks) is similar to the benefit of conventional (three months) duration. The risk of recurrence and bleeding in this study was similar to the previously reported EINSTEN-Junior trial that included 11% of patients with unprovoked VTE.

Reference: JAMA 2022;327(2):129-37
Abstract

Eltrombopag treatment of patients with secondary immune thrombocytopenia: retrospective EHR analysis

Authors: Patwardhan P et al.

Summary: Pallavi Patwardhan and colleagues retrospectively evaluated data on 242 patients with secondary immune thrombocytopenia (ITP) to delineate the effectiveness of eltrombopag for this indication in a real-world setting. Data was extracted from electronic health records in the US Optum Clinical Database for patients diagnosed with ITP between 2008 and 2018 with a known predisposing condition, most commonly hepatitis C or systemic lupus erythematosus, who underwent eltrombopag therapy alone or in combination with other ITP treatments (average treatment duration, six months) with follow-up to the end of 2018. Increased platelet counts to threshold median levels of ≥30,000, ≥50,000 and > 100,000/μL were achieved by 81.4% of patients rapidly (mean 0.7 months), 70.2% at 0.95 months and 47.1% at 1.43 months, respectively. There was no increase in bleeding events. The study authors stated that patients with secondary ITP achieve comparable platelet responses to eltrombopag as that reported in patients with primary ITP.

Comment: The thrombopoietin receptor agonists are available for second-line treatment of primary ITP. However, this option is not available for the management of secondary ITP. This study was performed using electronic health record data from more than 700 hospitals and 7,000 clinics covering more than 64 million unique US patients. Eligible secondary ITP conditions were systemic lupus erythematosus, Evans syndrome, antiphospholipid syndrome, common variable immunodeficiency disorders, selective IgA deficiency, autoimmune lymphoproliferative syndrome, HIV, hepatitis C, chronic lymphocytic leukaemia, and small lymphocytic lymphoma and correlation was made with the use of eltrombopag over a follow-up period of six months or more. Amongst the cohort studied, it is encouraging to note that 47.1% achieved a complete response of>100,000 platelets/μL. Among those with at least 12 months of follow-up, the mean treatment-free period was 9.9 months. The use of eltrombopag was not associated with increased thrombotic risk. Bleeding events were not significantly reduced in the six months after the start of treatment, probably because platelet counts were generally in a haemostatic range pre-treatment. This study demonstrates that eltrombopag is an effective option in secondary ITP.

Reference: Ann Hematol 2022;101(1):11-19
Abstract

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Independent commentary by Prof Harshal Nandurkar

Prof Harshal Nandurkar, is the Director of the Alfred Cancer Program and Clinical Haematology, Head of the Australian Centre for Blood Diseases. He is the past President of the Thrombosis and Haemostasis Society of Australia and NZ and past Vice President of the International Union of Angiology (Australian Chapter).

Prevention of non-vitamin K oral anticoagulants-related gastrointestinal bleeding with acid suppressants

Authors: Dong Y et al.

Summary: This systematic review and meta-analysis evaluated the efficacy of acid suppressants for mitigation of non-vitamin K oral anticoagulants (NOACs)-related gastrointestinal bleeding. Six retrospective studies published prior to August 10, 2021 were identified from a search of four online databases - Cochrane, Embase, PubMed and Web of Science. Results showed that acid suppressants such as proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2Ras) were efficacious for prevention of drug-induced gastrointestinal bleeding conferring an overall 30% reduction in risk (relative risk 0.70; 95% CI, 0.61-0.82; $p<0.001$; $I^2=56.3\%$). Subgroup analyses revealed a greater effect size in risk reduction for upper versus lower gastrointestinal bleeding (relative risk 0.45) and a greater protective effect from dabigatran-induced versus apixaban- or rivaroxaban-induced bleeding (relative risks 0.53, 0.67 and 0.73, respectively; all $p<0.001$).

Comment: NOACs/direct oral anticoagulants are the preferred anticoagulants in use for VTE and atrial fibrillation. These drugs are associated with higher rates of gastrointestinal bleeding, which can be up to 25% higher than vitamin K antagonists. The six studies were sourced from nationwide insurance and medical beneficiary databases (four studies) and from hospital databases (two studies) and covered 559,422 patients who newly started anticoagulant treatment. This study noted that bleeding events from the lower gastrointestinal tract are more common than upper gastrointestinal tract in patients receiving NOACs but most lower gastrointestinal bleeding events were 'mild' not requiring intervention. The risk reduction of gastrointestinal bleeding with acid suppressants was higher for dabigatran, and for Xa-inhibitors more protection was noted with apixaban over rivaroxaban. The study could not differentiate between PPIs and H2R-antagonists due to lack of source data, but correlation from gastrointestinal bleeding protection in the context of non-steroidal anti-inflammatory drugs and aspirin use suggests that PPIs are more potent than H2Ras.

Reference: Clin Appl Thromb Hemost 2022;28:10760296211064897
Abstract

Cell-specific and divergent roles of the CD40L-CD40 axis in atherosclerotic vascular disease

Authors: Lacy M et al.

Summary: A German group from the Institute for Cardiovascular Prevention, Ludwig-Maximilians-Universität in Munich conducted pre-clinical research in murine models to delineate the role that different co-stimulatory CD40 ligand (CD40L)/CD40-expressing cells (such as T cells and platelets) play in atherosclerosis. The researchers found that a more favourable atherosclerotic plaque phenotype could be elicited in atherosclerosis-prone mice by introduction of cell-specific CD40L/CD40 deficiency (i.e., deficiency of CD40L on T cells or CD40 on dendritic cells) to mitigate Th1 response and reduce interferon-γ levels. Conversely, induction of CD40L deficiency on platelets had no impact on severity of atherosclerotic disease but mitigated atherothrombosis. The authors concluded that the role of the CD40L-CD40 dyad in atherosclerosis is cell-specific.

Comment: This paper makes important contributions to our understanding of the pathophysiology of atherosclerosis and the individual contributions by platelets, T-cells and dendritic cells. Dendritic cells identified as CD11c-positive antigen presenting cells are present in the vessel wall. Macrophages are also present in that milieu and are generally CD11c-negative but can express CD11c on activation. When the atherosclerotic cap ruptures, subendothelial matrix and atherosclerotic core is exposed, which triggers profound platelet accumulation and thrombosis. Platelets release CD40L which interacts with its receptor CD40 present on dendritic cells. CD40L is also present on T-cells, monocytes, macrophages, and endothelial cells. This paper characterises the function of the most relevant CD40L-expressing cell types, which are T-cells and platelets in atherosclerosis. While CD40L released from platelets is known to initiate atherothrombosis, mice with platelet-specific CD40 deletion do not have any alteration in the composition of inflammatory cells in areas of vessel injury. However, T-cell–specific CD40L and dendritic cell-specific CD40 deficiency reduced plaque progression. The authors demonstrate that Th1 and T reg pathways were dysregulated in mice with CD40L-deficient T cells with impaired antigen dependent T-cell proliferation, reduced interferon-γ production, smaller necrotic cores in plaques, an increased number of smooth muscle cells and thicker fibrous caps. In human patients with cerebrovascular disease, solubleCD40L/solubleCD40 and Interferon-γ concentrations in carotid plaques and plasma were positively correlated. Therefore, the CD40/CD40L axis is an attractive molecular target in the progression of atherosclerotic diseases and several interventions are underway.

Reference: Nat Commun 2021;12(1):3754
Abstract

Regulatory T-lymphocyte subsets in children with chronic immune thrombocytopenia after high-dose of dexamethasone

Authors: Elsayh K et al.

Summary: This single-centre prospective interventional clinical trial from researchers at Assiut University in Egypt evaluated T cell subsets and the effect of high-dose dexamethasone treatment in a cohort of paediatric patients with chronic ITP. A total of 27 paediatric patients between the ages of three and 13 years (mean age 5.63 years) with chronic ITP (primary thrombocytopenia for at least one year in the absence of other haematological abnormalities or organomegaly; mean platelet count 12.09 x 10^9cells/L) were enrolled between December 2020 and May 2021 and administered six cycles of intravenous 24 mg/m^2 dexamethasone every two weeks. Twenty-one healthy age- and sex-matched children served as controls. Regulatory T cell subsets in peripheral blood were quantified by flow cytometry at baseline in both cohorts and at the conclusion of treatment in patients with ITP. While there were no differences in the proportion of CD4, CD4+CD25+ or CD4+CD25^{Intermediate} cells between patients with ITP and controls, abnormal T cell subsets including significantly lower proportions of CD4+CD25^{High} cells (5.47% vs 6.8%) and regulatory T cells (T-regs; 1.10% vs 2.58%) were seen pre-treatment in patients with ITP. Dexamethasone treatment significantly increased the proportions of both CD4+CD25^{High} and T-regs (mean CD4+CD25^{High} after treatment, 6.57%; mean T-reg, 1.43%).

Comment: There is evidence in ITP for antiplatelet antibodies produced by autoreactive B-lymphocytes that are stimulated and assisted by T-helper lymphocytes (CD4+ cells). Patients with ITP have an imbalance in cytokine levels and antiplatelet self-reactive T-lymphocytes, which indicates a loss of peripheral tolerance. T-regs (CD4+CD25+^{High} FoxP3+ cells) suppress the proliferation of B and T lymphocytes, and their autoreactivity. Insufficiency of T-regs is implicated in peripheral tolerance malfunction, which can result in autoimmunity. This report assessed the variations in the population of T-regs in untreated children with chronic ITP and evaluated the effect of high-dose dexamethasone on T cell subsets in these patients. The take home findings were that percentages of T-regs were significantly lower in the chronic ITP group in comparison to control group and they significantly increased after dexamethasone in chronic ITP patients in parallel with platelet increment. There are other studies that do not show such correlation of T-regs and ITP as observed here, and this is hypothesis-provoking at present.

Reference: Pediatr Res 2022; Feb 16 [Epub ahead of print]
Abstract

Neutrophil-to-lymphocyte ratio is a novel predictor of venous thrombosis in polycythaemia vera

Authors: Carobbio A et al.

Summary: Alessandra Carobbio and colleagues interrogated the database of the European Collaboration on Low-dose Aspirin in Polycythaemia Vera (ECLAP) study to assess the validity of neutrophil-to-lymphocyte ratio as a prognostic factor for venous and arterial incident events in patients with polycythaemia vera (PV). Analysis was based on 1,508 patients with PV followed for a median of two and a half years. The incident rate of thrombosis was 10.1% (n=166), consisting of mostly nonfatal events (160/166), with an equal proportion of arterial (myocardial infarction, stroke or transient ischemic attack) and venous events (deep vein thrombosis, pulmonary embolism, superficial thrombophlebitis). Assessment of continuous-scale nonlinear relationships between different blood cells and thrombosis using generalised addictive proportional-hazard modelling found a significant relationship in the risk of venous thrombosis only (positive correlation with absolute neutrophil count and negative with lymphocyte resulting in increased risk with higher neutrophil-to-lymphocyte ratio). No association was found with risk of arterial events. Previous venous events and neutrophil-to-lymphocyte ratio ≥5 were identified on adjusted multivariate models considering age, gender, previous thrombosis and treatment at baseline as independent factors increasing the hazard of venous thrombosis by five- and two-fold, respectively (HR 5.43 and HR 2.14; both $p \leq 0.01$).

Comment: PV displays an elevated red-cell mass, usually along with leukocytosis and thrombocytosis. Thrombosis can be the first presenting sign of myeloproliferative neoplasms and the incidence is the highest in patients with PV and similar in essential thrombocythemia and primary myelofibrosis. The relationship between leukocytosis and thrombosis has been extensively investigated and is stronger in essential thrombocythemia than PV. There is evidence for the role of non-myeloid inflammatory cells, such as T lymphocytes and monocytes in the process of immune thrombosis including role for T-reg lymphocytes in the regulation of the prothrombotic action of activated neutrophils. The present study included 1,508 of the 1,638 PV patients enrolled in the ECLAP trial. A significant association between the risk of venous thrombosis and the groups of patients with progressive lower lymphocyte counts was noted, leading to increase the neutrophil-to-lymphocyte ratio values. Neutrophil-to-lymphocyte ratio was more representative of the association of lymphocyte and neutrophil counts with venous thrombosis than individual counts alone. Absolute values of neutrophils and lymphocytes or neutrophil-to-lymphocyte ratio correlated with arterial events. Total leukocyte and platelet counts did not correlate with either venous or arterial thrombosis. The correlation between neutrophil-to-lymphocyte ratio values and venous thrombosis found in the learning cohort was validated in two Italian independent external cohorts, confirming the significant prognostic effect of neutrophil-to-lymphocyte ratio ≥ 5 in both external cohorts. It will be interesting to verify if the neutrophil-to-lymphocyte ratio values correlate with the allelic burden of *JAK2V617F*, which has recently been reported to be correlated with venous thrombosis.

Reference: Blood Cancer J 2022;12(2):28
Abstract

Foudroyant cerebral venous (sinus) thrombosis triggered through CLEC-2 and GPIIb/IIIa dependent platelet activation

Authors: Stegner D et al.

Summary: In a letter to *Nature Cardiovascular Research* Stegner and colleagues from the University Hospital Würzburg and the Rudolf Virchow Centre at the University of Würzburg, both in Germany detail their pre-clinical research elucidating the molecular cause of cerebral venous (sinus) thrombosis (CVT). The group's murine studies revealed that activation of two platelet surface receptors - C-type lectin-like receptor-2 (CLEC-2) and GPIIb/IIIa – resulted in brain-specific clots and death and that inhibition of signalling or function prevented CVT even after the onset of neurological symptoms.

Comment: Venous thrombosis typically occurs without endothelial injury at sites of blood stasis or in form of 'immunothrombosis' as an interplay with innate and cognate immune cells. Cerebral venous system, comprising the cerebral veins and the dural venous sinuses, is an unusual site of thrombosis. CVT is mainly idiopathic; oral contraceptive use, pregnancy and puerperium, smoking and brain infection/inflammation are recognised risks. Recently, CVT has been recognised as a prothrombotic sequelae of COVID-19 and also as an uncommon complication post AstraZeneca COVID-19 vaccine. Platelet activation and subsequent coagulation lead to thrombosis. Collagen receptor GPVI and CLEC-2 have been implicated in injury-related thrombus formation. Podoplanin is the only established CLEC-2 ligand. It is a transmembrane protein expressed outside the vasculature, including lymphatic endothelial cells, lung epithelial cells and the brain and is upregulated in many cancers and in different immune cells during inflammation. In this elegant research paper, the authors use Fab binding with and activating CLEC-2 to create a murine model of CVT. In further detailed characterisation, it is shown that GPIIb/IIIa (fibrinogen receptor) blockade is more effective than heparin, aspirin or clopidogrel in preventing and treating CVT. Thus, CLEC-2 could be an immune target leading to CVT, such as in the context of COVID-19. GPIIb/IIIa antagonists, or inhibitors of CLEC-2-ITAM signalling, could be effective therapeutic options for CVT.

Reference: Nat Cardiovasc Res 2022;1:132–41
Abstract

Platelet-mimicking procoagulant nanoparticles augment haemostasis in animal models of bleeding

Authors: Sekhon U et al.

Summary: A novel synthetic platelet product developed and tested by a group at Case Western Reserve University in Cleveland, Ohio, US, has demonstrated haemostatic activity in rodent models of bleeding. The artificial platelets – liposome-based platelet-mimicking procoagulant nanoparticles (PPNs) – expose phosphatidylserine in response to plasmin and have dual functions, to reduce blood loss by stimulating clot formation and to stabilise clots by way of a protein mesh in an injury-responsive manner. The PPNs reinstated thrombin and fibrin formation in *in vitro* studies in human plasma and blood devoid of platelets and reduced blood loss in rodent models of thrombocytopenia and traumatic haemorrhage. Although yet to undergo clinical testing, these synthetic platelet surrogates may offer a viable, more study and long-lasting alternative to natural platelet transfusion.

Comment: Resting platelet membrane predominantly contains the neutral zwitterionic lipid phosphatidylcholine on the outer leaflet, whereas the inner leaflet contains a higher amount of anionic phosphatidylserine. Upon platelet adhesion and activation, phosphatidylserine translocates to the outer leaflet of the platelet membrane, creating a 'procoagulant' milieu with access to coagulation factors and Ca^{2+} ions resulting in formation of the tenase complex and prothrombinase complex, followed by the conversion of prothrombin to thrombin and fibrin generation. The researchers have synthesised PPNs that interact with phosphatidylserine and activate coagulation cascade in platelet-depleted plasma (i.e., perform the role of activated platelets). To prevent unprovoked thrombosis, PPNs were modified with cholesterol-tethered polyethylene glycol that cloaked the phosphatidylserine in circulation but could be cleaved off by plasmin specifically at the injury site to expose phosphatidylserine, thereby improving safety. The authors demonstrate that the PPNs increase fibrin generation and reduce clot lysis in overall haemostatic potential assays. The *in vivo* haemostatic potential of PPNs was confirmed by their ability to control bleeding after tail tip transection in mice and in traumatic liver haemorrhage model in rats. Thus, while PPNs do not perform all of the functions of native platelets, they could provide clinically valuable haemostatic support.

Reference: Sci Transl Med 2022;14(629):eabb8975
Abstract

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