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ORIGINAL RESEARCH

Safety of Tonsillectomy and/or Adenoidectomy in Pediatric Patients with Prolonged Activated Partial Thromboplastin Time and Factor XII Deficiency

Jun Du[1], Qing-long Gu[1], Ying-xia Lu[1], Lei Zhang[2], Xiao-jun Zhan[1], Zhan Wang[1]

[1]Department of Otolaryngology, Head and Neck Surgery, Children's Hospital Capital Institute of Pediatrics, Beijing, 100000, People's Republic of China; [2]Department of Hematopathology, Children's Hospital Capital Institute of Pediatrics, Beijing, 100000, People's Republic of China

Correspondence: Qing-long Gu, Department of Otolaryngology, Head and Neck Surgery, Children's Hospital Capital Institute of Pediatrics, No. 2 Yabao Road, Chaoyang District, Beijing, 100020, People's Republic of China, Tel +86-13810091816, Email qinglonggugql@126.com

Objective: To evaluate the safety and feasibility of tonsillectomy and/or adenoidectomy (T&A) in pediatric patients with prolonged activated partial thromboplastin time (APTT) and coagulation factor deficiency.

Methods: A prospective study was admitted to the children undergoing T&A at our institution between October 2019 and January 2020, specifically focusing on preoperative coagulation function. Within this group, we identified 5 patients exhibiting prolonged APTT and coagulation factor deficiencies, constituting the experimental group, and 10 patients matched by gender and age with normal blood coagulation function were selected as the control group. Comparative analyses between the two groups were conducted, focusing on surgical duration, intraoperative bleeding volume, duration of hospital stay, and postoperative complications such as active bleeding across the groups. At the six-month postoperative mark, a reassessment of coagulation functions and factor assays was conducted within the experimental group.

Results: No statistically significant differences were discovered in terms of surgical duration or bleeding volume when comparing the experimental subgroups with their respective control counterparts. Furthermore, there were no incidences of postoperative active bleeding observed in any of the groups. Notably, postoperative APTT values (32.7 ± 1.7s) exhibited a significant disparity compared to preoperative levels (43.7 ± 1.8s, $p < 0.01$). Coagulation factors demonstrated normalization, evidenced by a significant difference in postoperative Factor XII levels (40.2 ± 5.4%) compared to preoperative levels (63.1 ± 5.9%, $p < 0.01$).

Conclusion: Prolonged APTT with FXII factor deficiency does not show a significant bleeding tendency and is not a contraindication for T&A surgery. Post T&A surgery, children with abnormal coagulation function and deficient clotting factors show significant improvement compared to pre-surgery. It is important to consider that chronic inflammation in adenoids and tonsils may contribute to the prolongation of APTT and the manifestation of Factor XII deficiency.

Keywords: adenoidectomy, children, factor XII deficiency, prolonged APTT, tonsillectomy

Introduction

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by the partial or total collapse of the upper airways with intermittent hypoxia, a chronic systemic inflammatory state, and an increased cardiovascular risk.[1] It also has an effect on adult OSA.[2] Tonsillectomy and adenoidectomy (T&A) rank among the most frequently performed surgical procedures[3,4] in children. The primary complications associated with these interventions primarily revolve around intraoperative and postoperative bleeding. The reported bleeding rate[5] for adenoidectomy is approximately 0.5%, while for tonsillectomy, it ranges from 0.5% to 5%.[6–8] Postoperative hemorrhage can lead to prolonged hospitalization, necessitate subsequent surgical interventions, and in severe instances, pose life-threatening consequences. The estimated mortality rate for tonsillectomy in the UK falls within the range of 1 in 10,000 to 1 in 28,700.[9] Existing research underscores a substantially elevated post-tonsillectomy bleeding rate of 15–53% in children with hemorrhagic disorders, in contrast to those with normal coagulation profiles.[10–12] Consequently, safely conducting T&A in children with

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coagulation function abnormalities, particularly those with mild coagulation disorders, presents a significant clinical challenge. The identification of optimal management strategies for such cases is imperative. This article presents a prospective analysis of clinical data derived from five children with coagulation function abnormalities who recently underwent T&A in our department, highlighting the critical importance of sensitive preoperative assessments and effective postoperative management.

Participants and Methods

General Information

Between October 2019 and January 2020, an assessment was conducted on 368 children scheduled for T&A at the Department of Otorhinolaryngology, Head and Neck Surgery, Affiliated Children's Hospital of Capital Institute of Pediatrics. Prolonged activated partial thromboplastin time (APTT) and coagulation factor abnormalities were observed preoperatively in 5 of these children. For comparative purposes, controls consisting of 10 children with similar gender and age, undergoing identical procedures by the same surgeon during the same period, were selected. Monitoring encompassed surgical duration, intraoperative and postoperative bleeding, and recovery time.

Detection Equipment and Reference Range

The performance of coagulation function and factor assays was executed using the ACL TOP system. The reference ranges for normal values of coagulation function and factors are delineated in Tables 1 and 2.

Detection Indicators and Criteria

Activated Partial Thromboplastin Time (APTT)

In this study, two measurements of APTT, with a prolongation of over three seconds relative to normal values were deemed significant.[4] The coagulation factor testing covered Factors II, V, VIII, IX, X, and XII. Inclusion criteria for the experimental group included extended APTT (surpassing the normal range by more than three seconds) and diminished levels of factors II, V, IX, X, XII, indicative of mild coagulation function abnormalities. Cases of hemophilia A (Factor VIII deficiency) were expressly excluded. Although three patients exhibited below-normal Factor IX levels, they did not meet the diagnostic criteria for hemophilia B (Factor IX deficiency).

Surgical Duration

The measurement of surgical duration involved tracking the time from the initiation of the surgery until achieving complete hemostasis. The surgeries were performed by the same skilled surgeon using a 70° endoscope system for assistance. The adenoid and tonsil tissues were removed using a low-temperature plasma radiofrequency system, and bleeding was controlled using the low-temperature plasma system.

Intraoperative Blood Loss Assessment

The estimation of intraoperative blood loss was determined by subtracting the volume of sodium chloride solution used during the surgery from the total volume of bodily fluids, including oronasal secretions collected in the drainage bag.

Postoperative Observation

Both groups of children received antibiotics for infection prevention post-surgery. Their postoperative body temperature, feeding status, presence of fever, sore throat, cough, and other symptoms were recorded. The recovery of the surgical wound was observed, paying attention to the color and extent of scab shedding. The presence of primary bleeding within 24 hours post-surgery and secondary bleeding after 24 hours was also monitored.

Statistical Analysis

Data analysis was performed using SPSS 24.0. Descriptive statistical methods were used for data analysis. Numerical data exhibiting a normal distribution are expressed as mean ± standard deviation. The surgery duration, bleeding volume, and length of hospital stay were analyzed using paired sample *t*-tests. Paired-sample *t*-tests were used for the comparison of numerical data before and after surgery, with a significance threshold set at $P < 0.01$.

Table 1 Preoperative Coagulation Function Indicators and Coagulation Factors

Patient Number	Gender	Age	Family History	APTT (24–37s)	PT (8.8–12.8s)	TT (10.3–16.6s)	INR (0.9–1.2)	Factor II (79–131%)	Factor V (62–139%)	Factor VIII (50–150%)	Factor IX (65–150%)	Factor X (77–131%)	Factor XII (50–150%)
1	Male	4	Yes	46.0	12.0	15.2	1.04	90.1	87.4	95.2	73.7	74.2	36.8
2	Male	5	No	42.4	11.6	17.3	1.01	85.9	85.4	79.2	64.0	82.4	35.3
3	Male	5	No	42.9	12.3	16.8	1.07	82.0	85.4	109.2	59.0	79.0	49.0
4	Male	3	No	45.3	11.5	16.1	1.00	73.4	87.4	59.0	53.0	65.1	38.4
5	Male	6	No	42.0	13.6	16.1	1.18	82.0	107.2	121.4	78.4	89.0	41.4

Note: APTT, PT, TT are the averages of two tests. Family history refers to the history of coagulation function abnormalities.

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Table 2 Pre- and Postoperative Intervention, Surgical Duration, and Hospital Stay Duration for Pediatric Patient

Surgery type Group 1	**Adenoidectomy Experimental group 1 (3 cases)**	**Adenoidectomy Control group 1 (6 cases)**	***p***
Surgical duration (min)	13.0±1.0	13.5±1.7	0.626
Intraoperative bleeding (mL)	8.0±2.6	10.0±3.4	0.388
Postoperative bleeding (mL)	0	0	/
Hospital stay duration (days)	5±2	3±0	0.225
Surgery type Group 2	**Tonsillectomy + adenoidectomy Experimental group 2 (2 cases)**	**Tonsillectomy + adenoidectomy Control group 2 (4 cases)**	***p***
Surgical duration (min)	21.0±0	20.5±3.3	0.822
Intraoperative bleeding (mL)	22.5±0	18.5±4.5	0.342
Postoperative bleeding (mL)	0	0	/
Hospital stay duration (days)	4±0	4±0	/

Results

The experimental group consisted of 5 male children aged 3 to 6 years, with a mean age of 4.6 ± 1.1 years. All pediatric patients within this group exhibited prolonged APTT in both assessments (Table 1). Further coagulation factor testing revealed deficiencies for Factors IX and XII in 2 patients, for Factors X and XII in 1 patient, for Factor XII in 1 patient exclusively, and multiple deficiencies in 1 patient (Factors II, IX, X, and XII). Notably, all patients presented with Factor XII deficiency. One pediatric patient had a familial history of coagulation abnormalities, with the father reporting a bleeding tendency without a formal diagnosis. None of the children had a history of spontaneous bleeding (Table 1).

Within the experimental group, 3 children underwent adenoidectomy using radiofrequency ablation, and 2 underwent T&A via radiofrequency ablation. All surgeries were performed by a single experienced otolaryngologist. The adenoidectomy surgery duration for children with coagulation abnormalities in the experimental group was 13.0 ± 1.0 minutes, while in the control group it was 13.5 ± 1.7 minutes, with a p-value of 0.626, indicating no statistically significant difference in surgery duration. The adenoidectomy combined with tonsillectomy surgery duration for the experimental group was 21.0 ± 0 minutes, and for the control group it was 20.5 ± 3.3 minutes, with a p-value of 0.822, also showing no statistically significant difference in surgery duration.

In terms of intraoperative bleeding volume, the experimental group of children with coagulation abnormalities had a volume of 8.0 ± 2.6mL during adenoidectomy surgery, while the control group without coagulation abnormalities had a volume of 10.0 ± 3.4mL, resulting in a p-value of 0.388, indicating no statistically significant difference in bleeding volume during adenoidectomy surgery.

For adenoidectomy combined with tonsillectomy surgery, the bleeding volume was 22.5 ± 0mL for the experimental group and 18.5 ± 4.5mL for the control group, with a p-value of 0.342, also showing no statistically significant difference in bleeding volume during this combined procedure. More details were displayed in Figures 1 and 2.

No active bleeding within 24 hours postoperatively was observed in any of the pediatric patients in the study, including those with coagulation disorders. Follow-up assessments at 1 week and 2 to 4 weeks post-surgery for both experimental and control groups consistently revealed no active bleeding episodes (Table 2). Among the 5 children, only the first experienced an extended hospital stay compared to typical cases; the remaining children did not have a notable increase in hospital stay duration. However, there was no statistically significant difference in the length of hospital stay between experimental group 1 and control group 1 ($p = 0.225$). The hospital stay duration was the same for experimental group 2 and control group 2 (both groups had a standard deviation of 0, making it impossible to compare statistical differences) (Table 2).

Post-discharge, outpatient follow-ups for the experimental group were scheduled at 1 week, 2 weeks, 1 month, and 6 months post-surgery. These children reported minimal pain or bleeding, and improvements in symptoms such as snoring and sleep quality were observed post-surgery. At the 6-month postoperative mark, reassessment of coagulation function and factors revealed that all children in the experimental group exhibited normal range values for both parameters (Table 3).

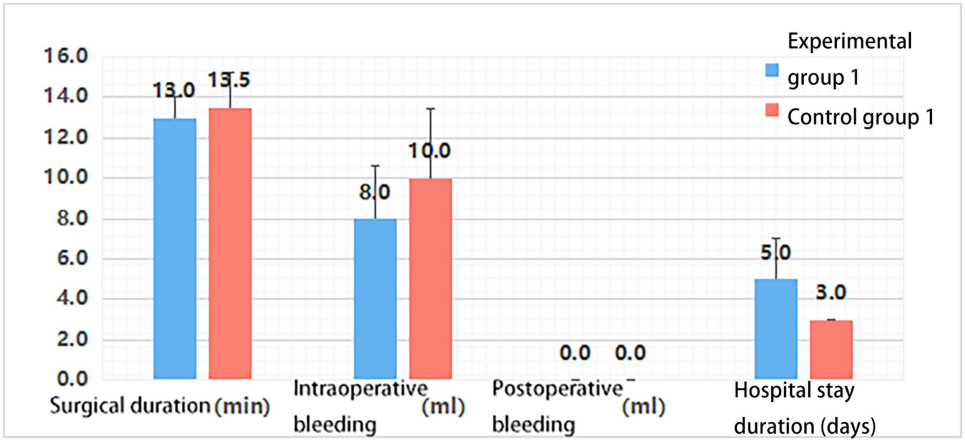

Figure 1 Surgical duration, intraoperative and postoperative bleeding and hospitalization days in adenoidectomy surgery group (experimental group 1/control group 1).

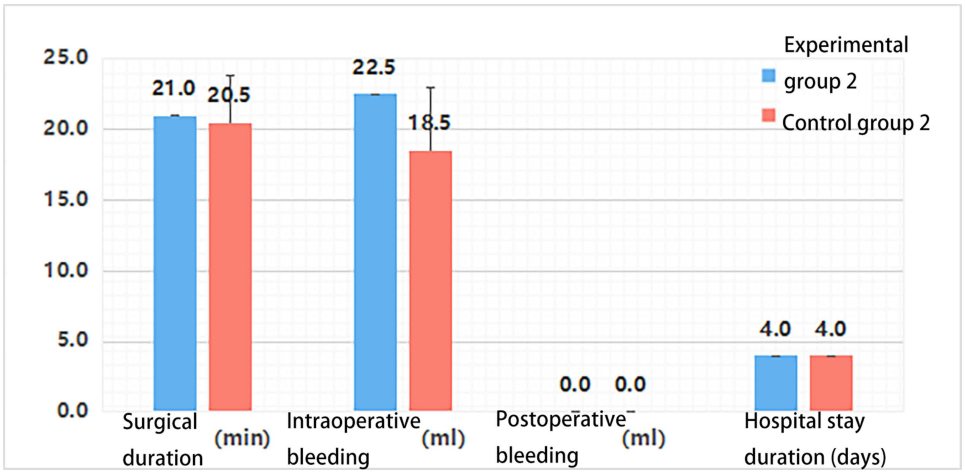

Figure 2 Surgical duration, intraoperative and postoperative bleeding and hospitalization days in adenoids combined with tonsillectomy surgery group (experimental group 2/control group 2).

Statistical analysis encompassing preoperative and postoperative coagulation functions, including APTT, prothrombin time (PT), thrombin time (TT), international normalized ratio (INR), and various coagulation factors (Factors II, V, V, III, IX, X, XII), was conducted. Notably, a comparison of pre- and post-surgery APTT values revealed a P value of less than 0.01 ($p = 0.001$, $p < 0.01$), PT ($p = 0.156$), TT ($p = 0.011$), INR ($p = 0.049$). Postoperatively, there was improvement compared to preoperatively, but no significant statistical differences were found, indicating a statistically significant difference. Furthermore, post-surgery values for Factor XII also exhibited a statistically significant change ($p = 0.004$, $p < 0.01$), extrinsic coagulation factors FII ($p = 0.047$), FV ($p = 0.165$), FX ($p = 0.138$), and intrinsic coagulation factors FVIII ($p = 0.192$), FIX ($p = 0.138$) all showed no statistically significant differences (Table 4, Figures 3 and 4).

Discussion

Adenoid hypertrophy, tonsil hypertrophy, and chronic tonsillitis rank as the primary causes contributing to obstructive sleep apnea (OSA) in children. In the absence of timely and effective treatment, these conditions have the potential to result in various severe complications, such as abnormal maxillofacial development, as well as growth and cognitive delays.[11] T&A are considered the most effective treatments for children diagnosed with moderate to severe OSA or recurrent tonsillitis.[3,13,14]

Table 3 Reassessment of Coagulation Function and Factors at Six Months Postoperatively

Patient Number	Gender	Age	Family history	APTT (24–37s)	PT (8.8–12.8s)	TT (10.3–16.6s)	INR (0.9–1.2)	Factor II (79–131%)	Factor V (62–139%)	Factor VIII (50–150%)	Factor IX (65–150%)	Factor X (77–131%)	Factor XII (50–150%)
1	Male	4	Yes	34.2	11.3	14.1	0.98	95.7	102.4	82.7	65.0	85.0	59.7
2	Male	5	No	33.5	11.5	13.1	1.00	108.6	107	120.7	97.4	112.8	68.9
3	Male	5	No	29.9	10.3	14.5	0.89	90.1	85.4	171.2	75.3	83.3	65.5
4	Male	3	No	33.4	11.9	14.2	0.95	97.3	103.6	115.7	89.8	105.3	66.8
5	Male	6	No	32.3	10.8	13.9	1.03	84.8	100.2	105.9	69.4	82.5	54.6

Note: Family history refers to the history of coagulation function abnormalities.

Table 4 Factors and Preoperative and Postoperative Coagulation Function Comparison

Coagulation Function	Preoperative	Postoperative	*P*
APTT (24–37s)	43.7±1.8	32.7±1.7	0.000*
PT (8.8–12.8s)	12.2±0.8	11.2±0.6	0.156
TT (10.3–16.6s)	16.3±0.8	14.0±0.5	0.011
INR (0.9–1.2)	1.1±0.1	1.0±0.1	0.049
Coagulation Factor			
Factor II (79–131%)	82.7±6.2	95.3±9.0	0.047
Factor V (62–139%)	90.6±9.4	99.7±8.4	0.165
Factor VIII (50–150%)	92.8±24.6	119.2±32.5	0.192
Factor IX (65–150%)	65.6±10.4	79.4±13.8	0.235
Factor X (77–131%)	78.0±9.0	93.8±14.2	0.138
Factor XII (50–150%)	40.2±5.4	63.1±5.9	0.004*

Note: *The difference was statistically significant.

Prolonged APTT is mainly associated with deficiencies in intrinsic coagulation factors such as FVIII, FIX, FXII, etc.,[15] while prolonged PT is related to deficiencies in extrinsic coagulation factors such as II, V, X, etc. In the context of hereditary coagulation factor deficiencies, Factors VIII and IX deficiencies are the most prevalent, giving rise to hemophilia A and B, along with von Willebrand disease (VWD). These disorders collectively account for 95% to

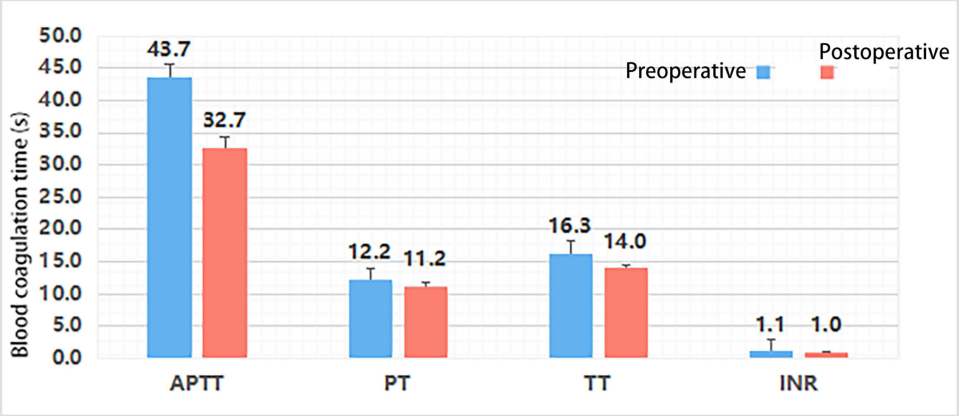

Figure 3 Preoperative and Postoperative Coagulation Function Comparison.

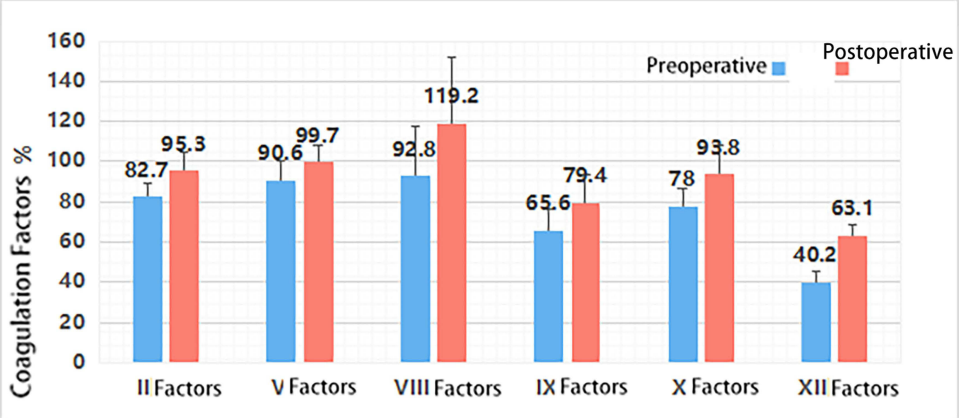

Figure 4 Preoperative and Postoperative Coagulation Factors Comparison.

97%[16] of cases of hereditary hemorrhagic diseases. The primary clinical presentation in hereditary hemorrhagic diseases is bleeding of varying degrees, with only a minority of patients experiencing thrombotic events.

For children with hereditary coagulation factor deficiencies undergoing T&A, hospitals typically implement established protocols for managing severe coagulation disorders, incorporating proactive preoperative preparation. However, addressing the safety of these surgeries in children with mild coagulation factor abnormalities, conducting necessary preoperative examinations, and assessing the potential impact of surgery on coagulation function remain critical concerns for otolaryngologist head and neck surgeons.

Importance of Assessing Coagulation Factor Abnormalities

The routine preoperative assessment of coagulation function has been a topic of international debate. German researcher Papaspyrou suggested that routine preoperative coagulation analysis does not significantly impact the assessment of postoperative bleeding risk.[17] Conversely, Wenzel,[18] another German researcher, advocated for the use of standardized questionnaires over routine coagulation tests for assessing coagulation function. Czech researcher Samková[19] proposed that laboratory coagulation screening should be reserved for patients with a positive personal or family history of bleeding. The American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) recommends hematological assessments solely for patients with histories indicative of bleeding disorders or unreliable medical records.[20] In contrast to these perspectives, in our study, we identified 5 children with coagulation abnormalities from a cohort of 368 hospitalized children over a four-month period. All these children exhibited elevated APTT, with two also presented prolonged TT. With the exception of patient number 5, who had an isolated Factor XII deficiency, the others had multiple coagulation factor deficiencies, notably patient number 4 with deficiencies in Factors II, IX, X, and XII. A critical case encountered in our department involved a child with slightly elevated APTT (≤40) preoperatively and no known bleeding history, who experienced uncontrolled bleeding during surgery. Emergency coagulation factor testing identified a deficiency in Factor VIII (FVIII), thereby aiding in the prevention of a catastrophic event through prompt interventions, including blood transfusion and Factor VIII administration.

Typically, hospitals do not further investigate or treat children with mild coagulation abnormalities. This incident, along with others, emphasizes that coagulation function abnormalities and factor deficiencies are not uncommon in the pediatric population. The lack of explicit bleeding history in many children, or parental oversight of minor bleeding episodes, poses risks of misdiagnosis or missed diagnosis, potentially leading to serious medical complications. It is therefore imperative to accurately determine specific coagulation factor deficiencies and identify abnormalities predisposing to bleeding tendencies, and it is also necessary to consider medical economics and the relevance of environmental protection and low-carbon.[21]

Consequently, we advocate for routine coagulation function testing in all children scheduled for surgical procedures. Should any coagulation function abnormalities be identified, it is imperative to conduct comprehensive coagulation factor testing, particularly to rule out hemophilia arising from FVIII and FIX factor deficiencies.

Clinical Significance of Factor XII Deficiency in Children

Coagulation Factor XII (FXII), also known as endogenous Hageman factor, plays a pivotal role in initiating the intrinsic coagulation pathway, contributing to the activation of the fibrinolytic pathway, complement system, and inflammatory responses.[22,23] A deficiency in FXII often leads to prolonged APTT and is frequently cited as a reason for repetitive laboratory assessments and surgery postponements. In our study, all 5 pediatric patients exhibited diminished FXII activity, emphasizing its prevalence among children with coagulation function disorders.

The concept of developmental coagulation, introduced by Andrew in the late 1980s, indicates that the coagulation system matures progressively with age, a theory widely accepted since then.[24,25] Li, in 2009, presented data on Chinese children, illustrating dynamic changes in APTT values across different childhood ages. Notably, APTT in children is significantly prolonged compared to adults, primarily attributed to reduced levels of FXII and FIX, along with the presence of lupus anticoagulant (LAC).[26]

This indicates that the coagulation system in children is still developing, contributing to lower FXII levels compared to adults and consequently elevated APTT. However, a critical question emerges: does the identification of FXII

deficiency warrant active intervention? Multiple studies have observed that patients with FXII deficiency typically exhibit prolonged APTT without significant clinical symptoms. Even in scenarios like surgeries or childbirth, such patients rarely experience substantial bleeding, although they may be prone to thrombosis.[27,28] In cardiac surgical procedures,[29] a markedly prolonged APTT with FXII deficiency is rather than a higher risk of surgical bleeding. Consistent with these observations, the five children in our study did not show a notable increase in intraoperative bleeding volume, aligning with the aforementioned findings.

Initially, the first child in the experimental group, undergoing adenoidectomy, was hospitalized for one week postoperatively due to concerns about bleeding. This child was discharged following satisfactory observations of white membrane shedding, and no fever or bleeding occurrences. The remaining children in the experimental group were discharged based on standard discharge times: three days following adenoidectomy (one day post-surgery) and four days after tonsillectomy (two days post-surgery). Hence, we concur with the views expressed by Wang[30] that children with reduced FXII activity identified in preoperative exams do not require special treatment; regular follow-up suffices.

Postoperative Six-Month Re-Assessment: Normalization of Coagulation Function and Factors

Several recent studies have established a correlation between APTT and Factor XII activity, particularly in the context of recurrent infections in children.[22,31] German researcher Frauenknecht[32] observed that recurrent infections could elevate antiphospholipid antibody (APL) levels, resulting in a mild increase in APTT.[28] Turkish researcher Malbora[33] emphasized the significant role of LAC in prolonging APTT after infections in children. Additionally, a recent study conducted by Zhou[22] indicates that the coagulation function and Factor XII in children are influenced by various factors, including infection, immunity, and ethnicity. Notably, the immune disease group exhibited significantly higher APTT and lower Factor XII activity than the control group and even the infection group. Microcirculatory and coagulation disturbances associated with thrombogenic events[31] commonly occur as pathological manifestations of systemic viral infections during COVID-19.

In our study, the five children underwent a six-month postoperative re-assessment, revealing the normalization of their coagulation function and factors. The APTT and Factor XII levels revealed statistically significant differences pre- and post-surgery, aligning with the findings of the aforementioned studies. This indicates that mild coagulation function and factor abnormalities in children often correlate with recurrent infections. Post T&A, a procedure that eliminates the source of infection and reduces the frequency of respiratory infections, both coagulation function and factor activity can return to normal levels. However, this study is limited by a small sample size of only five cases. In the future, we will expand the sample size to further confirm the conclusions of this study.

Conclusion

Abnormalities in coagulation factors are not uncommon in children, and it is very important to screen for children at risk and determine coagulation factors through preoperative coagulation function tests. In this study, children with elevated APTT accompanied by a deficiency in factor XII showed no significant bleeding tendency, and the deficiency of factor XII, which is an internal coagulation abnormality, is not a contraindication for adenoidectomy and/or tonsillectomy. Re-examination of coagulation function and coagulation factors six months after surgery showed significant improvement compared to preoperative levels, suggesting that the cause of this abnormality may be related to chronic inflammation of the adenoids and/or tonsils. Further research is needed to include more cases and to further study the microcirculatory thrombotic abnormalities related to factor XII.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Capital Institute of Pediatrics Ethical review No. SHERLLM2020025. A written informed consent was obtained from legal guardians of all participants.

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Disclosure

The authors report no conflicts of interest in this work.

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