

**AN AUDIT OF DENTAL PROCEDURES IN PATIENTS WITH INHERITED
BLEEDING DISORDERS AT THE CHARLOTTE MAXEKE JOHANNESBURG
ACADEMIC HOSPITAL HAEMATOLOGY UNIT**

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Declaration

I Sibongile Priscilla Mahlangu declare that this research report is my own, unaided work. It is being submitted for the Degree of Masters of Science in Dentistry (Oral Medicine) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature of candidate

_____ day of _____ 2017 in Parktown, Johannesburg.

Abstract

Background: Patients with inherited bleeding disorders have an elevated risk of bleeding, in which even relatively minimal invasive procedures can cause continuous bleeding.

Aim and study design: The aim of this study was to review dental procedures performed over a 16 year period in patients with inherited bleeding disorders (IBD) at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), and to compare the treatment approach to published international guidelines.

Method: The study population comprised of patients' files obtained from the Haemophilia Comprehensive Care Centre (HCCC) and Wits Oral Health Centre (WOHC) database.

Results: Dental extraction was the most commonly performed procedure. Post-extraction bleeding was observed in 3 subjects, and the protocol observed for the management of these correlated with those published.

Conclusion: A standard protocol for the dental management of IBD patients needs to be put in place in WOHC to ensure uniformity of clinicians, and compliance with the published protocols.

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List of abbreviations

ATP: Adenosine triphosphate

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CO₂: Carbon dioxide

DDAVP: Dihydro-d-arginine vasopressin or Desamino-8-d-arginine vasopressin

EACA: Epsilon aminocaproic acid

Er:YAG: Erbium-doped yttrium aluminium garnet

FVIII: Factor VIII

FIX: Factor IX

FV: Factor V

FXI: Factor XI

FRT: Factor replacement therapy

GIT: Gastrointestinal tract

HA: Haemophilia A

HB: Haemophilia B

HC: Haemophilia C

HCV: Hepatitis C virus

HCCC: Haemophilia Comprehensive Care Centre

HIV: Human immunodeficiency virus

HMW: High molecular weight

HTC: Haemophilia Treatment Centre

IBD: Inherited bleeding disorders

INR: International normalized ratio

LA: Local anaesthesia

mRNA: Messenger RNA

NaOCl: Sodium hypochlorite

Nd:YAG: Neodymium-doped yttrium aluminium garnet

NSAIDs: Non-steroidal anti-inflammatory drugs

ppm: parts per million

rFRT: Recombinant factor replacement therapy

TA: Tranexamic acid

TAMW: Tranexamic acid mouthwash

t-PA: Tissue plasminogen activator

VWD: Von Willebrand disease

VWF: Von Willebrand factor

WOHC: Wits Oral Health Centre

CHAPTER 1 Introduction and Literature Review

1.1 Introduction

The most common and preventable dental diseases are dental caries and periodontitis, and they are the major reasons for tooth decay, dental pain and extractions.¹ Dental extractions and dentoalveolar surgery, such as third molar extraction, dental implant placement, root debridement, biopsy procedures and periodontal surgery are among the most commonly performed oral surgical interventions, and result in bleeding.²

Excessive bleeding following these invasive dental procedures can be idiopathic, or they can be caused by acquired or inherited conditions that are associated with vascular defects, platelet defects or coagulation disorders.³ Acquired conditions are as a result of liver diseases and platelet disorders or anticoagulant therapy. Congenital or inherited bleeding disorders (IBD) are characterized by impairment of the normal haemostasis; thus resulting in a tendency to bleed.² Prolonged post-operative bleeding following an invasive dental procedure may be one of the first signs of a bleeding disorder in an undiagnosed patient.³ In this study the focus was on inherited bleeding disorders.

Patients with IBDs have a higher incidence of bleeding intraoperatively and following dental interventions, even if the procedures are fairly minimal in nature. The severity and number of haemorrhages are determined by disease-related factors, as well as both local and systemic patient-related factors, and intervention-related factors. The disease-related factors include the severity of the condition, for example severe haemophiliacs bleed more than moderate or mild haemophiliacs. The patient-related factors include blood vessel disease or gingival inflammation, whilst the intervention-related factors include the type and the number of teeth extracted, or the surface area of the wound following extraction.²

Coagulation and platelet-mediated primary haemostasis are critical in the prevention of bleeding.⁴ Wound healing follows once the haemostatic plug is formed. Excessive bleeding in patients with IBD, resulting from failure of a haemostatic plug formation, can delay wound healing.^{5,6} Invasive dental procedures can be complicated by severe, often life threatening bleeding if the patients are not appropriately managed.⁷

The introduction of clotting factor concentrates, desmopressin (DDAVP) and antifibrinolytic agents has considerably reduced the frequency of bleeding complications following dental treatments of patients with IBD.⁷ Prior to the introduction of these agents most dental

treatments were performed under general anaesthesia, and the only procedures which could be performed were extractions followed by denture construction.⁸ The use of clotting factor concentrates comes with the challenge of developing inhibitors or antibodies towards the replacement factor.²

A major anxiety of IBD patients regarding dental treatment relates to the risk of bleeding intra-operatively or post-operatively. Another concern they have is the understanding that dentists have of their bleeding disorders and its management.⁸ The ability of general dental practitioners to provide special care dentistry to these patients and other groups has been a concern.⁹ Consequently, based on these concerns, and sometimes also the general dislike of dental treatment, these patients may avoid regular visits to the dentist until a problem is severe and calls for extensive treatment.^{8,10} This may explain the high incidence of dental caries and periodontal disease in these patients.¹⁰

The nature of some dental treatments encompasses bleeding inductive procedures, thus maintaining good oral health must be a priority among patients with inherited bleeding disorders.¹¹ Inappropriate dental management of these patients can lead to potential dangers including airway obstruction, which makes it absolutely important for dental practitioners to be knowledgeable about these conditions and the dental management guidelines for such patients.⁸ Successful dental management of patients with IBD must be a joint approach between the dentist and a haematologist.^{6,8}

The treatment guidelines for haemophilia in South Africa specify the management guidelines for extractions and bleeding gingiva.¹² It is however deficient, as it does not include all dental procedures that may cause bleeding. This would be the first review of dental procedures performed in patients with IBD in the country.

1.2 Objectives

The objectives of the study were to collate records of all IBD patients who had undergone dental procedures at Wits Oral Health Centre (WOHC), and to also report on dental procedures performed on these patients in terms of procedure indication, perioperative haemostatic management, intraoperative and postoperative bleeding assessment and documentation of any other complication. Another objective was to compare the protocols followed at the WOHC to those published, and to make recommendations, where necessary, on how these patients undergoing dental procedures should be managed at the WOHC.

1.2 Literature Review

1.2.1 The Overview of IBD in South Africa

South Africa had established 17 haemophilia treatment centres (HTCs) in the public health sector as reported in 2007, and this number increased to 18 HTCs in 2015. The number of adult outpatient visits at 11 of these HTCs between the period of 2004 to 2007 ranged between 2081 - 2249, and the number of paediatric outpatient visits ranged between 2198 - 2293. Patients with haemophilia A comprised the largest group (59%) followed by those with Von Willebrand disease (21%), haemophilia B (12%) and those with other bleeding disorders (7.8%). Patients with severe forms of haemophilia made up the majority of haemophiliacs followed by the mild then moderate phenotypes. The patients who had developed inhibitors were all severe factor VIII or IX deficient patients.¹³

1.2.2 Inherited Bleeding Disorders Overview

Inherited or hereditary coagulation disorders include haemophilia, Von Willebrand disease, contact factor deficiencies, extrinsic and common pathway factor deficiencies, anomalies in fibrinogen-to-fibrin conversion, and hereditary thrombotic tendencies as depicted in Table 1.1. Hereditary alteration of coagulation and other factors involved in haemostasis can result in mild or severe bleeding tendencies, or occasionally to, thrombosis either spontaneously or following invasive dental procedures.¹⁴ The focus of this study is on the inherited disorders of coagulation.

Among the inherited disorders of coagulation the most common are Von Willebrand disease (VWD), haemophilia A and haemophilia B; with the congenital platelet disorders being very rare and was therefore will not included in this study.¹⁵

VWD is as a result of Von Willebrand factor (VWF) deficiency or dysfunction.¹⁶

Haemophilia A is caused by deficiency of factor VIII (FVIII), whilst haemophilia B and C are caused by deficiency of factor IX (FIX) and factor XI (FXI) respectively.^{5,12} VWF is fundamental for the completion of primary haemostasis whilst FVIII and FIX are essential for

secondary haemostasis. VWF is also a carrier protein for FVIII in the circulation; this means that in the moderate and severe forms of VWD deficiency of FVIII is also seen, which accounts for the additional secondary haemostasis impairment.²

Haemophilia C is highly prevalent in Ashkenazi Jews and uncommon in South Africa, and thus was not included in the study as the number of patients undergoing dental procedures was extremely small.¹²

Table 1.1 Hereditary coagulation disorders^{12,14}

Hereditary coagulation disorder	Example/Description
Haemophilia	Haemophilia A Haemophilia B
Von Willebrand disease	Type 1 Type 2 Type 3
Contact factor deficiencies	Deficiency of factor XII or Hageman factor, pre-kallikrein Factor XI deficiency (haemophilia C)
Extrinsic and common pathway factor deficiencies	Factor VII (proconvertin) deficiency Factor X (Stuart-Power factor) deficiency Factor II (prothrombin) deficiency Global vitamin-K-dependent factor deficiency Factor V (accelerator globulin) deficiency
Abnormalities in fibrinogen-to-fibrin conversion	Fibrinogen alterations Factor XIII (fibrin-stabilizing factor) deficiency Antiplasmin-alpha 2 deficiency
Hereditary tendency to thrombosis	Protein C deficiency Protein S deficiency Antithrombin III deficiency Alterations in factor V (resistance to activated protein C)

1.2.3 Von Willebrand disease

VWD affects up to 1% of the general population, and is the commonest of the inherited bleeding disorders.^{5, 16} It is an autosomal dominant condition, affecting both genders. Von Willebrand factor (VWF) is an important plasma protein in haemostasis that binds and stabilizes factor VIII (FVIII).^{5,15,16} Defects in VWF therefore reduce the concentration of FVIII. VWF also mediates the initial adhesion of platelets at sites of vascular injury.¹⁶ Therefore defects in VWF can lead to haemorrhaging as result of either impaired adhesion of platelets or fibrin clot formation.^{5, 12,17} VWD results from quantitative or qualitative defects in VWF.⁵ Clinical manifestations of VWD are secondary to platelet dysfunction, with symptoms more severe in mucosal surfaces because of the specific characteristics of haemostasis and fibrinolysis in these tissues.^{5,15,16}

This condition is subclassified into three major categories as depicted in Table 1.2. Type 1 VWD accounts for about 70% of cases. It represents partial quantitative deficiency of VWF.^{5, 15,16,17} There are low levels of VWF in the plasma, and they mediate platelet adhesion and bind FVIII normally.¹⁶ Type 2 VWD is a qualitative defect with autosomal dominant or recessive inheritance, and the symptoms are mild. Type 2 is further subclassified into 4 variants (Type 2A, 2B, 2M, and 2N) based on the type of the functional defect present. Patients with type 1 and type 2 VWD present with significant mucocutaneous bleeding and trauma-related bleeding. These patients, inclusive of child patients, may not present until after a significant haemostatic challenge, which can include dental extraction. In the absence of a substantial haemostatic challenge some patients remain undiagnosed and asymptomatic. Type 3 VWD is a severe quantitative defect with autosomal recessive inheritance, and the symptoms tend to be severe. This type is characterized by VWF protein and activity that is not detectable, and very low levels of FVIII. In patients with the severe form of VWD there is complete deficiency of VWF with resultant severe symptoms of bleeding. These patients usually present in childhood^{1, 15,16,17}

This condition can also be classified as mild, moderate or severe. Mild VWD is defined as more than 30% of VWF activity, and the moderate form as 10% to 30% VWF activity, and the severe form as VWF activity that is less than 10%.²

The most common symptoms in VWD include ecchymosis, epistaxis, bleeding from minor cuts or abrasions, menorrhagia (in females), bleeding after dental extraction and other surgical interventions, gingival bleeding, haemarthrosis, and gastrointestinal (GI) bleeding. Life

threatening bleeding, like that involving the GI, can occur in type 3 VWD, in some individuals with type 2 VWD, but rarely in type 1 VWD.¹⁶

Haemarthrosis is more common in persons who have a more severe deficiency; and is experienced by up to 40% of type 3 VWD patients, with joint damage increasing with age.^{16,18} Coexisting illnesses or use of other medications may modify the clinical symptoms; for example, the use of oral contraceptives decreases bleeding in women with VWD, while the use of aspirin exacerbates the bleeding tendency.¹⁶

Three general strategies are followed in therapies to prevent or control bleeding in patients with VWD. The first strategy is to increase the VWF plasma concentration by releasing endogenous VWF stores using desmopressin. The second strategy is to use human plasma-derived, viral-inactivated concentrates in order to replace VWF. The third approach is to use agents that promote haemostasis and wound healing but not alter the VWF plasma concentration substantially. One strategy approach may be followed for a patient, or all three may be applied at the same time. The type and severity of VWD, the severity of the haemostatic challenge, and the nature of actual or potential bleeding determine which therapeutic approach is most suitable.¹⁶

Prophylaxis or infusions of VWF to prevent episodes of bleeding are less frequently required in patients with severe VWD compared to patients with severe forms of haemophilia.¹⁶

Alloantibodies to VWF in response to transfusion of plasma products have been observed in a small fraction of patients with type 3 VWD. These alloantibodies to VWF inhibit the haemostatic effect of blood product therapy and may cause life-threatening hypersensitivity reactions.¹⁶

Table 1.2 The classification of VWD^{16,17}

Severity	Description
Type 1	Partial quantitative VWF deficiency Normal VWF protein function
Type 2	Qualitative defect of VWF Abnormal VWF protein function
Type 2A	Decreased platelet-associated function with selective deficiency of high molecular weight (HMW) VWF multimers
Type 2B	Increased affinity for platelet glycoprotein
Type 2M	Decreased platelet-associated function without selective deficiency of HMW VWF multimers
Type 2N	Normal platelet-associated function Normal HMW VWF multimers Markedly reduced factor VIII-binding capacity
Type 3	Quantitative complete VWF deficiency Undetectable VWF protein function

1.2.4 Haemophilia

Haemophilia is an inherited X-linked chromosome bleeding disorder. The prevalence of haemophilia A is 1 in 5 000 live birth males, and 1 in 30 000 live male births for haemophilia B.^{5,19} Female carriers occasionally have low factor concentrations and may have bleeding symptoms due to extreme X inactivation.¹⁵ It is important to note that persons with haemophilia do not bleed more profusely than usual, they have prolonged bleeding. The frequency and severity of bleeding is dependent on the patient's plasma levels of FVIII or the FIX activity.²⁰ Both haemophilia A and B are clinically indistinguishable from each other.

They are further classified as mild, moderate, or severe, corresponding to a plasma coagulation factor concentration.²¹ This classification is depicted in Table 1.3.

Patients with the severe form of haemophilia have less than 1 % (1 IU/dL) of plasma coagulation factor concentration. These patients experience spontaneous and repeated bleeds into muscles and weight bearing joints, and these bleeds are mainly in the absence of identifiable haemostatic challenge.^{19,22} They have an average of 20 – 30 bleeding episodes annually, and may also bleed after minor trauma. Those with moderate form of haemophilia have 1-5% (1-5 IU/dL) factor concentration, and they have occasional spontaneous bleeding, but bleed for a prolonged period after minor trauma.^{19,22,23} Patients with the mild form of haemophilia have 6-30% of factor concentration, and generally have severe bleeding only after trauma or surgery. Spontaneous bleeding in the mild form is rare. These patients may not be diagnosed until a certain procedure leads to prolonged bleeding, and these include dental procedures.^{21,22} Female carriers have varying factor levels and may be asymptomatic.⁸ However, there may be an increased bleeding tendency in carriers with clotting factor levels of 40-60% of normal levels. Some of the carriers may have clotting factor levels that are in the haemophilia range, this makes up only a few carriers. These carriers may be asymptomatic with bleeding manifestations, particularly during trauma or surgery. The bleeding correlates with their degree of clotting factor deficiency. They are categorized as having haemophilia of appropriate severity. This group is mostly in the mild category, but there are rare instances where carriers can be in the moderate or severe range as a result of extreme lyonization (inactivation of the X chromosome).²² If the female carriers' factor level is less than 50% they should be treated as mild haemophilia patients.²³ The most common manifestations among carriers with significantly low factor levels are menorrhagia and bleeding after medical interventions.²²

Although the bleeding in patients with haemophilia occurs in limited sites the most challenging to manage are those that are life-threatening including potentially organ-threatening bleeds albeit rare, as depicted in Table 1.4.¹²

The prophylactic factor regimen for these patients encompasses the administration of factor replacement therapy (FRT) that is prescribed on an individual basis, to minimize spontaneous bleeding.²³ The missing factor is administered intravenously on a prophylactic basis or on-demand to manage bleeding. In bleeding situations it is the only effective treatment for haemophilia.¹⁹ Before the introduction of viral inactivated plasma derived factor concentrates, patients with haemophilia and other bleeding disorders were at risk of being exposed to

human immunodeficiency virus (HIV) and hepatitis C virus (HCV). In the mid-1980s viral inactivation of plasma-derived factor concentrates was introduced, followed by the use of recombinant or non-human derived factor concentrates in the early 1990s.²⁴ Recombinant factor replacement (rFRT) is more expensive than plasma products. It reduces the risk of blood borne infection.²⁰ Dental procedures should be scheduled to coincide with administration of factor to minimize the risks of therapies and to decrease the treatment costs.²³

The development of antibodies or inhibitors to factors VIII or IX is a complication of FRT, and occurs early in the treatment.²⁴ Inhibitors develop as an immune response to FRT in up to 20-30% of patients with type A and 5% of those with type B. Simple factor replacement is often not effective in these patients, and alternative bypassing agents, such as recombinant Factor VIIa are used to promote haemostasis.⁵

Table 1.3 The classification of haemophilia⁸

Bleeding phenotype	Coagulation Factor (%)
Mild	6-40%
Moderate	2-5%
Severe	<1%
Carrier	Factor level varies

Table 1.4 Sites of life-threatening or organ-threatening bleeds in haemophilia¹²

Life-threatening or organ-threatening bleeds
Intracranial
Muscle compartment
Neck/throat
Massive gastrointestinal
Genitourinary tract
Intraocular

Table 1.5 Prevalence of different sites of bleeding in haemophilia¹²

Sites of bleeding	Prevalence
Haemarthrosis	70% - 80%
Muscle and subcutaneous bleeding	10% - 20%
Life-threatening bleeding	5% - 10%

1.2.5 Factor V Deficiency

Factor V (FV) has both pro-coagulant and anti-coagulant functions. Most of the FV is present in plasma, whilst 20% is found within platelet α -granules.²⁵ Activated FV (FVa) is a non-enzymatic cofactor of activated factor X (FXa), it cleaves and activates prothrombin to thrombin.^{25,26} Activated protein C turns off the FVa procoagulant activity and converts it to an anticoagulant.²⁶

Congenital FV deficiency is as result of either mutations in the FV gene or in genes affecting the processing or storage of FV.²⁶ FV deficiency presents at birth or in early childhood, although some cases remain asymptomatic until later in life and may be diagnosed by chance during routine coagulation screenings.^{24,25} Individuals with homozygous factor V deficiency present with easy bruising and mucosal bleeding. Individuals with heterozygous factor V deficiency are asymptomatic or experience only mild bleeding.^{21,25} The prevalence of homozygous factor V deficiency is 1:1000 000. Haematomas and haemarthrosis rarely occur spontaneously, rather they may occur with injury.²¹ Replacement therapy for Factor V deficiency is with fresh frozen plasma as there is currently no Factor V clotting factor concentrate.²⁶

There is limited correlation between the activity levels of FV and the severity of bleeding. Patients with identical mutations or activity levels can have varying clinical manifestation or bleeding symptoms. Thus the clinical phenotype severity cannot be easily detected by using the activity level.²⁶ The most common symptoms are skin, and mucocutaneous bleed which include epistaxis, oral mucosal bleeding, and menorrhagia in females. Another common symptom is post-traumatic bleeding following delivery or surgery with only one quarter of patients presenting with haemarthrosis and muscle haematomas.²⁵

Severe bleeding manifestations include intracranial or gastro-intestinal haemorrhages; and these are confined to patients with undetectable FV levels, and are said to be rare.²⁵

There is no FV-specific concentrate. Fresh frozen plasma (FFP) is the treatment of choice in symptomatic FV deficiency despite the risk of volume overload due to the plasma half-life. Plasma exchange is used to bypass this complication.^{25,26} Recombinant FVIIa has only been approved for use in FVII deficiency and for patients with inhibitors. Theoretically it may stop bleeding in patients with FV deficiency, and is thus a possible alternative to FFP. The mechanisms in this setting are unknown, but the advantages of its use are the lower volume of infusion and no risk of viral infections.²⁵

Patients with FV deficiency rarely develop inhibitors. Anti-fibrinolytic agents, such as aminocaproic acid, are sufficient for mild bleeding episodes. Patients with FV deficiency, including the severe types, do not require routine prophylaxis, except for episodic treatment to stop bleeding, and before planned invasive procedures.^{25,26}

1.2.6 Factor XI Deficiency And Rare Bleeding Disorders

Factor XI (FIX) deficiency is of autosomal inheritance and occurs in both females and males. It has the highest prevalence in Ashkenazi Jews. It differs from haemophilia, in that bleeding does not occur into joints and muscles. Bleeding in FXI deficiency is often unpredictable and may occur secondary to surgery in sites that have high fibrinolytic activity, as seen in procedures such as tonsillectomy and invasive dental procedures such as extractions.²³

1.3 Dental Management of Patients With Inherited Bleeding Disorders

The main objective in the dental management of these patients is to minimize the need for future invasive dental procedures where possible. Where invasive dental procedures are indicated the patient should be informed of the risks involved, and a multidisciplinary approach should be followed together with a protocol to avoid or minimize postoperative complications including bleeding.

1.3.1 General Measures

During the dental procedures saliva ejectors should be used carefully to avoid trauma to the oral mucosa. Care should be exercised when placing radiographic films, especially in the sublingual area to avoid trauma.²⁷

1.3.2 Prevention

The dental caries and periodontal disease incidence among patients with IBD is higher and this is attributed to the lack of effective oral hygiene.²³ Prevention is the most important objective when looking at dental management of patients with IBD.^{11,28} The bacteria harboring biofilm that forms and remains on the tooth surfaces is the main etiological factor in caries and periodontal disease. This means that prevention of these conditions must be based on means that counter the accumulation of bacterial plaque.²⁹ Supportive care for patients with IBD should therefore include regular dental visits, plaque control, application of topical fluoride, regular oral hygiene education and application of fissure sealants.^{11,29}

Gingivitis and periodontitis are related to the age and quality of the bacterial plaque more than the amount of plaque. Therefore it is important to highlight the importance of effective plaque removal to patients, as this ensures its frequent disruption thus limiting the maturity of bacteria into more virulent strains.³⁰

Mechanical tooth cleaning procedures, including brushing and flossing, are considered to be the most reliable means of controlling plaque.³¹ Oral health professionals must provide oral hygiene instructions that are easy for the patient to understand and adopt. The patients can be given plaque disclosing solutions/tables so that while brushing they can assess if their brushing technique is effective or not.³⁰ Toothbrushing alone is able to clean only the buccal, lingual, palatal and occlusal tooth surface; interdental-cleaning devices should be recommended for the proximal and interdental areas. These are the areas in which dental caries most often develop, and where gingival and periodontal lesions are frequently found, hence the significance of interdental cleaning. Most of the devices designed for interdental cleaning require considerable dexterity and time as well as instruction and motivation in order

for them to be effective and established into the hygiene routine.³¹ This can lessen patient compliance and motivation.

Patients with inherited bleeding disorders should be viewed as high caries risk patients.⁸ Effective and efficient caries preventive measures in children with high caries risk include plaque removal, fluoride application and fissure sealants. Studies have shown that if prevention programs are merely educational and there is no application of fluoride then there is no caries reduction.³²

Fluoride is known to protect teeth against caries. Water fluoridation results in dental caries decrease of approximately 50%. It has been shown to be the most effective and wise means of preventing caries.³³ According to the report by Rand Water, fluoridation of tap water in SA has not been implemented. The reasons include the high cost implications and the fact that the targeted population, which do not use fluoridated toothpaste, in the rural areas do not receive piped water.³⁴

In areas where water supply contains fluoride that is less than 0.3 parts per million (ppm) fluoride supplements may be given daily. These can be given daily in the form of drops or tablets to children over the age of 6 months.³³

There are studies that indicate that frequent fluoride applications in combination with effective plaque removal are needed for caries reduction.³² In a study done by Zimmer et al, high caries risk in children from a low socio-economic status who received a minimum of 2 fluoride applications per year showed a significantly lower dental caries increment.³⁵

Diet counseling should be considered as part of supportive care for these patients. Refined carbohydrates and sugars are the major cause of caries. The frequency of intake of these sugars is more important than the amount of sugar consumed. The aim would be to reduce the consumption and also the frequency of sugar-containing food and drink intake.^{28,33}

Regular dental visits should be tailor made for the patient, bearing in mind the dental needs and oral hygiene practices of the patient.³¹ In these visits the following can be done: dental assessment including assessment of plaque index and where appropriate the bleeding index, fissure sealants and plaque removal and other dental procedures.^{31,33} Oral hygiene education can be reinforced and evaluated.³³ Fluoride varnish can be placed 3-4 times per year. The principles of keeping good oral hygiene to prevent dental caries and periodontal disease can be revisited and reinforced during the dental visits. Smoking should be strongly discouraged.⁸

1.3.3.1 Type of Anaesthesia

IBD patients undergoing invasive dental procedures are at high risk of secondary bleeding at the site of surgery, therefore the type of anaesthesia should be carefully chosen.³⁶

1.3.3.2 General Anaesthesia

General anaesthesia with tracheal intubation or a laryngeal mask in patients with IBD could trigger a laryngeal haematoma.^{36,37} Laryngeal haematoma can lead to upper airway obstruction, which is very difficult to control.²⁹ General anaesthesia should therefore be avoided.³⁷ It is more advisable that local anaesthesia be used as the bleeding risk only relates to the surgical site and the bleeding can be controlled by local hemostasis.³⁶

Sedation with nitrous oxide-oxygen, and use of anxiolytic agents should be considered as alternatives.²³

1.3.3.3 Local Anaesthesia

Local anaesthesia (LA) has varying degrees of risk for patients with IBD. The use of fine-gauge single-use needle is preferred and it lowers the risk of haematoma. The principle of using a slow injection technique allows time for a local anaesthetic to diffuse through the tissues and minimize bruising.²⁷ The use of local anaesthetic infiltration in adults is achieved without the need for factor replacement therapy (FRT). There are differing views when it comes to children, a dose of FRT may be administered prior to infiltrating. In adults, intra-ligamentous or intra-papillary injections do not require haemostatic cover. A buccal infiltration can be given prior to these techniques to avoid pain.²³

The techniques that are associated with a significant risk of haematoma are the inferior alveolar, posterior superior alveolar dental nerve blocks, lingual infiltration, and floor-of-mouth injections. The posterior superior alveolar and inferior alveolar dental nerve blocks in patients with IBD are associated with the risk of muscular haematoma with possible airway compromise due to a haematoma formation in the retromolar or pterygoid space. FRT levels with or without tranexamic acid is necessary prior to these techniques being administered or

carried out.²³ Alternatives to nerve block should be considered whenever possible, and include use of intra-ligamentous or intra-papillary injections. These are especially recommended as alternatives in children.²⁷

Table 1.6 Local anaesthetic techniques and replacement therapy in adults⁸

Procedures not requiring replacement therapy	Procedures requiring replacement therapy
Intra-ligamentous injections	Inferior alveolar nerve block
Intra-papillary injections	Posterior superior alveolar nerve block
Buccal infiltration	Lingual infiltration
	Floor-of-the mouth injections

There are no restrictions regarding the type of anaesthetic agent used. The use of vasoconstrictor improves local haemostasis. The use of articaine containing 1:100 000 epinephrine has shown to achieve more ideal bone penetration.^{23,38} Robertson et al did a prospective study that showed that 4% articaine with 1:100 000 epinephrine when infiltrated buccally on the first molar resulted in a higher anaesthetic success rate than 2% lidocaine containing 1:100 000 epinephrine, the duration of pulpal anaesthesia declined over 60 minutes with both formulations.³⁸ Infiltration using 4% articaine containing 1:100 000 epinephrine can be used as an alternative to inferior dental block when restoring mandibular molars, thus eradicating the necessity for factor replacement therapy prior to the procedure.²³

1.3.4 Pain Control or Analgesia

Analgesia is needed for managing dental pain or relief of pain following a dental procedure. Aspirin, and Aspirin-containing medication in IBD patients will worsen the haemorrhagic tendency as a result of platelet function inhibitory effect. Thus it is advisable that these medications be avoided in these patients. The use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of bleeding if taken prior to the procedure. This is because of their effect on platelet aggregation. Therefore their prescription should be discussed with the haematologist. Paracetamol and codein-based preparation are safe^{8,27}

Long-acting LA can offer 8 to 10 hours of effective pain control, therefore whenever appropriate they can be considered for postoperative analgesia.²⁷ An example is bupivacaine

hydrochloride 0.5% with adrenaline 1:200 000, which has long duration anaesthesia for soft tissue in both arches and the pulp of mandibular teeth. It has a duration of action of up to 340 minutes in soft tissue when used as infiltration in maxilla.³⁹

1.3.5 Extraction and Oral Surgery

Surgical treatment and routine dental extraction requires careful planning to minimize the risk of bleeding, excessive bruising or haematoma formation. The risk of local infection and inflammation should be reduced prior to extraction and surgical treatment.²⁷ Therefore before any surgical procedure or extraction there should be removal of plaque and calculus. This can be coupled by using topical antiseptics, like chlorhexidine or povidine, or antibiotics where appropriate.³³

FRT should be administered 30 minutes to 1 hour before surgery and routine dental extraction, and hemostasis should be assessed immediately before oral surgery to evaluate the increase in the missing factor.^{27,36} FRT administration is repeated 24 hours after surgery. An additional infusion for patients with hemophilia A and VWD is administered 12 hours after surgery.³⁶

Desmopressin (DDAVP) in patients who are good responders is an effective alternative to coagulation factor concentrates. It is cheaper than coagulation factor concentrates, and has no risk of viruses or new pathogen transmission. It also reduces the risk of immunization as it prevents exposure to coagulation factors. It is clinically effective in patients with moderate form of haemophilia A and also those with type 1 VWD and some type 2 VWD. It is ineffective in those with a severe and moderate form of haemophilia A, and in those with type 3 VWD, and many with type 2 VWD. It has to be tested for responder selection 2 weeks before surgery or extraction. Desmopressin should be infused 30 to 60 minutes before dental extractions or surgery. It induces FVIII and VWF release from storage sites.³⁶ DDAVP raises the FVIII level 3 to 6 times baseline levels in patients with mild and moderate HA.²² Haemophilia A patients who are treated repeatedly with desmopressin can become less responsive, and this might be attributed to stores of FVIII becoming exhausted. Repeated use can also cause fluid retention and symptomatic hyponatraemia.^{8,20} Thus its use in the management of haemophilia is limited.²⁰

Clot stabilization facilitates haemostasis. Antifibrinolytic agents are used to achieve this.²⁰ Saliva has fibrinolytic action, thus antifibrinolytic agents need to be administered as mouthwashes to neutralize the fibrinolytic activators.^{2,36} In addition to the fibrinolytic activity

of saliva in the oral cavity, there is also fibrinolytic activity of local tissue plasminogen activator (t-PA) production. These factors make the fibrinolytic activity in the oral mucosa to be particularly high. Inhibition of this fibrinolytic activity with antifibrinolytic agents limits oral bleeding after surgery or invasive procedures in patients with IBDs.²

Examples of antifibrinolytic agents are epsilon aminocaproic acid (EACA) and tranexamic acid (TA). These agents prevent degradation of the fibrin clot which supports blood clotting. They do this by binding reversibly to plasminogen preventing it from forming plasmin, and preventing or blocking the interaction of plasminogen with fibrin.^{2,20} TA is more potent than EACA. Tranexamic acid mouthwash (TAMW) produces therapeutic saliva concentrations by using it as mouthwash with 10ml of 5% TA of aqueous solution.²⁰ It has been suggested that TAMW be used before the dental procedure, and continued 6 hourly for 7-10 days⁸

Antifibrinolytic agents can be administered orally, intravenously, or as a mouthwash.³⁶

Intravenous TA can be administered 2 to 3 times daily as 0.5 g to 1 g in adults. While 0.5 g to 1 g oral TA can be given 2 to 3 times daily, and 10 ml of TAMW can be used as mouthrinse 4 times daily. Intravenous, oral TA and TAMW can be administered in children 1 year old and older it can be given 2 to 3 times as 20 mg/kg bodyweight per day.² Use of tranexamic acid in intermittent compression repeatedly for 3 days following dental extractions has been described.³⁷

Certain measures need to be followed, these include, reduction of flap size, surgical and closure techniques that permit easy access for packing, removal of granulation tissue, limiting trauma, and elective sectioning of teeth reducing the number of teeth to be extracted at a time. Such surgical technique modifications can reduce haemorrhage intraoperatively and postoperatively. A surgical stent helps protect the surgical site during healing.²⁷

1.3.6 Local Haemostasis

Pressure is the most effective method of achieving haemostasis. Pressure must be applied at the appropriate site for minimum of 30 minutes to an hour with wet gauze to prevent the clot from adhering to it.⁵ TA can be used to wet the gauze.

Local haemostatic agents include the use of oxidized cellulose or fibrin glue, a resorbable gelatin sponge, surgical splints, and resorbable or nonresorbable sutures.⁸ There are articles that promote the use of either absorbable or nonresorbable sutures.^{36,37} In the Piot *et al* study, they promoted the use of nonresorbable sutures to prevent the inflammatory reaction of

resorption, which may enhance fibrinolytic response.³⁶ In the Franchon *et al* study, they used absorbable sutures to avoid thread removal which would cause late bleeding.³⁷ The South African guidelines suggests the use of deep silk or Vicryl suture.¹²

Gelfoam is an absorbable gelatin sponge material that acts as a scaffold for clot formation. When using it one should avoid placing it under epithelial incisions or flap as it inhibits healing of the epithelial edges.⁵

Fibrin glue can be used along with an antifibrinolytic agent. Fibrin glue contains human or animal components, and they mimic the final pathway of coagulation cascade at the point where fibrinogen in the presence of thrombin, factor XIII, fibronectin, and ionized calcium is converted into fibrin.²⁴

Compression splints are said to cause discomfort and could possibly injure the mucosa, and the splint also stimulates saliva secretion, which increases the fibrinolytic enzymatic activity of saliva. Beneath the compression splint there can be maceration, which causes bacterial colonization and streptokinases production, which also exert fibrinolytic action. Use of intermittent tranexamic acid compression instead of the compression splint is therefore a better option.³⁷ Application of intermittent tranexamic acid compressions on an extremely regular basis for the first few days postsurgery mechanically protects the surgical site and produced a strong, local concentration of tranexamic acid, which limits the fibrinolytic action of salivary enzymes. The compressions also contain the clot in the alveolus.³⁰

Electrocautery slows intraoperative bleeding and stem postoperative episodes. It should be used cautiously to avoid tissue necrosis because necrosis delays healing and as the necrotic tissue sloughs off it becomes a potential source and site of postoperative bleeding.⁵

The onset of excessive postsurgical bleeding can be prevented by the use of combination of coagulation factor concentrate or dihydro-D-arginine vasopressin (DDAVP), and use of an effective local haemostatic technique. It was shown in a study done by Franchon *et al* that the combination of intermittent tranexamic acid compression technique immediately following the surgical procedure can reduce hospitalization duration to 1 day, a maximum of 3 days.³⁷

1.3.7 Postsurgical Bleeding

Postsurgical bleeding often occurs several days after the procedure, even with careful preoperative planning.^{27,37} Patients with IBDs should be informed of the risk of postoperative bleeding and the intervention plans should be described to them. The patients should be given a 24-hour a day contact and next-day reassessment. The significance of the bleeding and the nature and extent of the surgical procedure or extraction will determine the frequency and duration of reassessments.⁵

Techniques for managing postoperative bleeding include reapplication of pressure packs, packing of sockets with Gelfoam, reinjection of local anaesthetic containing epinephrine, removal of exophytic clots, and use of astringents. Pressure packs should be kept in place for at least 30 minutes without interruption. The second step is packing or repacking the sockets with Gelfoam, and the pressure packs replaced over the fresh Gelfoam. Reinjection of a local anaesthetic containing epinephrine gives the benefits of vessel constriction and slow haemorrhage, and allows stable clot formation. This is followed by vasodilation that may lead to significant haemorrhage. Exophytic clots provide a pathway for continued bleeding and also prevent application of adequate pressure to the bleeding site therefore they should be removed. Astringents in the form of tea bag pressure pack or commercial preparation should be used, especially on incisions and raw areas. It is also important that the patients be instructed to limit any physical exertion, to avoid smoking and alcohol consumption, and to sit or sleep in a semi-sitting position.⁵

1.3.8 Periodontal Treatment

Gingival bleeding is usually caused by gingivitis, as result of plaque accumulation. The bleeding is aggravated by bleeding disorders.²⁸ Concerns about bleeding gingival tissues in patients with gingivitis make them reluctant to brush their teeth, and this leads to further deterioration of their periodontal health.²⁷ Thus it is important to educate these patients about gingivitis and periodontitis, and the benefits of practicing good oral hygiene.

Periodontal probing, supragingival scaling and polishing are unlikely to cause prolonged bleeding.^{8,33} Ultrasonic instrumentation is recommended or preferred over hand scalers

subgingivally as they result in less tissue trauma.²⁷ Management of patients with poor gingival health requires several visits to prevent excessive bleeding.^{8,33} It is advisable that supragingival scaling along with oral hygiene education and use of chlorhexidine gluconate mouthwash be initially instituted. As soon as the inflammation has decreased then subgingival scaling can be carried out. Antibiotics can also help to reduce the initial inflammation.^{24,33}

Tranexamic acid mouthwash (TAMW) and/or factor replacement therapy (FRT) may be necessary to control bleeding.⁸ Lee *et al.* did a study that proved that the use of TAMW after dental scaling in patients with haemophilia was as effective in controlling gingival haemorrhage as using FRT. This means that FRT can be reserved for more severe bleeding situations. FRT is expensive and there is a risk of developing factor antibodies.²⁰

There is a significant risk of bleeding associated with periodontal surgery. Periodontal surgery offers a greater challenge to haemostasis than does a simple extraction.²⁴ It should be considered a high-risk procedure, and should only be considered where conservative treatment has failed.³³ Bone grafting and sinus floor elevation are contraindicated in patients with IBD.²⁷ Periodontal surgery requires FRT and monitoring post-procedure.³³ Other ways of controlling bleeding is by locally applying direct pressure or periodontal dressings with or without topical antifibrinolytic agents.²⁴ The use of periodontal packing materials and stents aids in haemostasis and protection of the surgical sites. Severe hemorrhage or formation of subperiosteal haematoma can dislodge these local haemostatic agents. Incorporation of antifibrinolytic agents into periodontal dressings can enhance their effect. Periodontal surgery should be carefully planned with the haematologist, and the risks must be discussed with the patient.²⁷ Guidelines for oral surgery apply for periodontal surgery.

1.3.9 Restorative Procedures

Routine restorative procedures are associated with low risk of bleeding. Guidelines for local anaesthetic use must be followed.^{36,37} Care must be taken to protect the mucosa.⁸ The use of minimal invasive techniques such as air abrasion and hard tissue lasers can reduce the need for local analgesia.^{11,33} Care must be taken to protect the mucosa. Bleeding with the use of the matrix bands or wooden wedges can be controlled by local means or the application of topical agents.²⁴

1.3.10 Endodontic Treatment

Endodontic treatment is associated with low risk of bleeding.²⁴ Pulpectomy and pulpotomy are preferable to extractions. Pulpectomy should be carried out carefully within the working length of the root canal to ensure that the instrument does not perforate the apex of the canal.²⁷ Bleeding in the canal during the procedure can be indicative of pulp tissue remaining at the apical foramen, and this can cause pain. Bleeding in the canal can also be due to a perforated apex. In these instances one can irrigate using 4% sodium hypochlorite and calcium hydroxide paste to control the bleeding.^{8,27}

Pulpotomy in primary teeth should be carried out according to the accepted guidelines. Electrosurgical coagulation of the pulp stumps or use of ferric sulphate are recommended for haemostasis.²⁷

1.3.11 Prosthodontic Treatment

Care should be taken to avoid tissue trauma, and dentures should be adjusted to avoid any over extension.²¹

Full or partial dentures may be used in patients with IBD. Care should be taken to avoid tissue trauma during fabrication, and dentures should be adjusted to avoid any over extension.^{27,33} It is important to maintain periodontal health of remaining teeth in cases where a partial denture is provided.²⁴

There are no established and verified evidence based protocols for use of implants in IBD patients. Proposed use of implants should be discussed with the haematologist. Routine placement of implants may pose no more risk than extraction of third molars. The suitability of a proposed implant site must be verified using three-dimensional imaging and treatment planning software. This would minimize complications such as lingual plate perforation, which have a potential to cause deep bleeding that could be difficult to control.²⁷

1.3.12 Orthodontic Treatment

Fixed and removable orthodontic appliances may be used in conjunction with regular preventive education and therapy. Sharp wires or edges should be avoided as they will traumatize the mucosa or gingiva. After appliance insertion soft periphery wax can be used to minimize the risk of tissue trauma. Orthognathic surgery has an unfavourable risk:benefit

ratio, but it is not absolutely contraindicated. Careful planning must be done with the haematologist before orthognathic surgery or surgical procedures that support orthodontic treatment.²⁷

1.3.13 Other Considerations

1.3.13.1 Antibiotics

Antibiotics that do interfere with coagulation include certain penicillins, cephalosporins, sulfonamides and trimethoprim. An important mechanism by which selected antibiotics can cause bleeding is by causing dysfunctional platelet aggregation. The problem is dose related and is additive to other factors in patients that have dysfunctional platelet aggregation. Dysfunctional platelet aggregation is mostly seen with penicillins. The most likely among penicillins is penicillin G and also advanced-generation penicillins. Antibiotics that are associated with international normalized ratio (INR) prolongation include cefamandole, moxalactam, cefoperazone, cefmetazole, and cefotetan. Antibiotics can affect the normal gastrointestinal flora, thereby impairing vitamin K absorption.⁴⁰

1.3.14.2 Use of Lasers

Low level laser therapy, also known as bio-stimulation, has been shown to increase the release of endorphin, decreased C-fibre activity and bradykinin with resultant analgesic effect.⁴¹ Low power lasers promote wound healing in experimental models of tissue repair and also in human cases of wounds and ulcers. Laser therapy does accelerate tissue repair processes. It was reported that in a majority of animal experiments low-intensity lasers enhanced wound healing by promoting cell proliferation, accelerating collagen synthesis and promoting the formation of both type I and type III pro-collagen specific pools of messenger RNA (mRNA), increasing the synthesis of adenosine triphosphate (ATP) within the mitochondria, activating lymphocytes, and increasing the ability of lymphocytes to bind pathogens. Many variables are involved to achieve this outcome, and these include the wavelength, power, energy, treatment duration, and method of application etc.⁴²

Different wavelengths are available for clinical use in hard dental tissue management, oral surgery, endodontic purposes, periodontology, soft tissue surgery, diagnosis and disinfection.

Soft tissue applications include exposure of teeth to aid eruption, gingival contouring, frenectomy, operculectomy, fibroma removal, aphthous ulcers and herpes labialis lesions. For these procedures the following lasers can be used: argon, carbon dioxide (CO₂), diode, and Nd:YAG lasers. There are advantages of using these lasers, including the ability of lasers to coagulate and seal blood vessels, vapourise the tissue, accurate incision, antimicrobial properties with resultant improved healing effect and minimal post-operative pain and swelling. Less anaesthesia and analgesia are needed with the use of lasers.⁴¹

Temperature increase within the hard tissues results in enamel and dentine melting, and this leads to a release of carbonate and improved crystal structure. This results in an increased acid resistance, and hence the prevention of caries. Lasers can be used in conjunction with fluorides for caries prevention. Argon laser and CO₂ are for these application.⁴¹

Er:YAG laser can be used for hard tissue ablation. CO₂ laser can be used for endodontics, and this includes application in primary teeth. Another advantage of using lasers especially in children is the improved acceptance of therapy or treatment, and there is more cooperation during treatment.⁴¹

1.4 Aim

The aim of this retrospective study was to review dental procedures, inclusive of invasive and non-invasive procedures, performed in patients with IBD at the Wits Oral Health Centre (WOHC) at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

CHAPTER 2: Methodology

2.1 Methodology

Ethical clearance for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa, under the protocol number M150425. The ethics clearance certificate is attached as Appendix A. The study population comprised of patients with IBDs who were referred from the Haemophilia Comprehensive Care Centre (HCCC) at the CMJAH for dental procedures at the WOHC. Approval to access the HCCC and WOHC database was obtained from the relevant authorities, these letters are attached as Appendix B and C respectively. The patient data evaluation was retrospective and anonymous and therefore informed consent was not required.

The IBDs included haemophilia A and B, Von Willebrand disease and other coagulation bleeding diatheses. Patients with inherited platelet disorders, and those with acquired bleeding disorders were excluded from the study as these numbers were generally small in the HCCC and none had undergone dental procedures.

All age groups, with the abovementioned IBDs, who had undergone dental procedures at the CMJAH from January 2000 to December 2015 were included in the study. Dental records were retrieved from the WOHC database and the demographic data, bleeding condition and severity, dental procedure information and replacement therapy, and post bleeding complication data was extracted from the files. The data collection sheet is attached as Appendix D and E.

Patients with incomplete file records were also excluded. Each eligible patient record was assigned a study number and data was extracted from the files from both centres, that is, the HCCC and WOHC at CMJAH.

Data analysis was performed using a statistic program (STATA). Quantitative data was summarized in tables and figures and described using medians and ranges; counts with percentages (%); the Fischer's exact test; and the Mann-Whitney U test. A p-value of <0.05 was considered statistically significant.

CHAPTER 3: Results

3.1 Study population demographics

A total of 39 patients out of 106 patient records from the HCCC met the inclusion criteria. Only 21 patient files were available from the WOHC with had the complete data set required for the study.

The demographic and baseline characteristics of the study population are depicted in Table 3.1. The majority of the study population was male (81%) and black (52%). The average age was 26 with the range from 3 to 61 years. The HA patients comprised 48% of the study population, VWD patients made up 33%, with HB patients making up 14%, and only 5% had FV deficiency.

Table 3.1: Demographic and baseline characteristics of the patients

Variable		(N=33)
Age, Average (Range)	Average	26 (3-61)
Gender, n (%)		
Male		17(81)
Female		4(19)
Race, n (%)		
Black		11(52)
White		8(38)
Indian		1(5)
Coloured		1(5)
IBD*, n (%)		
Haemophilia A		10(48)
Haemophilia B		3(14)
Von Willebrand		7(33)
Factor V deficiency		1(5)

*IBD: inherited bleeding disorder

3.2 Dental procedures performed in IBD patients

Figure 3.1 outlines the dental procedures performed during the period of 2000 -2015. There were 33 procedures performed which included 58% dental extraction, 21% endodontic and restorative procedures, 12% scaling and polishing, and 3% for periodontal probing with polishing, 3% for scaling and polishing with full mouth debridement (root planing), and 3% for fissure sealant.

Procedures were further classified according to the type of bleeding disorder and severity as depicted respectively in Figure 3.2 and Figure 3.3. Restorative procedures were observed in 27% VWD subjects, and 57% of HA subjects had extractions. In terms of severity, 75% of the severe group had extraction, 6% had scaling and polishing, and 6% had fissure sealant application.

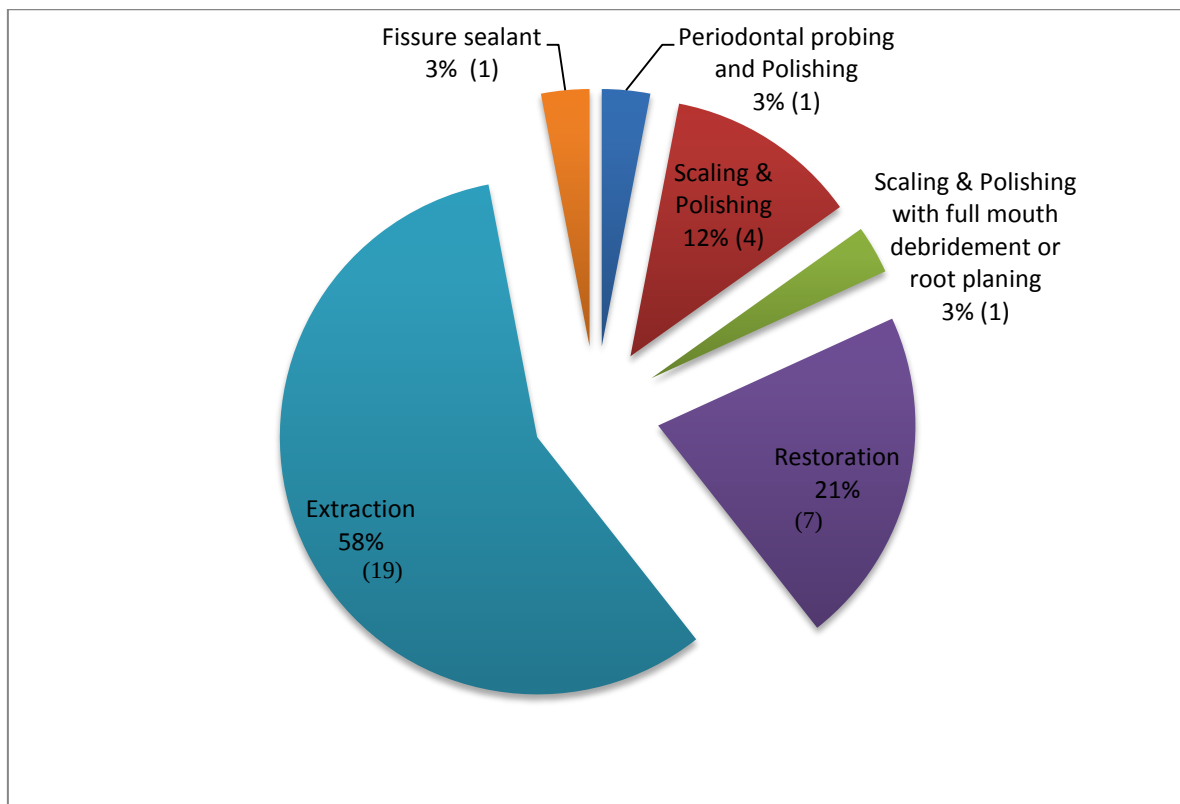


Figure 3.1 Dental procedures performed during the study period (2000 – 2015)

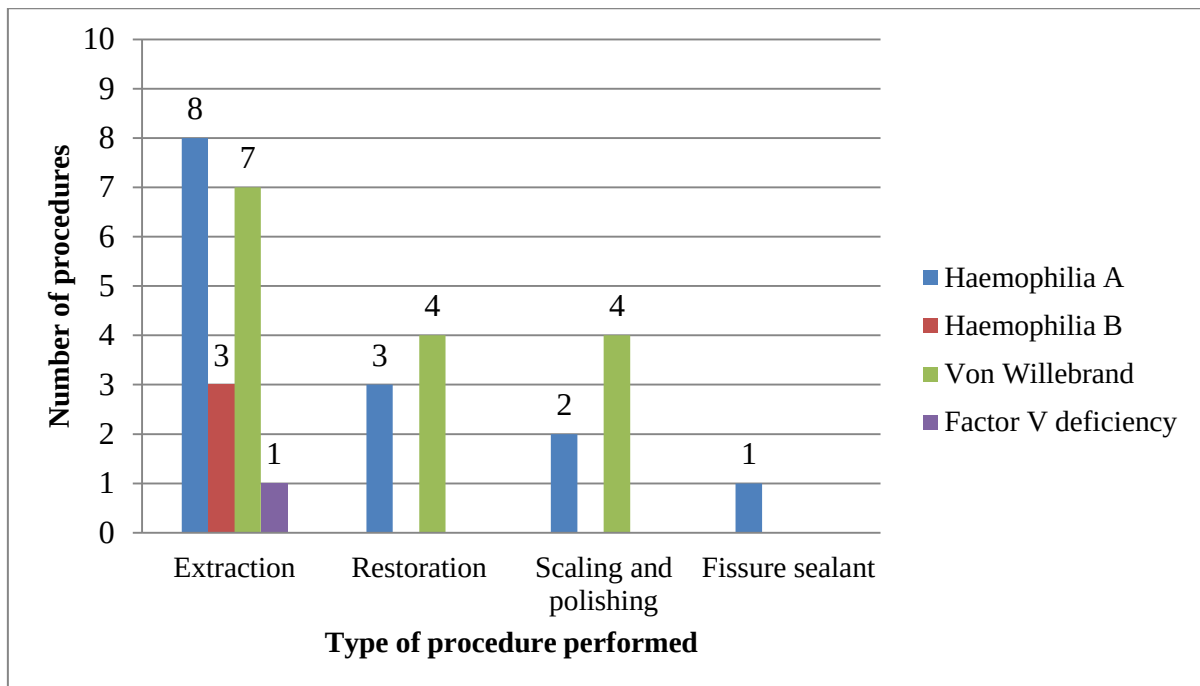


Figure 3.2 Dental procedures classified according to IBD diagnosis

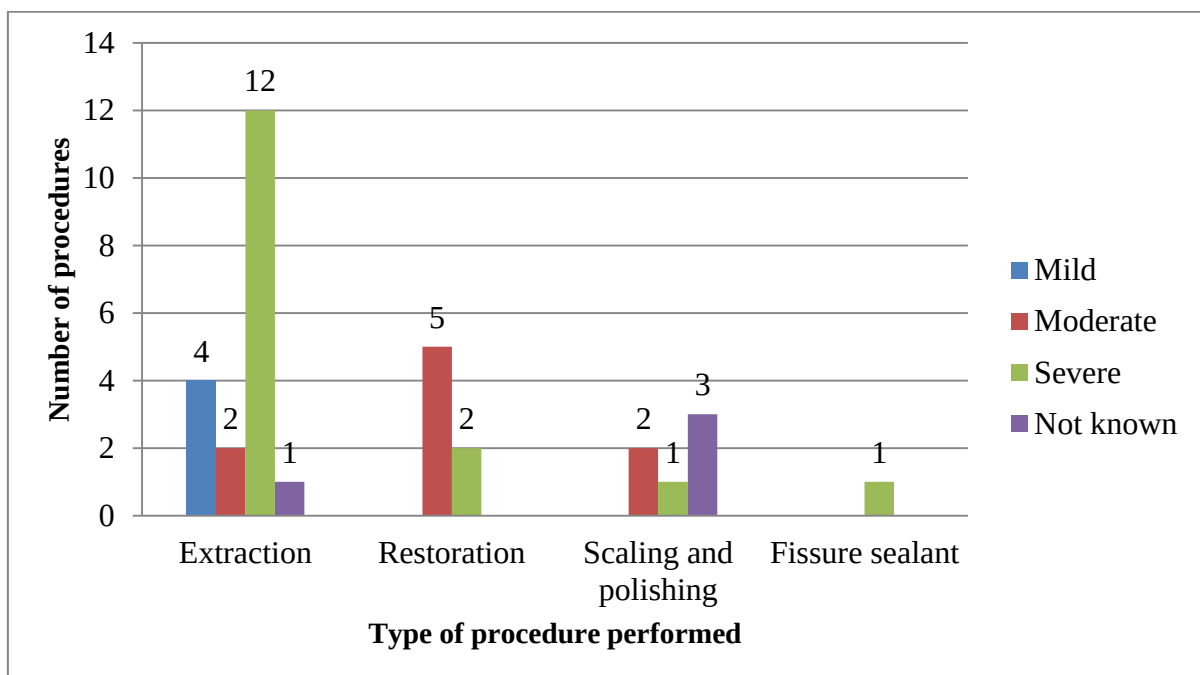


Figure 3.3 Dental procedure categorised according to severity

3.3 Replacement therapy and antifibrinolytics

Tables 3.2, 3.3 and 3.4 outline the FRT and DDAVP protocols used in the centre. Patients with FVIII or FIX deficiency received FRT as outlined in Table 3.2. Tranexamic acid 15-25

mg/kg was administered orally 8 hourly a day before the procedure and continued up to 5 days after the procedure. Clotting factor was administered at 80-100 IU/kg IV 30 minutes to 1 hour before the procedure. This dose was repeated at 50 IU/kg 6 hours after the procedure. Factor administration was continued for days after the procedure if there was bleeding. The protocol for patients receiving DDAVP is depicted in table 3.3. DDAVP was administered at 300 µg/kg in 50 ml normal saline IV over 30 minutes, and tranexamic acid 15-25 mg/kg in 50 ml normal saline was given IV 1 hour prior to the procedure.

Table 3.4 outlines the protocol for patients with FV deficiency, 4 bottles of bioplasma were administered IV 1 hour before the procedure together with tranexamic acid 15-25 mg/kg 8 hourly orally starting the day before the procedure up to 5 days post procedure.

In terms of the clotting factor replacement therapy prior to a dental procedure, as depicted in Figure 3.4, FRT and tranexamic acid were administered in 73% of the subjects, tranexamic acid alone was administered in 15% of the subjects, and only 12% received no FRT and/or tranexamic acid. Administration of FRT and/or tranexamic acid administration in the different dental procedures is depicted in Figure 3.5. Replacement therapy and tranexamic acid administration was observed in all the patients that had undergone extractions, and in 3 patients that had restorative procedures, and in 1 patient that had undergone extirpation. Factor replacement therapy and/or tranexamic acid administration amongst this population was further categorised according to severity as depicted in Figure 3.6. Four subjects who had extractions were mild bleeding phenotype, 2 were moderate bleeding phenotype, 12 had severe bleeding phenotype, and 1 case was not specified. Out of the subjects that had undergone restorative procedures 1 was moderate bleeding phenotype and 2 had severe disease, and only moderate bleeding phenotype had undergone extirpation and restorative procedure. Tranexamic acid was administered orally to 1 subject with unknown severity prior to periodontal probing and plaque control (scaling and polishing), and to 1 subject with unknown severity prior to scaling and polishing, and in 3 moderate bleeding phenotype subjects that had under restorative procedures excluding endodontic procedures. The use of tranexamic acid was categorised according to severity was depicted in Figure 3.7. There were subjects who did not receive FRT or tranexamic acid, these included 1 severe and 2 moderate subjects who had undergone scaling and polishing, and 1 severe subject that had undergone fissure sealant placement (on 4 teeth). FRT was administered to 1 moderate subject who had scaling and polishing with full mouth debridement (root planing) done.

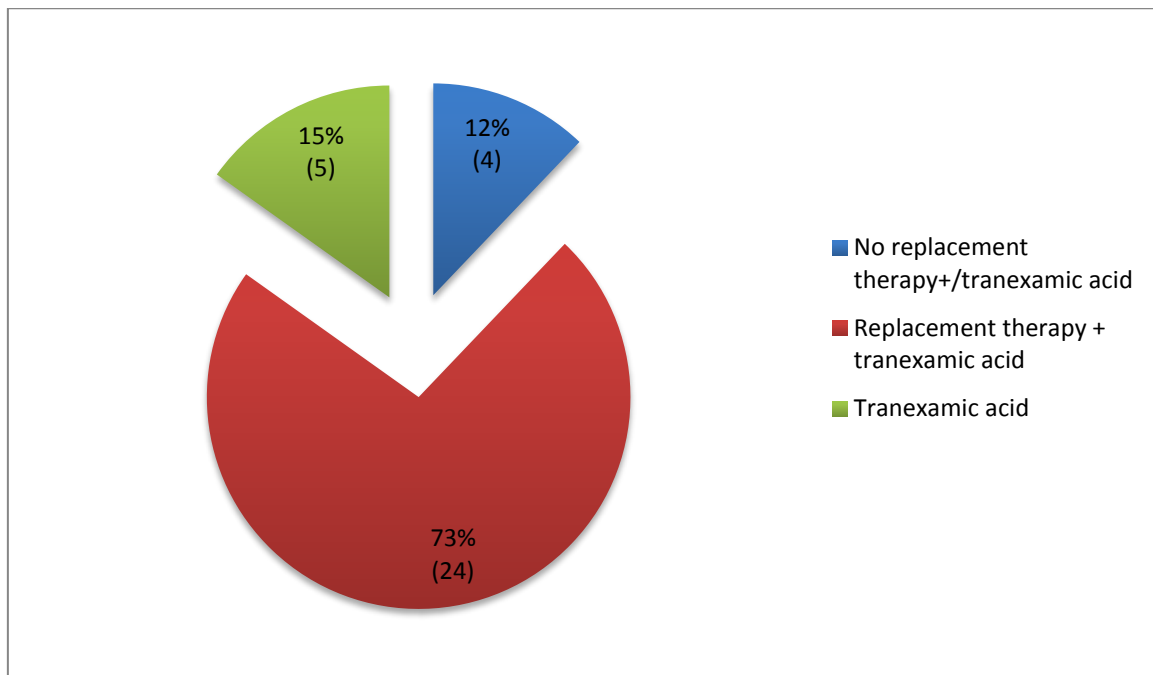


Figure 3.4 Use of factor replacement therapy and antifibrinolytics

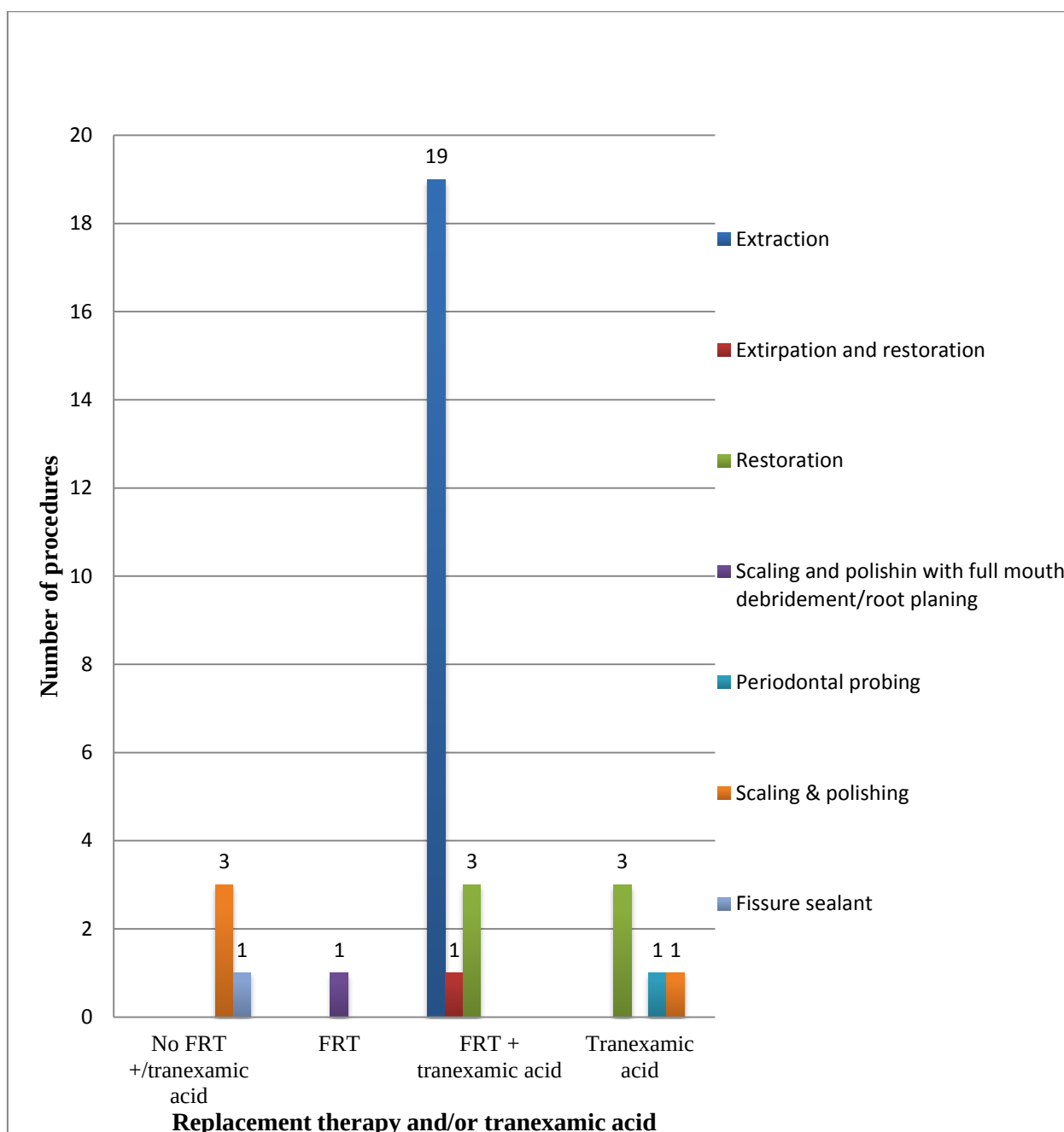


Figure 3.5 Use of replacement therapy and/or tranexamic acid categorised according to dental procedure

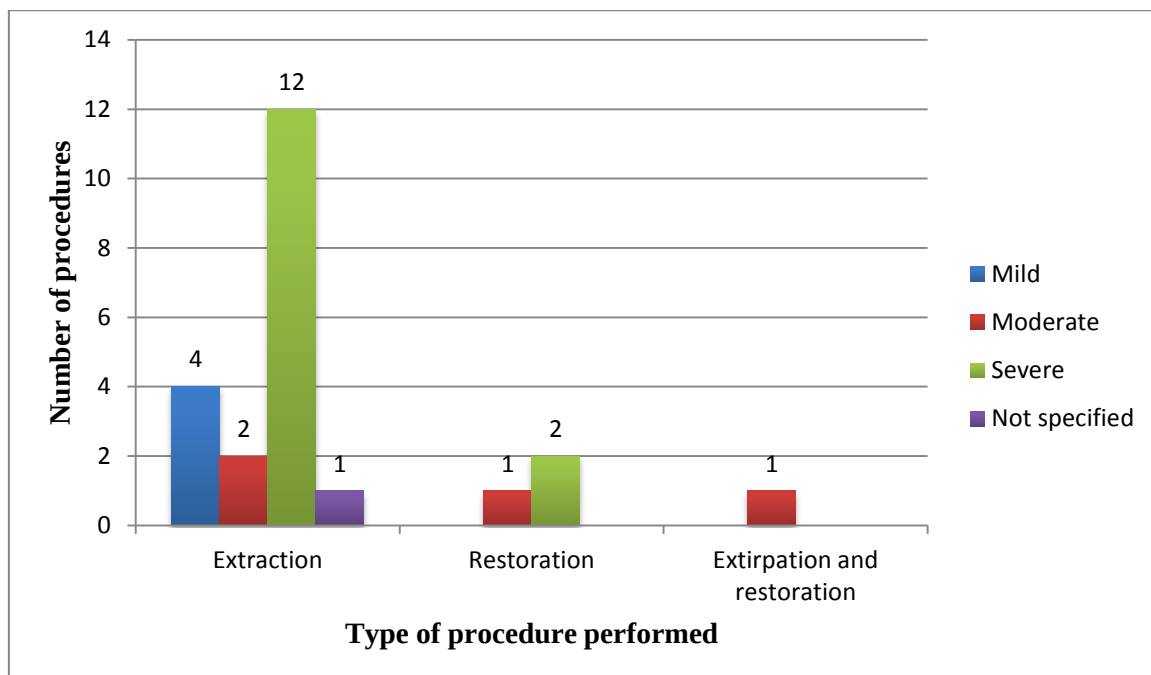


Figure 3.6 Use of replacement therapy and tranexamic acid categorised according to severity and procedure

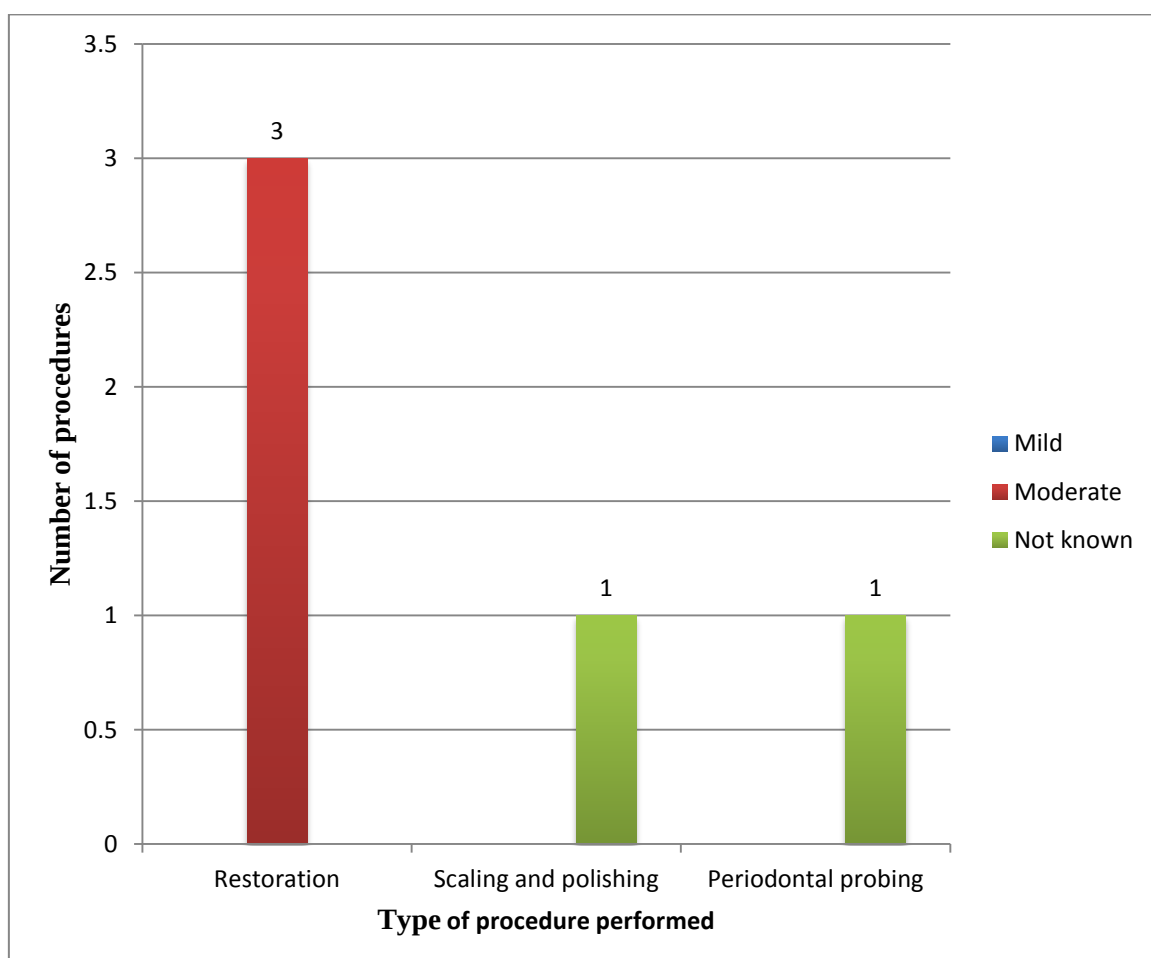


Figure 3.7 Use of tranexamic acid categorised according to severity and procedure

Table 3.2 Haemostatic protocol for FVIII and FIX deficiency

Period and agent used	Dose
Day before the procedure Tranexamic acid	15-25 mg/kg body weight PO 8 hourly
30 minutes to 1 hour prior to procedure FVIII or FIX and Tranexamic acid	80-100 IU/kg body weight IV bolus 15-25 mg/kg in 50 ml normal saline IV to run over 30 minutes
6/24 hours after procedure FVIII	50 IU/kg body weight IV bolus
Day after the procedure Tranexamic acid	15-25 mg/kg body weight PO 8 hourly for 4 days
FVIII or FIX	50 IU/kg repeated if the patient bleeds

Table 3.3 DDAVP protocol

Agent used	Dose
DDAVP	300 µg/kg added to 50 ml normal saline IV over 30 minutes
Tranexamic acid	15-25 mg/kg in 50 ml normal saline IV prior to procedure
Tranexamic acid	15-25 mg/kg in 50 ml normal saline PO 8 hourly for 5 days

Table 3.4 Haemostatic protocol for FV deficiency

Agent used	Dose
Bioplasma	4 bottles IV 1 hour before the procedure
Tranexamic acid	15-25 mg/kg PO 8 hourly starting a day before the procedure for 5 days

3.4 The type of anaesthesia used

The type of anaesthesia used is depicted in Figure 3.8; 70% of the dental procedures were performed under LA, while only 30% were performed under GA. The procedures performed under GA were extractions only.

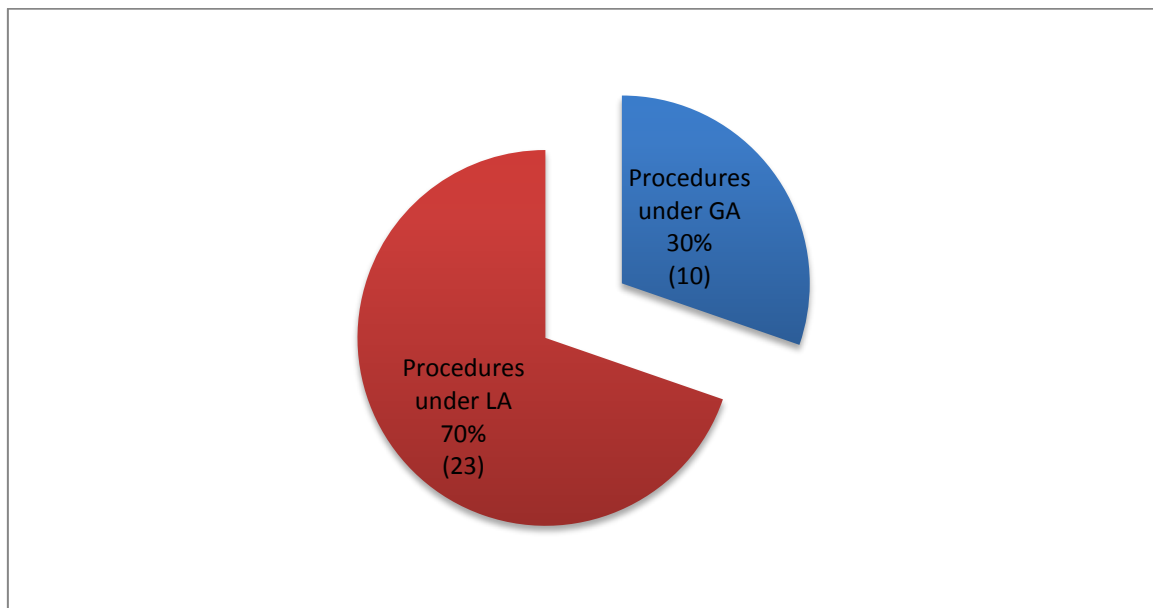


Figure 3.8 Type of anaesthesia used in dental procedures

3.5 Dental extractions

According to verifiable records, a total of 74 teeth were extracted during the period of 2000 and 2015, as depicted in Table 3.5. The average age of IBD subjects that had extractions was 17, and the average number of teeth extracted per subject was 4. A total of 61 teeth were extracted under general anaesthesia and 13 teeth were extracted under local anaesthesia. The mean average age of subjects who had extractions under general anaesthesia was 9, and 27 under local anaesthesia. The mean average number of teeth extracted under general and local anaesthesia was 1 and 6 respectively.

Table 3.5 Dental extraction in IBD patients

Variable	Number of teeth or age in years
Total number of extracted teeth	74
Average of teeth extracted (range)	4 (1-14)
Median	3
Mean age (range)	17 (3-60)
Teeth extracted under GA	61
Mean of teeth extracted under GA (range)	6 (3-14)
Median of teeth extracted under GA	5
Mean age (range)	9 (3-21)
Teeth extracted under LA	13
Mean teeth extracted under LA (range)	1 (1-4)
Median of teeth extracted under LA	1
Mean age (range)	27 (4-60)

3.6 The use of local haemostatic agents

The use of local haemostatic agent was seen only in the subjects that had undergone extractions, this is depicted in Figure 3.9. The use of local haemostatic agent was not specified in 58% of the subjects. The combination of surgicel and suture usage was in 16% of the subjects, and the use of suture alone was seen in 5% of the subjects, whilst the combination of suture, surgicel and tranexamic acid gauze compression was seen in 5%. The combination of suture, surgicel and tranexamic acid swish and swallow was seen in 5%, and tranexamic acid as a swish and swallow was seen in 11% of the subjects.

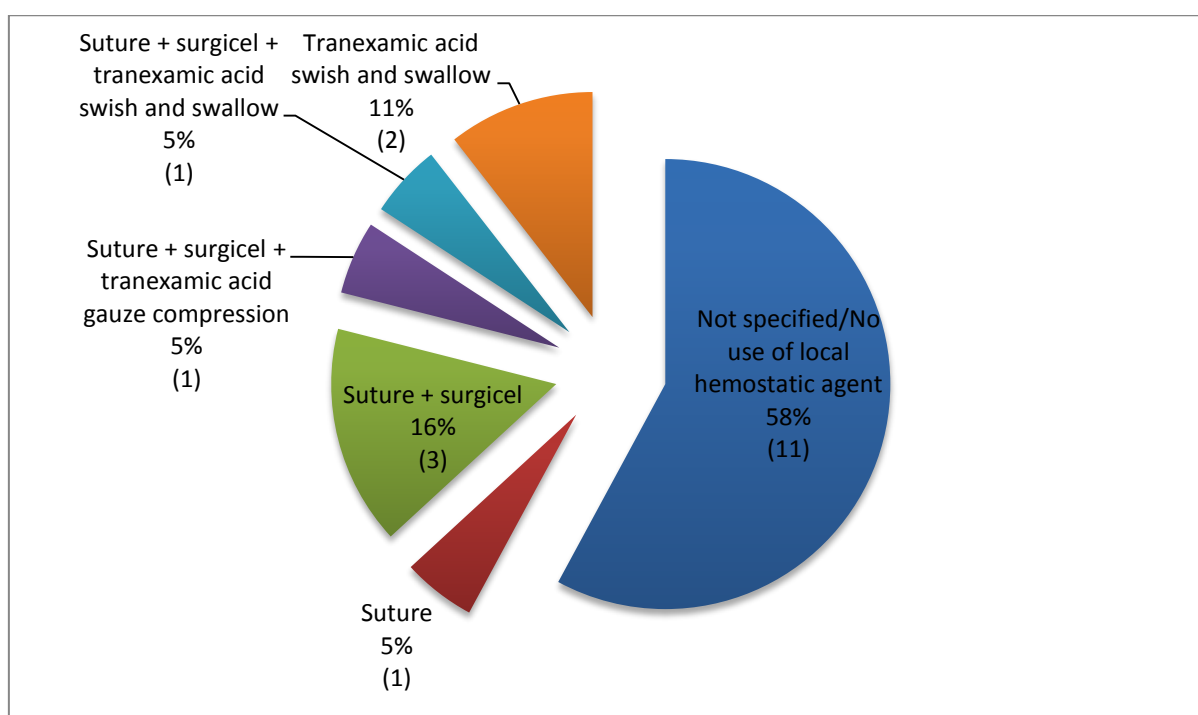


Figure 3.9 Use of local haemostatic agents in IBD patients

3.6 Post-operative bleeding

Post-operative bleeding was seen only in patients who had undergone extraction. Post-extraction bleeding complications was observed in only 3 subjects, of which 2 were severe HA patients and 1 was a mild VWD patient as depicted in Table 3.3. In 1 of the subjects with severe HA the bleeding was observed 17 days post-extraction of 1 tooth and the use of suture and surgicel. The management of this subject comprised of FRT and tranexamic acid IV administration, and tranexamic acid was prescribed as a mouthwash and for oral intake. The use of local haemostatic agents was not recorded in the 2 subjects with post-extraction bleeding. A severe HA patient had extraction of 8 teeth under GA and experienced bleeding 9 days post-extraction. The patient was managed with FRT and tranexamic acid IV administration, and tranexamic acid was prescribed for oral intake. The mild VWD subject had bleeding 2 days post-extraction of 6 teeth under GA, and was managed by tranexamic acid per oral. The amount of bleeding for each was not recorded, and therefore could not be evaluated and reported.

Table 3.6: Post-extraction bleeding complications

Diagnosis	Local Haemostatic agent	Dental procedure	Start of bleeding	Treatment
Severe HA	Suture and surgical	Extraction 1 tooth under LA	17 days post procedure	FRT and tranexamic acid IV + tranexamic acid PO + tranexamic acid mouthwash
Severe HA	None	Extraction 8 teeth under GA	9 days post procedure	FRT + tranexamic acid IV + tranexamic acid PO
Mild VWD	None	Extraction 6 teeth under GA	2 days post procedure	Tranexamic acid PO

CHAPTER 4: Discussion and Conclusion

4.1 Study limitations

This was a retrospective review study which lends itself to all the limitations of this type of studies. The lack of complete data in the hospital records meant that a large number of patients were excluded from the study. The study focused exclusively on patients attending the CMJAH HCCC which also looks after a large number (35% of total patient population) of patients with medical aid and therefore accessing dental care outside the CMJAH. These patients were not included in the study. Finally, this study raised an important question of poor liaison between the HCCC and WHOC at the CMJAH.

4.2 Discussion and Recommendation

The public oral health service in South Africa has been described as palliative and demand-driven, and it lacks a structured budget and operational concepts. There is also a critical shortage of oral health professionals. This leads to delivery of limited dental procedures, the main focus being extractions.⁴³

A study conducted by Mickenautsch *et al.* in Gauteng province in South Africa revealed that extractions were the predominant treatment provided in the public sector compared to restorative procedures. This was attributed to lack of resources and a high load of patients on a daily basis.⁴³

This service delivery observation is reflected in this study where dental extraction was the most common performed procedure, while the placement of fissure sealant, and polishing were the least commonly performed procedures. The mean average age of subjects that had undergone extractions was 17 years, while the mean average number of teeth extracted per subject was 4. This calls for concern as this means that there is premature loss of teeth, and this impacts on the quality of life.

A report on oral health services by the World Health Organization (WHO) stated that oral health services in Western industrialized countries comprise preventive and curative services and are available to the population. The report also states that many countries in Africa, Asia

and Latin-America the majority of services is limited to pain relief or emergency care. One of the challenges that was highlighted was the shortage of oral health personnel.⁴⁴

Dental intervention and promotion of oral health is essential from the early stages of life in order to maintain optimal oral health. The absence of this results in a lifetime of oral health problems.⁴⁵ IBD patients are mostly diagnosed at a very early age, and should therefore be placed in the preventive program from the early stages of development. This would then reduce the need for future invasive procedures. One of our challenges as dental practitioners is trying to alter the oral hygiene practices of adults. If professionals initiate proper oral hygiene education early then we may avoid such challenges in the future.

Fissure sealant application is recommended as an effective adjunct to other caries preventive procedures. They are placed to prevent caries initiation and to also arrest caries progression.^{46,47,48} A study done in Hammanskraal, an area in Gauteng Province of South Africa, revealed a 75,2% caries reduction amongst 15 year-old children who were treated twice with fissure sealants over a seven year period. These children were also exposed to high levels of fluoride.⁴⁶

If there will be an attempt to implement preventive and supportive oral program it would be wise to first know and understand what factors contribute to the current state in terms of dental procedures.⁴³ It is possible that the factors might be similar to those mentioned in the study by Mickenautsch *et al.* There needs to be an assessment of access to dental care by IBD patients, as this too may be a factor.⁴³

The use of replacement therapy alone and in combination with tranexamic acid was observed among the subjects that had undergone extractions, full mouth root debridement (root planing) and scaling and polishing, restorative, and endodontic procedures. According to the published protocols extractions and root debridement are considered as invasive procedure that are associated with high risk of bleeding, and therefore require replacement therapy to be administered 30 minutes to 1 hour before the procedure. Restorative and endodontic procedures are associated with low risk of bleeding, and therefore do not require replacement therapy administration. This means that the protocol observed for the extractions and root debridement (root planing) correlated with the published protocols, whilst the protocol observed for the restorative and endodontic procedure did not correspond with the published protocols. Therefore the recommendation is that replacement therapy to be administered only in invasive procedures that carry a high risk of bleeding, and not for restorative and endodontic procedures.^{8,33}

No replacement therapy or tranexamic acid was administered in subjects that had undergone scaling and polishing, and fissure sealants. This practice is in keeping with the published protocols.

The use of replacement therapy in conjunction with TA or an antifibrinolytic agent, as observed in this study, has been described and is supported by literature. Prior to the introduction of viral inactivated plasma derived factor concentrates the aim in the management of patients with IBD was to reduce the amounts of blood products used wherever it was safe to do so. In achieving this goal, clotting supplies would be conserved and the possibility of transmitting viral infections would be minimized. Based on this Walsh *et al.*⁴⁹ conducted a study and used replacement therapy in conjunction with EACA, a plasminogen activation inhibitor, in a group undergoing extractions. This was done in order to impede clot lysis. EACA was administered IV prior to and post-extraction followed by oral administration 4 times daily for 10 days. The conclusion was that EACA in conjunction with replacement therapy was effective in the management of dental extractions in patients with IBDs and that the frequency and administration of concentrates and the total quantity used could be reduced drastically.⁴⁹ Recombinant factor replacement reduces the risk of transmitting blood borne infections, but it is expensive. Development of antibodies to factor therapy is also another challenge. Based on this we can still benefit from the study by Walsh *et al.*⁴⁹ Replacement therapy in combination with antifibrinolytic therapy is more effective in reducing blood loss than the use of FRT alone.^{8, 49}

In this study sixty one teeth were extracted under GA, with the mean average number of teeth per subject being 6 and the average age being 9 years. According to the published protocols GA should be avoided as they can trigger laryngeal haematoma which can lead to upper airway obstruction.^{36,37} Local anaesthesia when compared to general anaesthesia poses the risk of bleeding at the surgical site, and this can be controlled using local haemostasis.³⁶ The recommendation is that alternatives to GA to be explored, these being anxiolytic agents and appropriate sedation.²³

Local anaesthesia containing a vasoconstrictor reduces the bleeding during the procedure and also promotes local haemostasis.³⁷ The type of LA and technique used could not be reported on this study due to the information not being included in the patients' files.

According to the literature, extraction or any other dental surgical procedures should be modified to minimize intra-operative and postoperative bleeding, this is achieved by limiting trauma, reducing flap size in the case of surgical procedure, and using local haemostatic

agents.³³ Topical or local haemostatic agents promote haemostasis by stopping the bleeding either mechanically or by augmentation of the coagulation cascade. These agents and their metabolic breakdown products are safe for the body. Locally active haemostatic agents increase the rate of vasoconstriction, seal blood vessels or vascular channels, or promote platelet aggregation.⁵⁰ The use of local haemostasis is very beneficial in reducing the risk of postoperative bleeding, and therefore should not be neglected.^{8,51,52} In this study the use of local haemostatic agents was observed only in subjects who had extractions, meaning that local haemostatic agents were not used in other dental procedures including root debridement (root planing), and scaling and polishing. Local haemostatic agents were used in only 42% of the subjects that had extractions.

There is high fibrinolytic activity in the oral mucosa due to saliva and local t-PA production. Thus it is important to use local haemostatic agent to inhibit this fibrinolytic activity.² A study done by Sindet-Pedersen revealed that after TA had been used as a mouthwash (10 mL of a 5% aqueous tranexamic acid solution for 2 minutes) the concentration of TA in saliva were very high, above 200 micrograms per milliliter after 30 minutes, and it remained at a therapeutic level for more than 2 hours.⁵³ When TA is administered per oral (1 gram of tranexamic acid) no saliva samples had TA at detectable levels. This means that the fibrinolytic activity in the oral cavity can only be inhibited by local administration of an antifibrinolytic agent.⁵³ In this study TA was used postoperatively as a swish and swallow alone in 11% of the subjects who had extractions, and in conjunction with suture and surgical in 5% of the subjects who had extractions. The use of TA as mouthwash has been described as being effective in controlling bleeding in subjects who had scaling and polishing.²⁰

To make up a 5% mouthwash solution 500 mg of TA could be crushed and dissolved in 10ml water. TA mouthwash should be swilled in the mouth for 2-3 minutes and either swallowed or expelled, preferably in children it should be expelled to avoid exceeding the recommended dose. This is done at least 30 minutes before the procedure, and continued 6 hourly for 7-10 days.⁸ 2 ampoules of 500 mg of TA can be used to irrigate the socket or surgical site prior to suturing.⁵²

Franchon *et al.* described another approach to managing the extraction or surgical site. The extraction or surgical site is cleansed, and a combination of fibrinogen-based biological glue and calcium thrombin is inserted.³⁷ This is followed by insertion of a resorbable gelatin packing, and the packing is then covered with a layer of biological glue. Resorbable sutures

are placed and also covered with a layer of biological glue. The intermittent TA compressions are applied after the procedure and for the first few days after the procedure.³⁷

The recommendation is that local haemostatic agents should be used as described in the literature, and for protocol to be put in place for extraction or surgical site management. This would then ensure uniformity in the management of the sites.

Post-extraction bleeding was observed in 3 subjects, only 1 of these subjects had local haemostatic agent applied. Even with careful preoperative planning post-extraction bleeding may occasionally be seen, in this study post-extraction bleeding was observed also in an individual who had administration of local haemostatic agents.²⁰ We may attribute the post-extraction bleeding to lack of local haemostatic agents with regards to those subjects who received none, and other factors such as lack of home care or patients not following postoperative instructions may also play a role.³⁶ Management of post-extraction bleeding include administration of additional systemic haemostatic therapy, repeated local compression, and use of a local anaesthetic containing a vasoconstrictor.^{27,37} The protocols for the management of post-operative bleeding correlate with those published.

4.3 Conclusion

All IBD patients should be seen on a regular basis for general dental assessment and to develop a personalized comprehensive dental management plan. This would aid in eliminating dental caries related bleeding and obviate the need for future invasive procedures. When invasive dental procedures in IBD patients need to be performed the approach should be to provide optimal haemostatic care, and it is important to plan for treatment in conjunction with a haematologist or the treating haemophilia centre.

Most of the protocols for the dental management of IBD patients observed in this study are similar to those that are used and published internationally. There is however room for improvement. Some of the recommended improvements include more use of preventive and supportive dental procedures. The use of replacement therapy in procedures with low risk of bleeding should not continue. The deficiency in the use of local haemostatic agents should be corrected, and thus a standard protocol should be in place for all invasive procedures. There should be less use of GA. Also requiring attention is the implementation of standard protocol for management of extraction site. If the goal is to implement an effective preventive and supportive oral program for IBD patients then more insight is required to understand the factors contributing to the current state of dental management of IBD patients prior to

implementation of these measures. A standard protocol for the dental management of IBD patients needs to be discussed and put in place in CMJAH WOHC to ensure uniform practice by clinicians in the management of IBD patients, and to align the practice to internationally accepted norms.

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APPENDIX A:

Ethics Clearance Certificate



R14/49 Dr Sibongile Priscilla Mahlangu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M150425

NAME: Dr Sibongile Priscilla Mahlangu
(Principal Investigator)

DEPARTMENT: Oral Medicine and Periodontology
Charlotte Maxeke Johannesburg Academic Hospital
Haemophilia Comprehensive Care Centre
University of Witwatersrand Oral Health

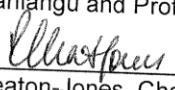
PROJECT TITLE: An Audit Postoperative Bleeding Disorders in
Academic Hospital the Haematology Unit, at the Charlotte Maxeke Johannesburg

DATE CONSIDERED: 24/04/2015

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Johnny Mahlangu and Prof Sindisiwe Shangase

APPROVED BY: 
Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 12/06/2015

APPENDIX B

Approval from Charlotte Maxeke Johannesburg Academic Hospital



GAUTENG PROVINCE

HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Fax: (011) 488-3753
15 May 2015

Dr. S. Mahlangu
CMJAH

Dear: Dr. Mahlangu

RE: An audit of dental procedures in patients with inherited bleeding disorders at Charlotte Maxeke Johannesburg Academic Hospital Haematology unit.

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

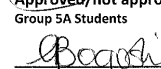
Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office this office with the results of your study on completion of the research.

~~Supported/not supported~~


Dr. M.I. Mofokeng
Clinical Director
DATE: 18/05/2015

~~Approved/not approved~~
Group 5A Students


Ms. G. Bogoshi
Chief Executive Officer
DATE: 20/05/2015

APPENDIX C

Approval from the School of Oral Health Science



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

WITS ORAL HEALTH CENTRE

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9 September 2015

Dr S Mahlangu
School of Oral Health Sciences
University of the Witwatersrand
Johannesburg

REGARDING: "An audit of dental procedures in patients with inherited bleeding disorders at Charlotte Maxeke Johannesburg Academic Hospital Haematology unit"

REFERENCE: IIREC/SEPT2015/04

It is my pleasure to grant final approval access Wits Oral Health Centre Patient records in order to conduct your research with the above title. The Hospital Research and Ethics Committee allocated a unique reference number to this application – Kindly quote this reference number in all future correspondence regarding this research topic.

Please note that the Hospital Research and Ethics Committee should be informed of the estimated date the research will commence, as well as regular status reports until the research have been concluded. Within a month after conclusion of the research project, a written report must be submitted to the Head of School / CEO, summarizing the final results / outcome as well as recommendations made based on the research conducted.

Regards,


Prof P Hlongwa
CEO/Head of School

APPENDIX D

Data Collection Sheet

Study number	Bleeding disorder	Severity	Gender	Age	Race	Dental procedure	Number of teeth	Replacement Therapy	Cyclokapron PO	Anaesthesia: GA/LA	Type of Local Anaesthetic	Local Haemostatic agent	Prescribed medication

APPENDIX E

Delayed bleeding post-dental procedure

Study Number	Bleeding disorder	Severity	Bleeding disorder known or reported to the dentist	Systemic treatment or Factor Replacement therapy	Dental Procedure	Number of teeth (tooth number)	Local Haemostatic Agent	Onset of bleeding	Management of post-operative bleeding	Days of hospitalization