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Platelet function testing in patients with post-operative tonsillectomy bleeding may be a useful early identifier of inherited platelet function disorders

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Main Article

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Abstract

Background. Post-tonsillectomy bleeding is the most frequent complication of tonsillectomy. Inherited platelet function disorders have an estimated prevalence of 1 per cent. Any association between post-tonsillectomy bleeds and undiagnosed inherited platelet function disorders has not been investigated before.

Objectives. To assess the prevalence of inherited platelet function disorders in a cohort of post-tonsillectomy bleed patients.

Methods. An observational cohort study was conducted using hospital digital records. Platelet function analyser 100 ('PFA-100') closure time was tested on post-tonsillectomy bleed patients who presented to hospital.

Results. Between 2013 and 2017, 9 of 91 post-tonsillectomy bleed patients who underwent platelet function analyser 100 testing (9.89 per cent) had positive results. Five patients (5.49 per cent) had undiagnosed inherited platelet function disorders. Four patients had false positive results secondary to a non-steroidal anti-inflammatory drug effect (specificity of 95.3 per cent) proven by repeat testing six weeks later, off medication. The false negative rate was 0 per cent.

Conclusion. The prevalence of inherited platelet function disorders in our post-tonsillectomy bleed cohort is five-fold higher than in the general population. Platelet function analyser 100 testing when patients present with a post-tonsillectomy bleed allows management of their inherited platelet function disorder.

Introduction

Tonsillectomy is one of the most commonly performed operations and often an individual's first operation. However, tonsillectomy is not without risk, as post-tonsillectomy bleeding is a significant and potentially life-threatening complication, estimated to affect 0.2–4 per cent of patients.[1,2] Previous studies have attempted to identify patients with bleeding tendencies through pre-operative screening of clotting time, bleeding time and platelet function assays. However, given the low prevalence of bleeding disorders, the pre-operative screening of patients undergoing surgery is not advocated.[3,4]

The most common disorder associated with primary haemostasis is a platelet function disorder.[5] Acquired platelet function disorders are common and often associated with medication use, principally non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (aspirin). Liver disease, uraemia, trauma and acute illnesses can also cause an acquired platelet function disorder;[6–8] however, in patients undergoing tonsillectomy, these conditions are rare and easily identified pre-operatively if present. von Willebrand's disease is by far the most common of the inherited platelet function disorders, with an estimated prevalence in the general population of around 1 per cent.[9] Other considerably rarer inherited platelet function disorders exist, but might occur in up to 1 in 1 000 000 births.[10] Similarly, a small number of the population have other serious, yet uncharacterised 'mild disorders of platelet function', the prevalence of which is relatively poorly appreciated although still considered to be lower than that for von Willebrand's disease.[11] With precedent, for the purposes of analysis, we are defining the general population prevalence of inherited platelet function disorders as 1 per cent.

Patients with inherited platelet function disorders are typically identified by persistent haemorrhage after surgery, dental extractions and trauma childbirth, or menorrhagia in women. The pre-operative administration of diamino-d-arginine vasopressin allows patients with von Willebrand's disease to achieve an adequate haemostatic response, reducing their higher likelihood of significant haemorrhage requiring blood transfusion.[12] Identifying patients with this condition early in their life is good medical practice.

To our knowledge, no prior study has assessed the prevalence of undiagnosed inherited platelet function disorders in patients who suffer a post-tonsillectomy bleed, defined as a 'persistent haemorrhage after surgery'.

The primary aim of the current study was to analyse a cohort of post-tonsillectomy bleed patients, to identify if there is a disproportionately high prevalence of inherited platelet function disorders within that population, and therefore to determine whether the routine screening of post-tonsillectomy bleed patients for inherited platelet function disorder is appropriate.

Materials and methods

Study design and setting

An observational cohort study was undertaken following institutional approval at a single otolaryngology unit in Christchurch, New Zealand, from 2013 to 2017. The hospital serves a population which is predominately (88 per cent) of Caucasian origin.[13]

In 2012, the improved availability of platelet function analysis testing and the senior author's interest in this topic led to more frequent use of such testing when patients presented with post-tonsillectomy bleeding. Patients with positive platelet function analyser 100 results (i.e. platelet dysfunction) after post-tonsillectomy bleeding underwent repeat testing six weeks after discharge and NSAID cessation, followed by haematology input if necessary. Patients with normal platelet function when tested on admission had no further testing.

Patient selection

Patients presenting with post-tonsillectomy bleeding were identified using hospital admission statistics and confirmed by reviewing electronic patient records. The hospital admission statistics patient coding terms searched were: 'arrest of haemorrhage following tonsillectomy', and an admission with 'tonsillectomy' followed by an admission with 'haemorrhage'. Patients were eligible for inclusion if they underwent tonsillectomy for any indication during the study period and had post-tonsillectomy bleeding (managed as an in-patient or by re-admission after discharge). By convention, a primary post-tonsillectomy bleed was defined as bleeding that occurred within 24 hours of surgery; bleeding that occurred more than 24 hours post-operatively was defined as a secondary post-tonsillectomy bleed. Patients coded on hospital admission statistics as suffering a post-tonsillectomy bleed but with no documented tonsillectomy or post-tonsillectomy bleeding were excluded.

Platelet-function analysis

A platelet function analyser 100 device (Siemens Medical Solutions, Malvern, Pennsylvania, USA) was used for all analyses.[14] Samples were initially tested with platelet function analyser 100 collagen and adrenaline cartridges. If this demonstrated abnormal closure time (greater than 160 seconds), the sample was tested with a platelet function analyser 100 collagen and adenosine diphosphate cartridge; an 'NSAID effect' was determined using these latter cartridges when the closure time was less than 120 seconds. If both assays were prolonged – defined as a positive result – patients underwent repeat testing six weeks after NSAIDs were stopped, as NSAIDs can prolong the platelet function analyser 100 collagen and adenosine diphosphate closure time in some individuals.[15] Haematology follow up took place if a platelet function disorder was confirmed.

Data collection

The data collected included: patient characteristics (age, gender and post-operative day of bleed), category of post-tonsillectomy bleeding (primary or secondary), use of post-operative NSAIDs, need for transfusion, need for surgical management and platelet function analyser 100 results.

Data analysis

Data are summarised as median and interquartile range for continuous data, and number and percentage for categorical data. Continuous data were compared using the Mann–Whitney U test, and categorical data were compared using chi-square analysis.

We were testing for inherited platelet function disorders. Therefore, for sensitivity analyses, inherited platelet function disorders corroborated by haematologists were defined as true positives. Patients with normal collagen and adrenaline cartridge closure times, or prolonged collagen and adrenaline cartridge closure times but normal collagen and adenosine diphosphate cartridge closure times, were defined as true negatives. Patients who had abnormal collagen and adrenaline results, or abnormal collagen and adenosine diphosphate results, which normalised on repeat platelet function analyser 100 testing, were deemed to have false positive findings, secondary to platelet dysfunction acquired from NSAIDs (or another acquired cause that resolved and was not further investigated). In cases where the platelet function analyser 100 test results were negative but there was a subsequent diagnosis of inherited platelet function disorder after the post-tonsillectomy bleeding event, the platelet function analyser 100 result was considered to be a false negative.

Results

Patient characteristics, platelet function testing and sensitivity analysis

A total of 142 patients were identified via clinical coding as presenting with post-tonsillectomy bleeding during the study period. Five patients were excluded because they were captured by the hospital admission statistics coding search but had not suffered post-tonsillectomy bleeding.

Of the remaining 137 patients, 91 (66.4 per cent) underwent platelet function analyser 100 testing. Nine of 91 patients (9.89 per cent) had both prolonged collagen and adrenaline cartridge closure times and collagen and adenosine diphosphate cartridge closure times. Five of these patients (5.49 per cent) were confirmed as having inherited platelet dysfunction, based on raised collagen and adrenaline test and collagen and adenosine diphosphate test results that persisted when repeated six weeks after stopping NSAIDs. Subsequent testing differentiated between von Willebrand's disease and other platelet function disorders. Eight of the 91 patients (8.79 per cent) had a prolonged collagen and adrenaline cartridge closure time and a normal collagen and adenosine diphosphate cartridge closure time (i.e. an 'NSAID effect'). No patients were re-admitted. Patient characteristics are shown in Table 1. Sensitivity analysis results are shown in Table 2.

Platelet function testing and sensitivity analysis

Five of the 91 tested patients (5.49 per cent) were diagnosed with a newly identified inherited platelet function disorder. Four of nine patients with positive initial platelet function analyser 100 test results (44.4 per cent) were considered to have

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Table 1. Study patient characteristics, with comparison between patients with inherited platelet dysfunction and those without

Characteristic	All PFA-100 tested patients*	Acquired PFD or no PFD†	Inherited PFD‡	*P*-value
Age (median (IQR); years)	19 (9–25)	19 (10–26)	6 (4–21)	0.156
Male gender (*n* (%))	42 (46.2)	40 (46.5)	2 (40)	0.777
Post-operative day of bleed (median (IQR))	5 (2–7)	5 (2–7)	5 (1–7)	0.431
Category of bleed (*n* (%))				0.279
– Primary	19 (20.9)	17 (19.8)	2 (40.0)	
– Secondary	72 (79.1)	69 (80.2)	3 (60.0)	
Taking NSAIDS (*n* (%))	54 (59.3)	53 (61.6)	1 (20.0)	0.065
Return to operating theatre (*n* (%))	62 (68.1)	58 (67.4)	4 (80.0)	0.526
Blood transfusion (*n* (%))	5 (5.49)	5 (5.81)	0 (0.00)	0.579

*$n = 91$; †$n = 86$; ‡$n = 5$. PFA-100 = platelet function analyser 100; PFD = platelet function disorder; IQR = interquartile range; NSAID = non-steroidal anti-inflammatory

Table 2. Sensitivity analysis

PFA-100 test findings	Inherited PFD	Acquired PFD or no PFD	Total
Positive result (*n*)	5	12	17
Negative result (*n*)	0	74	74
Total (*n*)	5	86	91
Sensitivity (%)	100		
Specificity (%)	95.3		
PPV (%)	55.6		
NPV (%)	100		

PFA-100 = platelet function analyser 100; PFD = platelet function disorder; PPV = positive predictive value; NPV = negative predictive value

false positive platelet function analyser 100 results; that is, an acquired disorder of platelet function likely secondary to an NSAID effect (specificity of 95.3 per cent). All patients with normal platelet function analyser 100 test results had no further evidence of coagulopathy or disordered platelet function, making the false negative rate 0 per cent.

Management of inherited or acquired platelet dysfunction

Four of the five patients who had a confirmed inherited platelet function disorder required surgical management. Two had primary bleeds; none required blood transfusion. The diagnosis for these patients was von Willebrand's disease in three cases and 'non-specific platelet dysfunction' for the others.

Of the 12 patients who had an acquired platelet dysfunction as a result of NSAIDs (8 cases identified at initial testing and 4 cases identified on the return of normal platelet function on subsequent testing), 7 patients (58.3 per cent) required surgical management, 1 had a primary bleed (20 hours after surgery), but none required blood transfusion.

Patients with a normal collagen and adenosine diphosphate cartridge closure time at admission were discharged without follow up. Those patients with a prolonged collagen and adenosine diphosphate closure time at admission that normalised on repeat testing were advised by mail.

Discussion

The main finding of the current study is that patients who present with bleeding following tonsillectomy have a higher proportion of inherited platelet function disorders than the normal population (5.49 per cent *vs* 1 per cent respectively). This discovery supports the routine testing of platelet function in patients presenting with post-tonsillectomy bleeding, allowing the diagnosis and subsequent appropriate management of previously unrecognised inherited platelet function disorders.

In this series, nearly one-fifth of all post-tonsillectomy bleeds were associated with either an acquired or inherited disorder of platelet function, with the use of post-operative NSAID analgesia being the commonest cause of acquired disorders.

A recently published investigation of the effect of NSAIDs on platelet function analyser 100 closure times in a cohort of Korean blood donors showed that 27 per cent of this group had prolonged closure times for both the collagen and adrenaline cartridge and the collagen and adenosine diphosphate cartridge, which is this study's classification of a 'positive test'.[15] This suggests the need for delayed repeat platelet function analyser 100 collagen and adrenaline cartridge and collagen and adenosine diphosphate cartridge tests, after the cessation of NSAIDs, to identify true positive findings. The authors went on to conclude that the platelet function analyser 100 test is likely ineffective at accurately diagnosing drug-induced platelet dysfunction. Therefore, our recommendation is that patients with initially positive collagen and adrenaline and positive collagen and adenosine diphosphate closure times undergo repeat platelet function analyser 100 testing, six weeks after stopping NSAIDs, followed by haematology review if required.

After haematology review, patients diagnosed with an inherited platelet function disorder received a management plan for any future surgery. In accordance with longstanding clinical practice, patients with von Willebrand's disease and patients with non-specific disordered platelet function received advice regarding the use of diamino-d-arginine vasopressin and tranexamic acid before future procedures and childbirth, to reduce their risk of haemorrhage, complications and blood transfusion.[16,17] Those with von Willebrand's disease also received guidance regarding the potential use of factor VII and von Willebrand's factor concentrates.

All regional tonsillectomy patients received prescriptions for NSAIDs post-operatively, as recommendations from the literature largely support the analgesic benefits outweighing any potential bleeding risks.[18,19] The presented study has not directly analysed the effect of NSAID-induced acquired

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platelet dysfunction on post-tonsillectomy bleedings and therefore we do not suggest a change to routine practice regarding regular post-tonsillectomy NSAID use.

Patients with post-tonsillectomy bleeds were otherwise managed in line with accepted 'best practice', including the standard check of full blood count, coagulation screen (prothrombin time, activated partial thromboplastin time and fibrinogen levels) and withdrawing NSAIDs, as platelet function analyser 100 results were often not available until after any bleeding was controlled. Arguably, post-tonsillectomy bleed patients with normal platelet function analyser 100 closure times could remain on NSAIDs, simplifying their analgesic regimen. Future research could investigate the re-bleed rates in post-tonsillectomy bleed patients with normal platelet function who continue to take NSAID analgesia.

It remains unclear at this time whether tranexamic acid is justified for all tonsillectomy patients in the post-operative period, and we did not specifically analyse the use of tranexamic acid in our post-tonsillectomy bleed cohort.[20] However, given the efficacy this has in the management of bleeding in inherited platelet function disorders, as discussed previously, and the significant minority of patients found to have inherited platelet function disorders within this post-tonsillectomy bleed cohort, we conject that the use of oral or intravenous tranexamic acid as part of the initial management of post-tonsillectomy bleeding is likely appropriate. Further research may be required to corroborate this.

With regard to the pre-operative assessment of post-tonsillectomy bleeding risk, current National Institute for Health and Care Excellence guidance advises against performing pre-operative clotting screens (by analysis of prothrombin time and activated partial thromboplastin time) for American Society of Anesthesiologists ('ASA') physical status classification 1 and 2 patients (normal patients or patients with mild systemic disease).[21] This is justified by the low prevalence of haemostasis disorders and the low sensitivity of clotting screens for these patients, leading to an inadequate risk stratification of patients for post-tonsillectomy bleeding.[22] In light of this and the nature of our study design, we did not include patients' clotting screen findings.

Similarly, recommendations from the literature advise against the need to pre-operatively screen platelet function, because of the very low general population prevalence of platelet function disorders.[3,4] Given the 5.49 per cent inherited platelet function disorder prevalence found only in this study's post-tonsillectomy bleed population, and having not assessed the general tonsillectomy population, there remains no conclusive evidence to suggest that there would be any benefit in pre-operatively screening for inherited platelet function disorders with the platelet function analyser 100 test ahead of tonsillectomy.

In our centre, the platelet function analyser 100 test costs approximately NZ$18 (£9.00). We performed single platelet function analyser 100 tests on 82 patients, and 2 sets of tests on 9 patients, which resulted in the identification of 5 inherited platelet function disorders. This equates to roughly NZ $360 (£185) per diagnosis, or 20 tests per diagnosis. It is therefore an inexpensive and simple test, with excellent sensitivity. As part of a cost–utility analysis, it is difficult to quantify the costs of missed diagnoses; however, as previously discussed, undiagnosed inherited platelet function disorders have a higher rate of blood transfusion, with an associated increased length of hospital stay and longer surgery times.[12] A multicentre study, conducted to aggregate a larger sample size, would allow a more accurate cost–utility analysis.

- Inherited platelet function disorders have a prevalence of approximately 1 per cent
- Platelet function analyser 100 ('PFA-100') testing is sensitive in identifying inherited platelet function disorders
- This testing found the prevalence of inherited platelet function disorders to be 5.5 per cent in a cohort of post-tonsillectomy bleed patients
- Platelet function analyser 100 tests should be performed on all post-tonsillectomy bleed patients

This pilot study revealed inherited platelet function disorders in a significant minority of post-tonsillectomy bleed patients. We therefore suggest that routine platelet function testing in all post-tonsillectomy bleed patients is likely to be worthwhile. Future audits should be used to corroborate applicability with local populations.

Limitations

The current study is an observational cohort study, with the limitations and risks of bias associated with such a study design. In particular, not all patients presenting with post-tonsillectomy bleeding during the study period underwent platelet function analyser 100 testing. Not all junior staff assessing these patients were aware of the perceived value of platelet function analyser 100 testing, so this limitation is unlikely to have caused selection bias. Follow up ranged between one and five years, by the nature of our cohort. Absence of further platelet function test results on the electronic records was interpreted as meaning that patients did not have a platelet function disorder. The known incidence of von Willebrand's disease in the local population is the same as in other populations of predominantly Caucasian descent. This study was not designed to assess the pre-operative risk of post-tonsillectomy bleeding.

Competing interests. None declared

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