Amotosalen/UVA pathogen inactivation technology reduces platelet activability, induces apoptosis and accelerates clearance

With interest we read the paper by Stivala et al., \(^1\) recently published in Haematologica, evaluating the structural and functional consequences induced by Amotosalen/UVA treatment using the Intercept Blood System (IBS) on platelets from apheresis platelet concentrates (PCs) during storage. This study provides results of early diminished platelet function in IBS-treated PCs as compared to conventional PCs, i.e., reduced aggregation response to collagen or thrombin and adhesion to collagen or vWF under flow, increased platelet apoptosis, MAPK p38 activation, and glycoprotein Ibα (GPIbα) shedding and enhanced clearance from the circulation of mice.

These results strikingly contrast with our previous published study\(^2\) which evaluated the impact of IBS on platelets isolated from buffy coat PCs, washed and suspended in Tyrode’s buffer. Surprisingly, Stivala et al.\(^1\) quote our study in a way which may lead to the conclusion of convergent results, which is obviously not the case. Indeed, we showed that washed IBS-platelets were fully responsive to various agonists including collagen, thrombin, and the so-called weak platelet agonist ADP up to Day 4.5, while a slight decline in responsiveness was observed on Day 6.5, which was, however, exactly the same in washed IBS-platelets as washed untreated platelets, whatever the agonist. The preserved reactivity of IBS-platelets was further confirmed in perfusion studies over adhesive protein-coated surfaces under relevant shear rates, in accordance with previously reported results.\(^3\) The expression of the major GPs (GPIbIIa, Iaalpha and VI) remained stable, while GPIbα declined similarly in both washed untreated and IBS-platelets during storage. P-selectin expression remained low in both groups during storage. Finally, IBS did not substantially alter platelet proteome as could be evaluated by the 2D-DIGE technology, indicating overall that IBS did not induce any clear intrinsic defect in integrity, function or aging of platelets isolated from the storage milieu. The sole difference we reported between IBS and non-treated platelets was a faster decrease of GPV\(^\alpha\) which is what the authors cite without any discussion about the clear discrepancy between their results and ours.

The most likely explanation for the discrepancies between our results and the study by Stivala et al.\(^1\) and others\(^4-9\) is the fact that we isolated platelets from the storage milieu in order to explore their intrinsic functional properties, independently of the storage milieu which may have an inhibitory-yet-reversible effect on platelet responsiveness. We also looked at the reactivity of platelets in their storage milieu and, indeed, found there was already inhibition of platelet aggregation in response to ADP on Day 1.5, and to collagen on Day 6.5, which was, however, similar between the untreated and the IBS-PCs\(^5\) (see Online Supplementary Figure S2B). In addition, spontaneous P-selectin exposure was higher in both untreated and IBS-PCs compared to washed platelets at Day 1.5 and further increased in IBS-PCs compared to untreated PCs at Day 6.5 only\(^5\) (see Online Supplementary Figure S2A).

In the discussion of our study we speculated that transfused platelets are isolated from the storage milieu and somehow “washed” in the recipient blood stream. We reasoned that the presence of prostacyclin (PG\(_I\)\(_2\)) during the washing procedure to inhibit platelet activation and of apyrase in the suspending milieu to degrade trace amounts of ADP released from platelets and thus prevent the desensitization of the ADP receptors, might mimic the inhibitory role of the vascular endothelium, known to express ectonucleotidase activities and to produce PG\(_I\)\(_2\), the natural strong vasodilator and inhibitor of platelet activation.

Of note, independently of IBS, we showed that the level of spontaneous P-selectin expression on platelets kept in their storage milieu resulted in approximately 30% positive cells at Day 1.5, which is the lowest amount reported by others.\(^5,6\) In addition, in our study, the pH values of the storage milieu remained similar in both untreated and IBS-PCs, while Stivala et al. reported a significant decrease in pH in IBS-treated PCs compared to untreated units by Day 1.5. Thus, independently of the washing procedure, differences in the overall initial collection procedure and/or storage conditions may play a role and could explain such differences between centers.

We did not evaluate the life span of IBS platelets in comparison to non-treated platelets in our study. Previous studies in healthy volunteers indicated acceptable viability of IBS-treated PCs after five days of storage.\(^7\) Thus, one can question the method used by Stivala et al.\(^1\) in a mouse model, and we shall have to wait for impending human studies in order to gain more relevant insights. There are a large number of studies showing no increase in IBS-treated PCs utilization during routine use which would be expected if hemostasis or survival were inadequate.\(^8-10\) The use of IBS platelets is now evermore frequent in many countries, and the precise impact on transfusion medicine practices, if any, should become common and consensual knowledge.

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References


