Dear Editors,

Platelet counts are a heritable trait\(^1\) that can be modified by inheritance of some bleeding disorders. Several years ago, we published observations on low platelet counts in Quebec platelet disorder (QPD).\(^2\) QPD is an autosomal dominant bleeding disorder, associated with a unique, gain-of-function defect in fibrinolysis that reflects increased (>100-fold) levels of urokinase plasminogen activator (uPA) in megakaryocytes/platelets, without associated increases in uPA in plasma, urine, or other cells.\(^3\)\(^5\) The cause is a duplication mutation of PLAU\(^6\) that selectively increases the production of normal PLAU transcripts by the disease chromosome in megakaryocytes but not leukocytes.\(^4\) The >100-fold increased uPA in QPD megakaryocytes and platelets triggers intraplatelet but not systemic fibrinolysis.\(^6\)^\(^7\) Although persons with QPD have normal thrombopoietin levels, their platelet counts are reduced (median: 143, range 113-198 × 10\(^3\)/L),\(^2\)\(^3\)\(^8\) with some showing chronic, mild thrombocytopenia.\(^3\)\(^5\) Although lower platelet counts in QPD do not show significant relationship to bleeding scores (R\(^2\) = 0.21, P = 0.21, based on data for n = 9), they are associated with wound healing problems.\(^8\)

Fibrinolytic inhibitor drugs, such as tranexamic acid (TXA), are very effective for treating and preventing QPD bleeding and wound healing problems.\(^2\)\(^4\)\(^8\) Previously, we noted that the highest platelet counts ever recorded for persons with QPD (~2.9-fold above baseline) were for samples drawn postoperatively, during fibrinolytic inhibitor therapy.\(^3\) While this suggests that QPD thrombocytopenia is a direct consequence of their fibrinolytic defect and increased megakaryocyte/platelet uPA, we recommended further observations as platelet counts can change significantly after surgery.\(^7\) For example, after major orthopedic surgery, platelet counts drop in the first 24 hours, recover to baseline by ~5 days, and then increase to levels about twice the preoperative value before gradually returning to baseline by ~14 days.\(^9\) Although TXA has not been reported to alter platelet counts, most persons receive only 1-2 doses (eg, to reduce bleeding from major surgery or trauma, or to treat postpartum hemorrhage) or take TXA for a limited number of days when platelet counts are rarely evaluated (eg, during menses to reduce heavy menstrual bleeding; with dental extractions for persons with bleeding disorders).

Recently, we had the opportunity to prospectively follow the blood counts of several persons with QPD who required prolonged TXA therapy to treat or prevent bleeding (Figure 1). Both had participated in QPD studies (with written informed consent, and approval from the Hamilton Integrated Research Ethics Board). The first was 57-year-old male with known QPD (International Society on Thrombosis and Haemostasis-Bleeding Assessment Tool [ISTH-BAT] score: 12), who was prescribed TXA after presenting with a ten day history of worsening right flank pain, without hematuria, due to a spontaneous, right, subcapsular renal hematoma (6.0 × 6.0 × 5.3 cm on ultrasound, without evidence of a vascular malformation on a subsequent angiogram). At presentation, his platelet count was slightly above his baseline, whereas after one week of TXA therapy (1 g orally every 8 hours), his platelet count peaked at ~3.2-fold above baseline and it remained ~1.2- to 2.0-fold above baseline during continued TXA therapy (Figure 1A) that he recalled pausing for ~7-10 days sometime during the first three months of treatment, then resumed due to worsening pain. His pain gradually improved, and his hematoma showed continued improvement on ultrasound. After TXA was discontinued, his subsequent platelet counts (evaluated several months and years later) were near baseline (Figure 1A).

The second person with QPD who was followed during prolonged TXA therapy was his 55 year brother with QPD (ISTH-BAT score: 21), chronic thrombocytopenia, and arthropathy from recurrent joint bleeds. He required an elective right hip replacement for increasing pain and progressive arthropathy. To prevent bleeding from hip replacement surgery, he received TXA intravenously (10 mg/kg every 8 hours; first dose given just before surgery), followed by oral TXA that was dose reduced on day 14 (from 1.5 to 1.0 g every 8 hours) because of nausea. He remained on TXA until he completed 35 days of prophylactic, rivaroxaban anticoagulation therapy. His surgery and postoperative course were uncomplicated, without the significant bleeding and wound healing problems that complicated his prior surgeries, which were done before he was diagnosed with QPD and without TXA. His platelet counts showed the expected, initial drop on postoperative day 1, then improved, peaking at ~3.4-fold above baseline by day 16 postop (Figure 1B), when platelet counts are expected to have returned to baseline after major

\(\text{DOI: 10.1111/ijlh.13311}\)

\(\text{Received: 1 June 2020 | Revised: 9 July 2020 | Accepted: 26 July 2020}\)

\(\text{LETTER TO THE EDITOR}\)

\(\text{Improved platelet counts during prolonged tranexamic therapy for Quebec platelet disorder implicate the underlying fibrinolytic defect as the cause of lower platelet counts}\)
orthopedic surgery. His platelet counts remained -1.7-fold above baseline on a lower dose of TXA. Five days after stopping TXA, his platelet count was still above baseline (-1.4-fold), and 12 days after stopping TXA, he had thrombocytopenia, with a platelet count close to baseline (Figure 1B).

These observed improvements in platelet counts during prolonged TXA therapy for two persons with QPD that required bleeding or surgery are interesting. Nonetheless, they represent limited clinical observations, for only two persons, as TXA therapy for QPD is rarely given for prolonged periods and only when there is a justifiable need (ie, bleeding, surgery). Accordingly, uncertainties remain about the effects of TXA on QPD baseline platelet counts. Reactive thrombocytosis is a probable explanation for why both of the persons that we followed had higher platelet counts during initial compared to final weeks of TXA therapy for QPD (Figure 1). It is important to note that the maximal postoperative platelet count in the second case occurred when reactive thrombocytosis after surgery is expected to have resolved and that his platelet count dropped after TXA was stopped (Figure 1B). Our observations indirectly suggest that the lower baseline platelet counts of persons with QPD are a direct consequence of their fibrinolytic defect and increased megakaryocyte/platelet uPA. TXA has a relatively short half-life (necessitating frequent dosing), and it does not reduce PLAU expression or platelet uPA levels in QPD (Hayward and Rivard, unpublished observations). Interestingly, it appears to take several days or weeks for TXA to have maximal effects on QPD platelet counts (Figure 1, panels A and B), and about as long for the improvement to reverse once the drug is stopped (Figure 1B). This timing suggests that drug-induced inhibition of fibrinolysis normalizes QPD platelet production, clearance, consumption, and/or lifespan. It is likely that TXA prevents or reduces excessive plasmin generation within the bone marrow and wounds as QPD does not cause systemic fibrinolysis and QPD megakaryocytes constitutively secrete abnormally large amounts of uPA, in addition to sequestering uPA in α-granules for activation-induced release by platelets. As plasmin has a number of effects on platelets, and promotes platelet activation, other factors that increase platelet counts following significant bleeds or surgery also appear to influence QPD platelet counts, given that the most striking improvements in QPD platelet counts occurred during the initial weeks of TXA treatment for such challenges (Figure 1).

Low platelet counts have not been reported in fibrinolytic defects caused by severe α2-antiplasmin deficiency or plasminogen activator inhibitor 1 deficiency, nor did we observe low platelet counts in a patient with α2-antiplasmin deficiency who was followed for many years. Nonetheless, it would be interesting to evaluate whether TXA therapy increases platelet count above baseline in other bleeding disorders with increased fibrinolysis to determine whether the improvements in platelet counts on TXA therapy are specific to QPD.

We conclude that the beneficial effects of TXA therapy for QPD include the correction of reduced platelet counts, in addition to correction of the wound healing and bleeding problems.

ACKNOWLEDGEMENTS
The authors’ studies on QPD are funded by the Canadian Institutes for Health Research (201603PJ-T-364832, CPMH). All authors contributed to the study design and manuscript preparation. ST prepared figures.
CONFLICT OF INTEREST
The authors have no conflicts of interest to disclose.

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