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Screening for undiagnosed bleeding disorders in post-tonsillectomy bleed patients: Retrospective review and systematic review of the literature

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ABSTRACT

Objectives: There is currently no standard for screening children with post-tonsillectomy bleeds (PTB) for coagulopathy disorders. This study aims to identify children with occult coagulopathy diagnosed at PTB and to identify factors associated with diagnosis. A systematic review of the literature further identified trends in this topic.

Methods: A retrospective chart review of patients returning to the operating room for PTB at a tertiary children's hospital was undertaken from 2012 to 2016. A systematic review using Medline OVID was subsequently performed.

Results: Of 12,503 tonsillectomies, 311 children (52% male, mean age 8 years) required surgery for PTB (2.5% rate). Twenty-one patients (7%) had multiple episodes. Only two patients (0.6%) (both with known coagulopathy) underwent pre-tonsillectomy labs and 260 (84%) had labs at PTB. Six patients (2%) were diagnosed with a new coagulopathy, most commonly von Willebrand's Disease (vWD) in five (2%). Three patients (1%) were diagnosed at first PTB and three (1%) at second PTB. Of the three diagnosed at second PTB, two had normal partial thromboplastin time (PTT). In systematic review, 1243 manuscripts were reviewed and 8 papers discussing this topic are presented.

Conclusion: Occult coagulopathy was rarely diagnosed at PTB, but this may be limited by inconsistent screening. PT and PTT are not sensitive tests for vWD, and normal coagulation labs may lead to delayed diagnosis. The literature reveals occult coagulopathy is rare but often diagnosed after severe or recurrent hemorrhage. In order to provide efficient care and medical management, a standardized algorithm and sensitive labs for screening PTB patients are needed.

1. Introduction

More than half a million children under 15 undergo tonsillectomy annually in the United States [1,2]. Despite extensive experience and research, post-tonsillectomy bleeds (PTB) remain a significant risk of this common surgery, affecting 3–5% of all patients [3,4]. This complication has a significant impact on children, often requiring a second general anesthetic to stop the bleeding surgically. It can rarely be life-threatening [5]. There have been several large studies looking at factors influencing bleed rates. Several potential causes have been evaluated including surgical technique, pre-operative comorbidities and coagulopathies, indications for tonsillectomy and pain management practices. To date, older age, surgical technique and recurrent tonsillitis have been correlated with increased rates of bleeding [2,6–9].

An additional factor which may influence bleeding is an undiagnosed bleeding disorder. Preferably, bleeding disorders would be diagnosed pre-operatively. However, screening for bleeding disorders in children can be difficult because they have not often been exposed to significant bleeding challenges [10]. It has been shown that labs screening for coagulopathy have little predictive value in patients without history of bleeding episodes [11,12]. Using the prospective studies examining this question, a meta-analysis from 2001 [13] concluded that pre-tonsillectomy coagulation laboratories had a low positive predictive value for PTB, and therefore recommended against their routine use. In fact, current American Academy of Otolaryngology—-Head and Neck Surgery consensus guidelines for otherwise healthy

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children recommend laboratory screening prior to tonsillectomy only for patients with personal or family history of bleeding disorder [14,15]. However, a more recent retrospective article from 2019 found that 2.8% of children undergoing tonsillectomy had abnormal coagulation labs and half of these patients had a previously unknown bleeding disorder [16]. Based on the fact that pre-operative history had a low sensitivity and the number needed to treat (35.7) was relatively low, these authors argued that pre-operative laboratory testing may be cost effective depending on surgeons' PTB rate [16]. Part of the reason for ongoing controversy is that tonsillectomy may represent the first significant bleeding challenge for otherwise healthy children, and PTB may be the first sign of a bleeding disorder [17]. PTB marks an opportunity to recognize and treat previously unknown coagulopathy. There are no current standard guidelines for evaluation and work up of patients presenting with PTB, although multiple retrospective reviews have suggested screening labs in the appropriate clinical setting [15,18,19]. The purpose of this study is to identify how many patients with PTB were eventually diagnosed with such a bleeding disorder and to identify factors associated with abnormal coagulation profiles. Furthermore, we present a systematic review of the literature to discuss the new diagnosis of bleeding disorder at time of PTB.

2. Methods

This study was approved by the institutional review board at Baylor College of Medicine (Houston, Texas). Records were identified for all children presenting to the operating room for control of oropharyngeal hemorrhage (CPT 42960, 42961) from 2012 to 2016. All patients less than 18-years-old who underwent tonsillectomy and returned to the operating room for operative control of PTB were included. Retrospective review of the included patients was performed. Patient health information was collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Texas Children's Hospital [20]. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Charts were reviewed for demographic information, length of hospitalization, American Society of Anesthesiologists (ASA) status, and other recorded medical comorbidities. Disease course, including the indication for surgery and number of reported episodes of PTB were recorded. Pre-operative labs and laboratories obtained at the time of PTB, including complete blood counts, prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT), and von Willebrand panels were included. Finally, post-operative course was reviewed for further bleeding episodes or subsequent diagnosis of coagulopathy. Descriptive statistics are reported.

2.1. Systematic review

A systematic literature search was executed by a trained Medical Librarian (LO), to review perioperative screenings for undiagnosed bleeding disorders in post-tonsillectomy hemorrhage patients. Using Medline OVID (Medline on OVIDSP) as the foundational database upon which to develop the search, three encompassing concepts were investigated and developed, including: Tonsillectomies, Hemorrhages, and Coagulation Screenings. Each concept was worked on using both the controlled vocabulary of the database and keywords. MeSH (Medical Subject Headings) terms were identified for each concept in Medline OVID. Keywords or natural language terminology were added to each concept, along with their various synonyms. The natural language terminology was searched using the title, abstract, and keyword fields within the Medline OVID database. Once each concept was thoroughly developed, the three concepts were added together to create one complete search. The foundational search strategy was finalized March 2019. No limiters were used to maximize results. The complete search strategy was then given to the PI for approval, before translation to the additional agreed upon databases: Embase, Scopus, and the Cochrane Library, four in total.

Upon approval from the PI, the searches were translated to the Scopus, Embase and Cochrane Library databases. The final searches were all run on the same day in each database for consistency. The results were then uploaded to the EndNote citation manager for the automatic and manual de-duplication process. The de-duplication process was also completed in March 2019. Once the de-duplication process was carried out, and the search strategies recorded, a compressed EndNote library was delivered to the PI for the exclusion/inclusion review process. Search Coverage: Medline OVID (Medline on OVIDSP): (1948–March 29, 2019), Embase (1947–March 28, 2019), Scopus (1788 – March 29, 2019), Cochrane Library (includes: *Cochrane Database of Systematic Reviews* (CDSR), and *Cochrane CENTRAL* (trials) through March 29, 2019).

Once the initial articles were identified, two independent authors reviewed each study to determine which met inclusion and exclusion criteria. Inclusion criteria were defined by PICOS questions (Table 1), and studies examining the utility of pre-tonsillectomy laboratory screening or patients with known coagulopathy were excluded.

3. Results

From 2012 to 2016, 12,503 tonsillectomies were performed at Texas Children's Hospital on children under the age of 18. Of these, 311 children (2.5%) returned to the operating room for control of PTB. Demographics of the patient population are presented in Table 2. Tonsillectomies were performed using either monopolar electrocautery, cold techniques or coblation, depending on surgeon preference. There was an even gender split (52% male), and mean age at PTB was 8. A majority of patients were classified as ASA class 2 (mild systemic disease). The most common indication for tonsillectomy was sleep disordered breathing (123 patients, 40%). The mean post-operative day of PTB was 6.3. There was a bimodal distribution of presentation days, with the highest number of bleeds on day 0–1 or day 7. A majority of patients only had one episode of bleeding (93%), but there were an additional 21 patients (7%) who reported multiple episodes of PTB (Table 3).

3.1. Laboratory testing

Only the two patients (0.6%), both with known coagulopathy, had lab work prior to tonsillectomy. At time of PTB, coagulation screening was physician-dependent, and screening labs were a decision made by the individual provider at time of presentation or operation. There were

Table 1
PICOS questions to evaluate the literature presented in the systematic review.

Population	Includes children < 25 years old
Interventions	Tonsillectomy ± adenoidectomy only
Comparisons	PTB in patients with occult coagulopathy vs patients without coagulopathy
Outcomes	PTB (or multiple PTB), new diagnosis of coagulopathy
Study design	Case report or series, retrospective review, prospective population studies

Table 2
Demographics of patients presenting to the operating room for control of oropharyngeal bleed.

Characteristic	Number	Percentage
Gender		
Male	163	52
Female	148	48
Age (years)		
Mean	8.0	
Median	7	
ASA classification		
Healthy (1)	32	12
Mild systemic disease (2)	172	64
Severe systemic disease (3)	64	24
Comorbidities		
None	134	43
Asthma	56	18
Obesity	36	12
ADHD	36	12
GERD	22	7
Genetic syndrome	15	5
Seizures	14	5
Depression/Anxiety	10	3
Congenital heart disease	7	2
Coagulopathy	2	1
Other	24	8
Indication for tonsillectomy		
Obstructive sleep apnea	79	25
Sleep disordered breathing	123	40
Recurrent tonsillitis	100	32
Other	28	9

Table 3
Tonsil bleed characteristics.

Characteristic	Number	Percentage
Post-operative day of PTB		
Mean	6.3	
Median	7	
Number of PTB(s)		
1	290	93
2	16	5
3	5	2

Table 4.1
Laboratory values in patients with PTB.

Lab value	Number tested	Number abnormal
Hemoglobin	260	10
Platelet count (> 150 normal)	240	3 (all ≥ 125)
INR (≤1.1 normal)	177	53 (all ≤ 1.5)
vWF panel	34	12

Table 4.2
Sensitivity, specificity and predictive values of PT/INR and riscocetin.

	PT/INR	Riscocetin
Sensitivity (95% CI)	33.3% (4.3–77.7%)	80.0% (28.4–99.5%)
Specificity (95% CI)	70.2% (62.7–76.9%)	72.4% (52.8–87.3%)
Positive predictive value (95% CI)	3.77% (12–11.1%)	33.3% (19.3–51.0%)
Negative predictive value (95% CI)	96.8% (94.4–98.2%)	95.5% (78.2–99.2%)

260 (84%) patients who had labs drawn at presentation (Table 4). Of these, 177 (57%) had coagulation panels and 34 (11%) had testing for von Willebrand disease (vWD). A majority of lab values were within normal limits. Ten patients (3%) were anemic at PTB—this represents 4% of all patients who had hemoglobin drawn. Six patients (2%) were diagnosed with a new coagulopathy, most commonly vWD in five patients (2%) (Table 5). Three patients (1%) were diagnosed with a bleeding disorder at first PTB and three (1%) at second PTB. Of the three diagnosed at second PTB, two had normal partial thromboplastin time (PTT). The sensitivity and positive predictive value of PT/INR and ristocetin were low but both had a fairly high negative predictive value in the setting of post-tonsillectomy hemorrhage (Table 4).

Table 5
Patients diagnosed with coagulopathy at PTB. (*abnormal value, POD = post-operative day, Hgb = hemoglobin, Plts = platelets).

	Age	Number of PTB	POD first bleed	Hgb	Plts	INR	Riscocetin	Diagnosis
1	16	3	9	15.0	297	1.1	35*	vWD
2	13	1	7	11.7	276	1.5*	–	Vitamin K deficiency
3	4	1	8	10.0	–	1.1	45*	vWD
4	4	3	1	9.5	291	1.2*	68	vWD
5	7	3	6	11.3	352	1.1	40*	vWD
6	7	2	8	9.2	462	1.0	40*	vWD

3.2. Patients with known coagulopathy

During the study period, 32 patients with known coagulopathy underwent tonsillectomy. Of these, 21 had sickle cell disease, four had von Willebrand Disease, and 7 had other coagulopathies. Of the 32 patients, 29 (91%) patients did not have any bleeding post-operatively. One of the four patients with known vWD had PTB that self-resolved with inpatient admission and hydration. Two patients (6%) with other coagulopathies (acute lymphocytic leukemia and low vWF without full vWD) had PTB that required surgery.

3.3. Systematic review of the literature

Using the study identification technique described above, 1243 studies were available for review. After two authors reviewed the titles and abstracts of the included studies, 70 were included for full-text review. Of these, 8 met final inclusion criteria. The 62 articles were excluded for reasons described in Fig. 1. Each of the studies identified

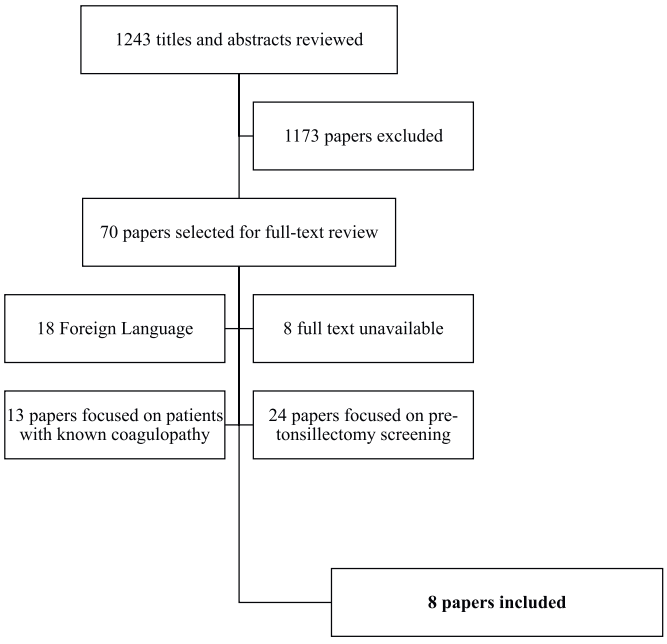

Fig. 1. Exclusion of papers from systematic review.

Table 6
Systematic review of the literature on occult coagulopathy diagnosed at the time of post-tonsillectomy hemorrhage.

Study	Sample Size	Age Range (years)	Number of PTB (%)	Number of patients with occult coagulopathy	Diagnoses	Signs of coagulopathy
Fuller 1970 [27]	1	6	–	1	Hemophilia A	Multiple episodes of primary PTB
De Diego 1999 [28]	385	1–14	5 (1.3%) primary bleeds	2 (40%)	vWD	Massive intraoperative and immediate postoperative bleeding
Prim 2003 [29]	1516	0.8–13.9	13 (0.8%) primary bleeds	6 (46.1%)	vWD, releasing thrombopathy	Hematologic workup at time of PTB
Windfuhr 2004 [22]	6966	0.4–93	201 (2.9%)	2 (1%)	Factor XIII deficiency, Factor IX deficiency	Severe post-operative bleeding
Zumtobel 2011 [30]	3	–	–	3	XII deficiency, XIIIa deficiency, vWD	Recurrent episodes of PTB; all had normal pre-tonsillectomy lab testing (CBC, clotting screen)
Sun 2011 [19]	3128	Mean age 8.4	182 (5.8%)	8 (4%)	vWD, platelet defect, factor XII deficiency, Hemophilia A	Abnormal aPTT, PFA values and/or multiple ED visits for PTB; *all patients had PFA at PTB*
Biggs 2014 [31]	1850	2–50	93 (5% overall, 0.7% return to OR)	0	–	All patients screened with CRP, INR, APTR, CBC at PTB
Altamimi 2016 [32]	6	4–27	6	6	Factor XIII deficiency	Recurrent episodes of PTB

patients with bleeding disorders only after PTB. Some began hematologic workup immediately at PTB, and some started the workup because of the degree of bleeding, inability to control the bleeding or number of recurrent PTB. The most commonly diagnosed disorder was vWD. A summary of the relevant studies is presented in Table 6.

4. Conclusions

This retrospective review of over 12,000 patients from 2012 to 2016 identified 311 patients requiring surgery for PTB. This represents the largest study identifying occult coagulopathy at PTB. Six patients (2%) were diagnosed with coagulopathy as a result of PTB, most commonly vWD in five patients (2%). This is higher than the 1% prevalence of vWD in the general population [21,22].

In this group, three patients (1%) were missed at first PTB and went on to have a second PTB prior to diagnosis. This delay in diagnosis represents a missed opportunity to begin treatment to limit or prevent further bleeding. Ideally, bleeding disorders are diagnosed prior to tonsillectomy so that treatment can begin prior to surgery. But, screening for bleeding disorders in children can be difficult because they have not often been exposed to bleeding challenges, and coagulation labs have little predictive value in patients without bleeding history [10–12]. Given these facts, there is an opportunity to develop improved screening for coagulopathy in both the pre-tonsillectomy and PTB setting.

This study sought to detect bleeding disorders in patients with a first significant bleeding episode—PTB. In the population presented here, sensitivity and positive predictive value of standard laboratory tests were low. The sensitivity, specificity, positive and negative predictive values of PT/INR to predict bleeding disorder in this study were all very similar to the values of pre-operative PT/INR to predict bleeding episodes after tonsillectomy [23]. Results here were similar to other studies that showed good negative predictive value of each of these lab tests, but low sensitivity [23,24]. Riscocetin cofactor activity is the standard screening lab for vWD, and INR would be expected to be normal in this disease [25]. Given that vWD was the most commonly diagnosed bleeding disorder, it is not surprising that risocetin (part of the vWD panel) was much more sensitive and had a higher positive predictive value for bleeding disorder than PT/INR (Table 4.2). Based on the fact that vWD is the most common bleeding disorder in the pediatric PTB population, we conclude that screening laboratories in these patients should focus on vWD panels. However, given the complexity of this lab, its interpretation and relative cost, further studies are warranted to evaluate which patients should undergo this test.

Other studies have recommended using different laboratory tests routinely to screen for bleeding disorders. Sun et al. recommended including platelet function assay (PFA) in the screening tools for patients with PTB [19]. This test is more sensitive for occult coagulopathies; however, it is expensive and requires special equipment and technician expertise to be run, limiting its broad use. Others have recommended the use of rotational thromboelastometry (ROTEM) as an alternative point-of-care test to evaluate coagulation. It has been shown to be more specific for clinically relevant bleeding disorders in pediatric surgical patients [26].

In this study, 51 patients (16%) did not have any labs at PTB and only 34 (11%) had vWD panels. Because of unstandardized screening and laboratory work up, it is possible that diagnosis of coagulopathy was missed in some children. In this study, pre-test probability of bleeding disorder was determined by each physician and labs were ordered based on individual practitioner's decision making. Based on the poor overall sensitivity of lab testing in this study and the fact that some patients were missed on first episode, some unnecessary labs were ordered and some patients were diagnosed late. In order to prevent both, a standardized algorithm is needed to identify patients with a high-pretest probability of underlying bleeding disorder.

In this population, the rate of PTB in patients with known

coagulopathy that were appropriately managed perioperatively (6%) was near the reported rate of PTB in the general population. This illustrates the fact that detecting coagulopathy early can limit the morbidity of the operation.

In conjunction with the results presented here, systematic review of the literature revealed that occult coagulopathy remains a difficult and controversial topic in the literature. While guidelines and recommendations for pre-operative screening exist, even these remain controversial [11–13]. The rate of coagulopathy amongst PTB patients varies dramatically in the current literature (from 0 to 46% of patients). Despite the rarity of bleeding disorders in this population, the severity, potential mortality and repetitive nature of PTB amongst patients with undiagnosed bleeding disorders make this a relevant problem for the pediatric otolaryngologist. Standardized screening with a combination of thorough history, bleeding questionnaires and more specific tests such as vWD panels, PFA or ROTEM provide a prospective solution to this controversial and life-threatening problem.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijporl.2019.06.009.

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