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Is Antifibrinolytic Therapy Effective for Preventing Hemorrhage in Patients with Hemophilia Undergoing Dental Extractions? A Systematic Review and Meta-Analysis

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Abstract

Objectives: This systematic review aims to analyze the systemic administration of antifibrinolytics (tranexamic acid and aminocaproic acid) to prevent postoperative bleeding in patients with hemophilia.

Methods: This systematic review was conducted adhering to PRISMA guidelines. Only randomized controlled trials that assessed human subjects of any age or gender with any severity of hemophilia undergoing dental extractions, and systemically administered antifibrinolytic therapy compared to placebo were included. Post-operative bleeding episodes and adverse events were presented. PubMed, Cochrane, Embase, CINAHL, Web of Science, and Scopus were searched through April 15, 2022. The risk ratio (RR) and odds ratio (OR) applying 95% confidence intervals (CI) were computed using RevMan 5.4.1 (Cochrane).

Results: Two randomized, placebo-controlled trials pooling in a total of 59 patients were pooled in this analysis. Among patients administered antifibrinolytic therapy, 84% reduced risk of post-operative bleeding was reported (RR = 0.16, 95% CI = 0.05–0.47, P = 0.0009). The chances of post-operative bleeding were reduced by 95% among the antifibrotics group (OR = 0.05, 95% CI = 0.01–0.22, P < 0.0001).

Conclusion: This review finds favorable outcomes for the routine use of antifibrinolytic therapy for dental extractions in hemophiliacs. Further trials are required to rationalize existing evidence.

Keywords

antifibrinolytic, aminocaproic acid, tranexamic acid, oral hemorrhage, hemophilia, postoperative bleeding, tooth extraction, randomized controlled trial

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Introduction

Hemophilia A (factor VIII deficiency) and B (factor IX deficiency) are inherited bleeding disorders.[1] Minor oral surgery or procedures such as dental extractions are widely performed and may lead to life-threatening oral bleeding in people with local and systemic disorders such as hemophilia.[2] Affected individuals tend to face prolonged bleeding due to clot instability.[3] The severity of single bleeding events post-dental extractions depends on disease-relative factors such as the severity of hemophilia, in addition to other factors such as the type of tooth being removed and the wound surface.[4] As highlighted by the World Federation of Hemophilia (WFH) guidelines for the management of hemophilia (third edition), it is imperative to search for methods that prevent bleeding complications among this cohort of patients because of the lack of or abysmal perioperative measures in practice today.[5] This paper intends to summarize existing strategies being used to counter such bleeding events, and also serve as a call to action for investigators in this area.[6]

Among individuals that have comorbidities, the use of clotting factor replacements confers a risk of thromboembolic

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events when utilized before or during dental extractions. In current practice, antifibrinolytic treatment administered intravenously or in some cases topically is being used to achieve peri- and postoperative hemostasis. It is common for individuals with inherited bleeding disorders to bleed based on the underlying coagulation factor deficiency. Hemophilia is the most prevalent inherited bleeding disorder (1 in 5000 males), that burdens health and care. Hemophilia is an X-linked disorder caused by a deficiency of factor VIII or IX. Dental extractions are among the most common invasive minor oral procedures. People with such inherited bleeding disorders are at increased risk of hemorrhaging during or after the procedure. If no antifibrinolytics are administered, reports suggest that post-operative bleeding has been reported in over 70% of patients with hemophilia post oral procedure.[7]

This systematic review and meta-analysis aim to analyze the systemic administration of antifibrinolytics (aminocaproic acid and tranexamic acid), in reducing post-operative bleeding complications, in patients with hemophilia, employing randomized placebo-controlled trials.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.

Study Selection and PICO Framework

Only randomized controlled trials in individuals with hemophilia that were undergoing dental extractions were included. There were no age restrictions for the patients undergoing the dental extraction. To ensure that we did not restrict our search, coagulation disorders included in this study were defined as an activity for factor VIII/IX less than 40%. Dental extractions were defined as the removal of any teeth, which were referred to as minor oral surgeries in the enlisted trials. The following databases were searched: PubMed (MEDLINE), Cochrane, Embase, CINAHL, Web of Science, and Scopus. An additional search was conducted at ClinicalTrials.gov. No language restrictions were applied and the search was conducted until April 15, 2022. The PRISMA flowchart is depicted in Figure 1.

A combination of the following keywords was used: Antifibrinolytic, Aminocaproic Acid, tranexamic acid, oral hemorrhage, Hemophilia A, Hemophilia B, postoperative bleeding, randomized controlled trials, and tooth extraction. The PICO framework is enlisted below.

Participants: Human adults or pediatric populations of any gender or age with any severity of hemophilia undergoing dental extractions;

Interventions: Antifibrinolytic therapy (Aminocaproic acid and/or Tranexamic acid) to prevent peri-operative dental extraction bleeding at any dose, delivery mode (intravenous, oral, topical), frequency, and duration;

Comparators: Placebo, standard care, or no intervention;

Outcomes: Post-operative bleeding episodes (primary outcome), and reported adverse events (if any) (secondary outcome).

Data Extraction and Statistical Analysis

Two mid-career researchers (ZS and AS) independently screened the titles and abstracts of the studies that were obtained using the search strategy. Of the studies that were identified using the search strategy, abstracts were shortlisted for full-text screening. The studies were assessed against the PICO framework. Any disagreement was resolved through active discussion. The studies were stored in the bibliographic management software (Endnote X9, Clarivate Analytics). All authors extracted data from the included trials onto a shared spreadsheet under the following subheadings: age, gender, dosage and route of administration, indication for antifibrinolytic administration, number of people with post-operative bleedings, and side effects leading to discontinuation.

Dichotomous data for post-operative bleeding outcomes were analyzed through a forest plot. The forest plots were generated based on risk ratio (RR) and odds ratio (OR), which were both reported separately. The data presented as RR and OR were accompanied by the I^2 index, which is a measure of heterogeneity among the included studies. the P-value was considered to reach statistical significance if the value was less than 0.05. A funnel plot was not generated as more than 10 randomized controlled trials are required to analyze as recommended by the Cochrane Handbook guidelines. The statistical analysis was conducted in RevMan 5.4.1 (Cochrane).

Risk of Bias

The risk of bias in the included studies was assessed using Cochrane's RoB 2 tool. The assessed categories included sequence generation (selection bias), allocation concealment (selection bias), outcome assessment blinding (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and any other source of bias.[8] The grading was completed by two authors (ZS and AS) independently. Any differences were resolved by active discussion. The final grading was reported as high, unclear, or low risk of bias, in the meta-analytical findings plot (Figure 2).

Funding

No funding was obtained for this study.

Results

The characteristics of patients with hemophilia are enlisted in Table 1. A detailed insight of studies that met the exclusion is listed in Table 2. Walsh et al, 1971[9] and Forbes et al, 1972[10] are two randomized, double-blind, placebo-controlled trials pooling in a total of 59 patients undergoing dental extractions. Walsh et al, 1971 comprised 31 patients with hemophilia with

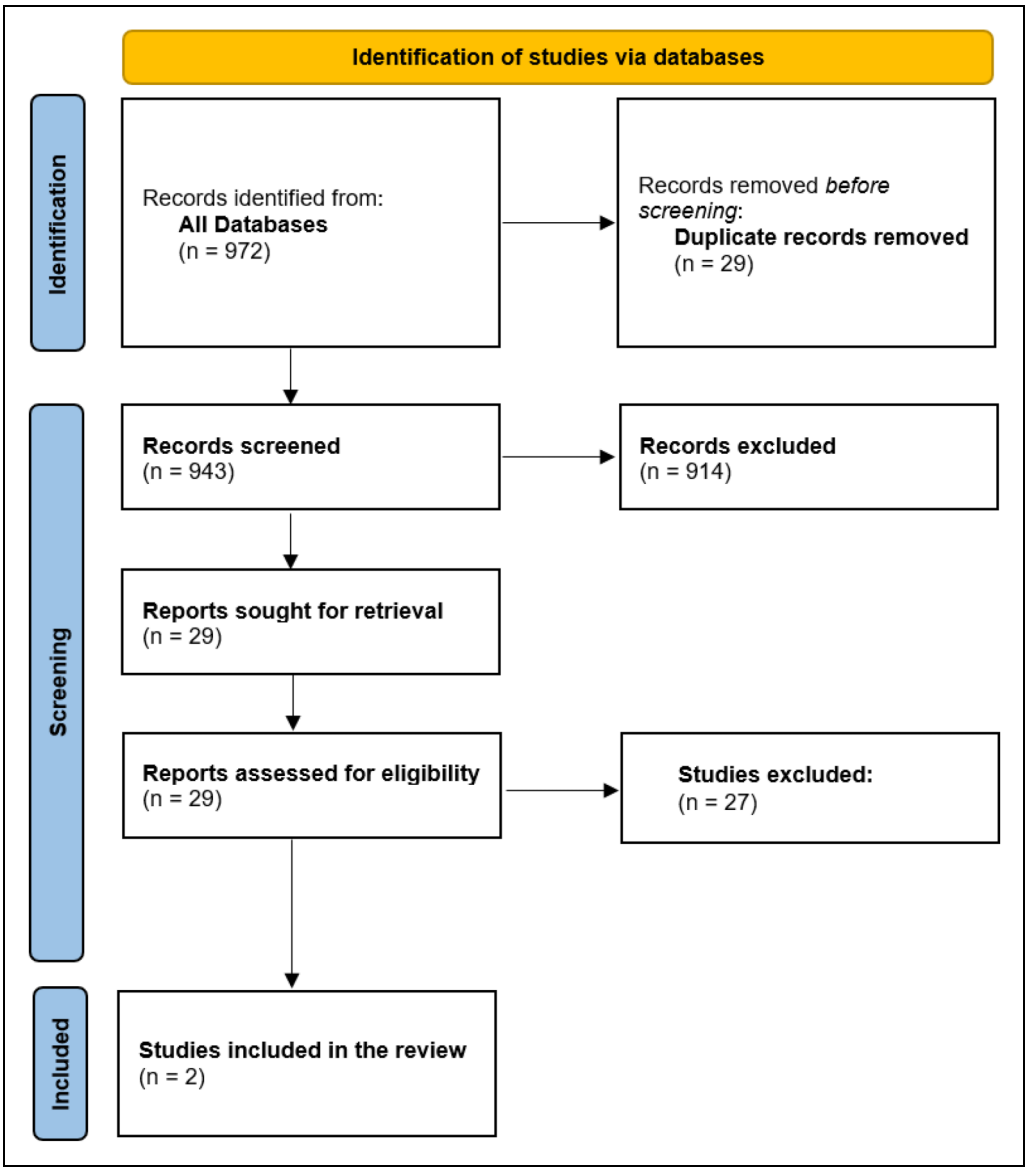

Figure 1. PRISMA flowchart.

factor VIII or factor IX with levels less than 15% being administered aminocaproic acid (6 grams daily for an average of 8.5 days among the different arms). In the antifibrinolytic group, 15 participants had an average of 7.6 number of teeth removed; in the placebo group, 16 participants had an average of 7.9 dental extractions. Forbes et al, 1972 comprised 28 patients with mild, moderate, or severe hemophilia A and B being administered tranexamic acid (1 gram three times a day for five days). In the antifibrinolytic group, 14 participants underwent 16 dental extractions; the mean number of roots extracted was 6.9; in the placebo group, 14 participants underwent 16 dental extractions, with a mean number of 5.5 roots extracted. The mean age in the two trials was comparable (24.8 and 28.6 years). The indications of antifibrinolytic therapy for Walsh et al, 1971 were plasma factor VIII/IX levels <1% on average in 66.7% of patients among IG and CG. Whereas, the indications for Forbes et al, 1972 were classic hemophilia (IG = 78.6%, CG = 64.3%) and Christmas disease (IG = 21.4%, CG = 35.7%). Overall, these two trials demonstrated that tranexamic acid and aminocaproic acid, which were systemically (IV) administered, were beneficial in reducing the post-operative bleeding; Walsh and colleagues reported 6.7% versus 56.3% rates of post-operative bleeding in IG and CG, whereas Forbes and colleagues reported 14.3% and 78.6% rates of post-operative bleeding in IG and CG groups, respectively. Concerning the safety of the drug intervention, one patient discontinued intervention (Walsh et al, 1971), with none discontinued owing to safety reasons reported by Forbes et al, 1972 (Table 1).

The studies pooled in a total of 59 patients reporting data on post-procedural bleeding outcomes. The findings were in favor of the antifibrinolytic therapy group, among the entire cohort of included patients. The results were yielded as follows: RR =

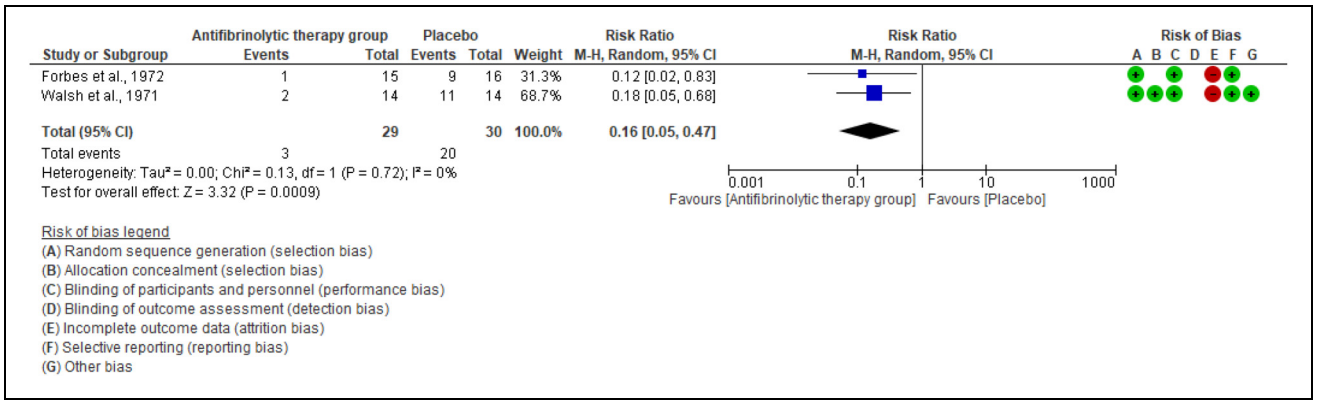

Figure 2. Post-operative bleeding outcomes among the included patients (RR). Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0\%$. Test for overall effect: Z = 3.32 (P = 0.0009)

Table 1. Characteristics of Included Studies (Patients with Hemophilia).

Author, Year	Intervention Group	Placebo Group
	Age in Years (Mean)	
Walsh et al, 1971[9]	24.8	28.6
Forbes et al, 1972[10]	Aged 13 to 65 years	
	Gender (Male), n (%)	
Walsh et al, 1971[9]	14/15 (93.3%)	16/16 (100%)
Forbes et al, 1972[10]	NR	NR
	Dosage and Route of Administration	
Walsh et al, 1971[9]	All patients received EACA (6 g four times daily for 10 days at Oxford or 7 days at Cardiff) excluding the placebo group, in conjunction with a single preoperative IV dose of therapeutic materials expected to raise the plasma factor-VIII or factor-IX level to 50%	
Forbes et al, 1972[10]	Each patient received the factor VIII or IX equivalent of 1000 ml of human plasma intravenously one hour before extraction and also tetracycline (250 mg four times a day). Intervened patients received tranexamic acid, 1 gram three times a day for five days	
	Indication for Antifibrinolytic Administration	
Walsh et al, 1971[9]	Plasma factor VIII or factor IX<1% average = 10 (66.7%)	Plasma factor VIII or factor IX<1% average = 10 (66.7%)
Forbes et al, 1972[10]	Classical haemophilia = 11 (78.6%); Christmas disease = 3 (21.4%)	Classical haemophilia = 9 (64.3%); Christmas disease = 5 (35.7%)
	Number of People with Postoperative Bleedings	
Walsh et al, 1971[9]	1/15 (6.7%)	9/16 (56.3%)
Forbes et al, 1972[10]	2/14 (14.3%)	11/14 (78.6%)
	Side Effects Leading to Discontinuation	
Walsh et al, 1971[9]	1/15 (6.7%)	0/16 (0%)
Forbes et al, 1972[10]	0/14 (0%)	0/14 (0%)

0.16, 95% CI = 0.05, 0.47, P = 0.0009. This meant that there was an 84% less risk of post-operative bleeding among patients with hemophilia compared to placebo post antifibrinolytic systemic therapy (Figure 2).

On computing the OR, it was determined that individuals in the antifibrinolytic group had a 95% less chance of post-operative bleeding. The results were yielded as follows: OR = 0.05, 95% CI = 0.01, 0.22, P < 0.0001. Overall, the findings were favorable for intravenous antifibrinolytics among the cohort of patients (Figure 3).

Discussion

In this systematic review, we included two placebo-controlled randomized controlled trials of participants with hemophilia undergoing dental extractions. Forbes and colleagues

Table 2. Overview of Studies that Met the Exclusion Criteria.

Title	Author, Year	Study Type	Participants	Interventions	Outcomes
Primary wound closure in haemophiliacs undergoing dental extractions	Stajcić, 1989	Case Control	62 males aged 11 to 55 with Hemophilia A	Single infusion of factor VIII supplemented with antifibrinolytics	Primary closure of the extraction wound protected the blood clot, making the postoperative period comfortable for patients and decreased the risk of postoperative bleeding
Activated prothrombin complex concentrate in combination with tranexamic acid: a single center experience for the treatment of mucosal bleeding and dental extraction in haemophilia patients with inhibitors	Windyga, 2016	Case Series	9 patients aged 20 to 59 years with Hemophilia A	TXA in combination with aPCC (FEIBA) for the treatment of mucous membrane haemorrhages or perioperative prevention of bleeding episodes in haemophilia patients with inhibitors who underwent dental extractions	In all 16 procedures among 9 patients, use of aPCC and TXA enabled effective prevention or control of bleeding. All treatment courses were successful without any adverse events, including thrombosis
Management of dental extraction in patients with Haemophilia A and B: a report of 58 extractions	Peisker, 2014	Case Series	15 patients exhibiting Hemophilia A and B undergoing a total of 58 dental extractions	Replacement therapy with recombinant and plasma-derived factor VIII and IX was applied systematically in combination with antifibrinolytic treatment and local haemostatic measures	Excellent hemostasis was achieved after dental extractions in patients with Hemophilia A and B; 2 patients had postoperative bleeding, 1 had secondary bleeding and needed additional factor concentrates injection; 1 patient had epistaxis that was managed with nasal tamponade
Dental extraction in a hemophilia patient without factor replacement therapy: a case report	Bajkin, 2012	Case Report	34 year old male with Hemophilia A without factor replacement therapy undergoing dental extraction	Antifibrinolytic agent tranexamic acid orally (500 mg three times a day for 7 days) and application of a fibrin sealant	Successful hemostasis was achieved with the fibrin sealant and suturing
Management of third molar removal with a single dose of recombinant Factor IX (BeneFIX) and local measures in severe haemophilia B	Hewson, 2010	Case Report	32 year old male with severe Hemophilia B	Single preoperative dose of Benefix (119 IU/kg) given within an hour before surgery, factor levels raised to 100% and local measures for postoperative haemostasis	Excellent haemostasis was achieved immediately postoperatively; no bleeding outcomes
Management options for dental extraction in hemophiliacs: a study of 55 extractions (2000–2002)	Frachon, 2005	Cohort	16 patients with hemophilia A or B undergoing 55 dental extractions	Injection of factor concentrates or (Desmopressin) DDAVP and local hemostasis using biological glue and gelatin packing	6 instances of postsurgical bleeding, with ovearll reliable outcomes
Proposal of a standard approach to dental extraction in haemophilia	Zanon, 2000	Case Control	77 hemophilia patients	20 mg kg-1 of tranexamic acid and single infusion of factor VIII or IX to	2 bleeding complications in the hemophilia patient group (one late

(continued)

Table 2. (continued)

Title	Author, Year	Study Type	Participants	Interventions	Outcomes
patients. A case-control study with good results			undergoing dental extractions	achieve a peak level about 30% of factor VIII or IX in vivo prior to dental extraction	bleeding and one haematoma in the site of the anaesthetic injection)
Safety and efficacy of purified factor IX concentrate and antifibrinolytic agents for dental extractions in hemophilia B	Djulbegovic, 1996	Clinical Trial	8 patients with hemophilia B undergoing dental extractions	One hour prior to tooth extraction, patients received approximately 60 U/kg of MAb factor IX	All patients achieved excellent hemostasis without clinical evidence of thrombosis
Intravenous administration of deamino-D-arginine-vasopressin (DDAVP) to patients with hemophilia A and von Willebrand's disease	Janczarski, 1990	Case Series	18 patients with mild haemophilia A undergoing tooth extractions	Intravenous infusion of DDAVP in a single dose of 0.3 microgram/kg; subsequent infusion of 4 g of epsilon-aminocaproic acid	Single infusion of DDAVP and epsilon-aminocaproic acid was effective in 4 of the 7 mildly affected haemophiliacs. In the other 3, the symptoms of bleeding subsided after repeated infusion of DDAVP
Prospective study examining the use of thrombin-gelatin matrix (Floseal) to prevent post dental extraction haemorrhage in patients with inherited bleeding disorders	Ali, 2022	Cohort	32 patients with Hemophilia A and B undergoing dental extractions	Intraoperative Floseal administration	4 patients reported postoperative bleeding requiring factor supplementation or desmopressin; the bleeding rate was 11.8%
Dental extractions in patients with mild hemophilia A and hemophilia B and von Willebrand disease without clotting factor supplementation	Lewandowski, 2018	Cohort	Mild hemophilia A in 12 patients; mild hemophilia B in 5 patients	Local dressing (TachoComb) with antifibrinolytic therapy	Secondary bleeding occurred in 3 individuals (15.7%); 2 patients with hemophilia A and 1 patient with hemophilia B
Dental extraction in congenital hemorrhagic patients	Dal Bo Zanon, 1986	Cohort	125 dental extractions were performed in patients with hemophilia A, B	Antifibrinolytics (tranexamic acid, 60 mg/kg/day) for 8–10 days before extraction; after tooth extraction, a fibrin sponge was positioned using anti-traumatic cross suture	90% of cases had no bleeding, in the others modest easily controllable hemorrhagic episodes
The combined local/systemic use of antifibrinolytics in hemophiliacs undergoing dental extractions	Stajcić, 1985	Cohort	43 hemophiliacs undergoing a total of 185 permanent teeth extractions	Local, systematic and combined use of antifibrinolytics	Antifibrinolytics, used both locally and systemically, show distinct advantages in outcomes
Local hemostasis after tooth extraction in patients with abnormal hemostatic function. Use of human fibrinogen concentrate	Baudo, 1985	Cohort	Tooth extraction was carried out in 405 patients with multuple hematologic disorders including Hemophilia A and B	Human fibrinogen concentrate used as local hemostatic agent; oral anticoagulants were continued	Minor postextraction bleeding occurred in the severe hemophilia A patient group and occasionally in the oral anticoagulant group
Evaluation of the effectiveness of DDAVP in surgery and in bleeding episodes in haemophilia and von Willebrand's disease. A study on 43 patients	Mariana, 1984	Case Series	43 patients with factor VIII deficiencies--mild and moderate haemophilia A	DDAVP given in association with antifibrinolytics	Bleeding occurred late in the postoperative period on only one occasion

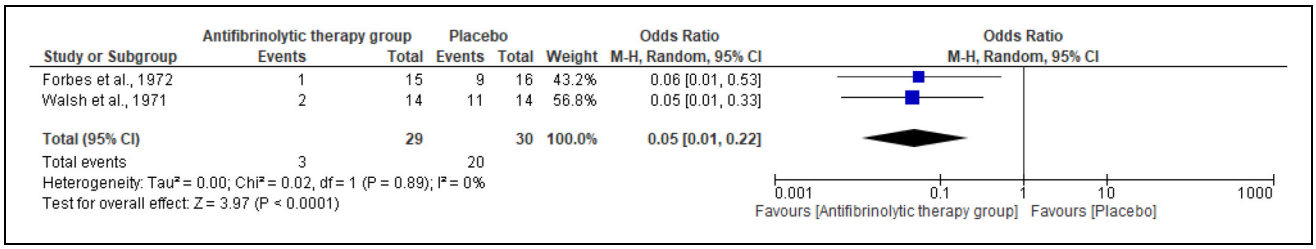

Figure 3. Post-operative bleeding outcomes among the included patients (OR). Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, $df = 1$ ($P = 0.89$); $I^2 = 0\%$. Test for overall effect: $Z = 3.97$ ($P < 0.0001$).

Table 3. Screening tests for hemophilia and vWD.[5]

Diagnosis	Platelet Count	PT	APTT
Hemophilia A/B	Normal	Normal	Prolonged
vWD	Normal or decreased	Normal	Normal or prolonged

administered tranexamic acid whereas Walsh and colleagues administered aminocaproic acid; both of these were given intravenously. The two trials showed benefits in post-operative bleedings, with negligible adverse events. It must be noted that there were a limited number of trials and small sample size, therefore the findings, while useful, did not ascertain the efficacy of antifibrinolytic therapy in dental extractions among people with hemophilia. None of the participants in Forbes et al's trial experienced adverse events. However, one participant in Walsh et al's trial experienced adverse events prompting withdrawal on the third post-operative day, which included headache, tingling in the fingers, postural dizziness and nausea. No thrombotic adverse events were reported in either trial; this included no minor postoperative bleeding episodes, immediate/delayed postoperative bleeding, and major bleeding.

To provide a more comprehensive review of current evidence, we reviewed trials registered on ClinicalTrials.gov. In one trial, global hemostatic methods (endogenous thrombin potential (ETP), overall hemostatic potential (OHP), fibrin clot structure), and microparticles are being utilized to predict the severity of bleeding and estimate response to treatment in patients with hemophilia. While the trial does not directly assess post-dental extraction status, the enlisted approach is intended to reduce the amount of necessary factor concentration in patients while decreasing the overall costs of treatment for patients.[11] While such trials intend to improve treatment outcomes among patients, it is important to account for mild bleeding disorders that are often considered "subclinical," and the patients may only present with uncontrolled bleeding in the setting of oral procedures such as dental extractions.[4] At present, coagulation screening tests are recommended tools to evaluate the risk of bleeding before oral surgeries, including dental extractions. The major indicators are prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count.[4] However, alarmingly, WFH states that whether these coagulation tests can correctly depict the status of mild disorders is still not ascertained.[5]

Furthermore, two case reports were published in BMC oral health presenting uncontrollable bleeding post tooth extraction among patients with asymptomatic, mild hemophilia.[12] The reports presented two patients reporting uncontrollable hemorrhage among individuals that reported no prior illness, allergy, anticoagulant medication use, family or systemic illness, the thrombotic profile and other coagulation tests were normal.[12] The patients were diagnosed with mild hemophilia A using coagulation factor assays.[12] The hemorrhage was stopped by receiving coagulation factor supplement therapy.[12] The reports highlight that mild hemophilia may remain undiagnosed until late adulthood; uncontrollable bleeding among individuals with mild hemophilia may come to light after tooth extraction.[12] We additionally located one registered trial protocol from Ecuador where the investigators intended to highlight the clinical and demographic information of patients with hemophilia among women with possible von Willebrand's disease (vWD), who are referred by dentists and physicians.[13] The trial is imperative as not many published studies on coagulopathies originate from Ecuador and the researchers wish to offer adequate therapeutic and diagnostic interventions to individuals with hemophilia.[13]

Frachon and colleagues (2005) in a cohort of 16 patients with hemophilia A/B inject factor concentrates or desmopressin in addition to local hemostasis measures using biological glue and gelatin packing.[14] The use of dihydro-D-arginine vasopressin (DDAVP) is an alternative to factor VIII use in mild-moderate forms of hemophilia A. DDAVP acts by releasing factor VIII reserves, but the mechanism of action varies patient by patient, and prior testing is necessary 1–2 weeks before dental extraction.[14] Franchon et al found that, in four patients with mild hemophilia A, DDAVP treatment increased factor VIII levels without antihemophilic factor concentrate injections.[14] Ehl and colleagues find that in clinical response to DDAVP in four patients with hemophilia B that had baseline factor IX levels of 1.4–5% for dental surgery, there was a reduction in the use of plasma products post treatment.[15] Another local hemostatic measure used in dental centers to achieve hemostasis is the fibrin glue that lowers the need for clotting factor replacement therapy.[16] Fibrin glue may also be utilized with oral antifibrinolytic agents to achieve hemostasis and reduce the need for clotting factor replacement therapy.[16] All fibrin glue materials contain animal or human components

that have conferred hesitancy among physicians and patients who have never received blood products derived from humans.[17] The fibrin glue tends to mimic the final pathway of the coagulation cascade at the time where fibrinogen is converted to fibrin, in the presence of factor XIII, thrombin, ionized calcium and fibronectin.[18] Fibronectin also promotes cellular migration and activating fibroblasts in the area where the fibrin glue is applied.[19] Additionally, recombinant activated factor VII (rFVIIa) has also been used to control bleeding. In one case series, rFVIIa was administered to five male pediatric patients with severe hemophilia A who underwent 7 dental extractions.[20] The age of the patients was between 8 to 13 years. The concentrate was administered at doses of 90–100 mg/kg and the duration/intervals between the doses were dependent on the bleeding severity.[20] In the case series, rFVIIa was highly effective and there were no side-effects of the product.[20] More studies are required to test the use of rFVIIa in hemophiliacs undergoing dental extractions.

Current Recommendations and Guidelines

It is important to note that the screening tests may not detect abnormalities with mild bleeding disorders, in addition to some variants of vWD, or other cases of genetically confirmed hemophilia A/B (Table 3).[5] As recommended by WFH, mixing or correction studies are required in addition to abnormal screening studies.[5] The current recommendations suggest that any individual suspected of hemophilia is required phenotypic screening for factors VIII and IX, Von Willebrand Factor (VWF) antigen, and activity before genetic testing referrals.[5] For obligate carriers of hemophilia, or females perceived at-risk, the inclusion of a detailed family pedigree is required to add support to genetic testing.[5] Moreover, the levels of factor VIII and VWF may be temporarily elevated due to stress, inflammation, or strenuous exercise, which may affect diagnosis.[21,22] The levels also increase during pregnancy.[21]

Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis classify the severity of hemophilia into three categories as followed: i) severe (factor level < 1% of normal; <0.01 U/ml), ii) moderate (factor level 1%–5% of normal; 0.01–0.05 U/ml), and iii) mild (factor level 5%–40% of normal; >0.05–0.4 U/ml).[23,24] In our meta-analysis, we considered all cases (mild, moderate, and severe). The most imperative objective of current recommendations of care is to prevent bleeding among those with any severity of the disease. given the nature of the high risk of secondary bleeding of hemophilia and vWD patients following dental extractions, current international guidelines advise the use of clotting factor replacement therapy for any level of invasive surgery.[23] Moreover, WFH recommends using factor concentrates or fresh frozen plasma for replacement therapy in hemophilia patients. The procedure ought to be planned to reduce the risk of hematoma or bleeding formation. The hematologist ought to be consulted before the initiation of treatment regarding the factor levels, type of surgery, and the requirement of systemic therapy for hemostasis. As a requirement, desmopressin and replacement are recommended.[25] The placement of proper sutures may prevent adverse outcomes. Of note, antifibrinolytic therapy including agents such as tranexamic acid (1 gram, three times a day) and aminocaproic acid (50 mg/kg, four times a day), when used at the start of the dental extraction for a total of 7 days are recommended.[26,27] These recommendations were made by the Australian Haemophilia Centre Directors' Organisation.[26] Early consultation with a dentist and hematologist along with oral hygiene are recommended. Recently, the local application of antifibrinolytics has gained traction, which ought to be further explored in prospective systematic reviews.

Limitations

There are certain limitations of this systematic review. First, there is a limited sample size meaning that the findings may not be generalizable. Second, the trials had different severity of diseases among the patient population. Third, the trials did not report the pre-operative factor levels making a sub-analysis based on factor levels not feasible. Lastly, the trials individually ascertained post-operative bleeding, where Forbes and colleagues determined bleeding within 5 days,[10] whereas Walsh and colleagues did not determine a cutoff.[9] However, the findings of this meta-analysis serve as a call to action for thrombosis/hemostasis societies and investigators to further quantify the best level of evidence.

Conclusion

This systematic review finds favorable outcomes for the routine practice of antifibrinolytic therapy for dental extractions in people with hemophilia. As the WFH guidelines suggest, the treatment is effective in dental extractions without adverse outcomes. Moreover, our recommendation is that antifibrinolytic agents including tranexamic acid and aminocaproic acid can be used in clinical practice, with minimized scope for thrombotic adverse events. However, we did not find notable ongoing clinical trials assessing the routine use of these agents in either the severe, moderate, or mild patient group. The routine use of these agents in clinical practice requires more robust high-quality research to rationalize existing evidence and pathophysiologic considerations.

Declaration of Conflicting Interests

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