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# Special Care Dentistry: Part 2. Dental Management of Patients with Drug-Related Acquired Bleeding Disorders

**Abstract:** The first of this series of three articles discussed the dental management of patients with inherited bleeding disorders. This paper will discuss and outline the dental management of patients with acquired bleeding disorders that can result from drug therapy. These may be associated with vascular defects, platelet defects or coagulation defects.

In an age when people are living longer, and medical interventions are continually becoming more advanced, clinicians will need to be aware of systemic disorders and treatments that may cause complications in the dental setting. According to National Statistics,<sup>1</sup> the UK population is projected to increase by 0.7% by 2016. This trend is shared with other European countries which also have ageing populations. The proportion of people aged over 65 is predicted to increase from 16% in 2006 to 22% in 2031.

**Clinical Relevance:** Being able to recognize which drugs may cause bleeding problems at an early stage will lead to good patient management, particularly in planning and delivering treatment following invasive procedures such as dental extractions. Whilst most patients can be successfully treated in general dental practice, the clinician may need to make a decision on whether or not to refer a patient to specialist services for all dental treatment, or to share care between primary care and specialist services for selected procedures.

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## Bleeding tendencies

As discussed in part 1, primary haemostasis is achieved by a platelet plug occluding the wound after blood vessel damage, and is mediated by interactions between platelets, coagulation factors

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and the vessel wall. Bleeding disorders can therefore arise as a result of a defect in vessels, platelets or the coagulation pathway and can be congenital or acquired. This paper will concentrate on acquired bleeding disorders.

Several hours of minor post-operative bleeding following dental extractions may be of little concern and usually managed using post-operative local measures. Prolonged bleeding could be defined as that which:

- Continues beyond 12 hours;
- Causes the patient to return to the dental surgery or to the Accident and Emergency Department;
- Results in the development of a large haematoma or ecchymosis within the oral soft tissues; or
- Requires a transfusion.

Features that might be noticed during extra-oral examination include:

- **Purpura** – This is discoloration that occurs in the skin or mucous membranes due to haemorrhage from small blood vessels and measures 0.3–1 cm and does not blanch on applying pressure.
- **Petechiae** – These are small purpuric lesions which measure up to 2 mm. They are usually associated with an underlying acquired disorder of platelets or coagulation and are commonly seen in children or older people as a result of injury, trauma, ageing skin or bacterial infections.<sup>2</sup>

Special tests for patients with bleeding disorders have been discussed in part 1. For acquired bleeding disorders, the Prothrombin Time (PT) is particularly valuable, especially when investigating bleeding tendencies for patients on

anticoagulant medication. It is derived from measures of prothrombin ratio and the International Normalized Ratio (INR), which measures the extrinsic pathway of coagulation. It is used to determine the clotting ability in patients on warfarin or patients with liver damage. The reference range of PT is usually 12–15 seconds. The normal range for INR is approximately 0.8–1.2. The PT measures factors II, V, VII and X as well as fibrinogen. It is used in conjunction with APTT.<sup>3</sup>

Acquired bleeding disorders can result from the use of the following drug therapy and each will be considered in turn:

- Antiplatelet drugs;
- Anticoagulants;
- Cortocosteroids; and
- Chemotherapy.

### Antiplatelet drugs

There is strong evidence from clinical trials which indicate the beneficial effects of antiplatelet therapy in patients with ischaemic heart disease.<sup>4</sup> There are many steps involved in platelet activation; all ultimately lead to platelet aggregation and subsequent thrombus formation via the clotting cascade.

The major role of antiplatelet drugs is to prevent thrombosis formation in atherosclerotic arteries leading to major complications such as ischaemic heart disease, stroke, intermittent claudication in limbs, and heart failure.

Several mediators lead to activation and subsequent aggregation of platelets. Binding of fibrinogen to the platelet surface receptor glycoprotein IIb/IIIa represents the final common pathway of platelet aggregation. Antiplatelet agents inhibit platelet aggregation by blocking specific pathways of platelet activation.

The most commonly used antiplatelet drugs are listed in Table 1.

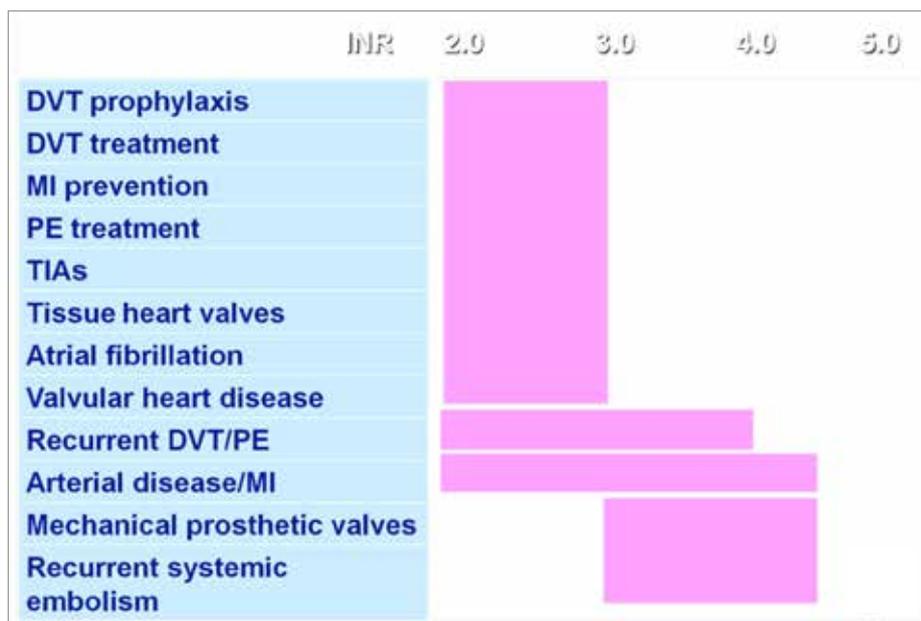
### Non-steroidal anti-inflammatory drugs (NSAIDs)

Aspirin prevents thrombus formation by irreversibly inhibiting cyclo-oxygenase 1 in platelets, therefore preventing the formation of

Thromboxane A<sub>2</sub>, a potent vasoconstrictor and platelet aggregant. Its effects can last for the lifespan of the platelet, which is 7–10 days, but recovery of platelet aggregation can occur by day 4 in 80% of cases.<sup>5</sup> Aspirin has a cumulative effect so that thromboxane formation is maximally inhibited by more than 95% after 4–5 days. Therefore aspirin has an effect on platelet function but not platelet count. Prolonged usage will have a greater effect.<sup>6</sup>

Aspirin is usually prescribed as an oral dose of 75–300 mg daily. Indications for its use include: prevention of thrombotic cardiovascular or cerebrovascular disease; and following coronary artery bypass surgery. It is important to note that many people take low dose aspirin prophylactically, even though it has not been prescribed to them.

Other NSAIDs, such as Ibuprofen and Diclofenac have a reversible effect on platelet aggregation and function, therefore



**Figure 1:** Indications for warfarin use and therapeutic range for each condition. DVT – Deep vein thrombosis; MI – myocardial infarct; PE – pulmonary embolism; TIA – transient ischaemic attack.

Antiplatelet drug	Action
Aspirin	Irreversibly inhibits cyclo-oxygenase pathway Duration of action 8–10 days
Other NSAIDs	Reversible effect on platelet aggregation
Clopidogrel	Inhibition of adenosine diphosphate so reducing platelet activation
Dipyradamole	Inhibits phosphodiesterase and inactivates cAMP
Fibrinogen receptor inhibitors	Glycoprotein IIb/IIIa inhibitors, block final common pathway for platelet aggregation

**Table 1.** Commonly prescribed antiplatelet drugs.

its effects last as long as the half life of the drug. They are not used clinically for their antiplatelet action.

#### Clopidogrel (Plavix)

Clopidogrel (Plavix) irreversibly inhibits platelet activity by disrupting platelet aggregation through inhibition of adenosine diphosphate within 2 hours of ingestion. It is metabolized in the liver to active compounds which bind to adenosine phosphate (ADP) receptors on platelets and this significantly reduces platelet activation.

Like aspirin, Clopidogrel is used for the prevention of athero-thrombotic events in patients who suffer with myocardial infarction, ischaemic stroke or in peripheral arterial disease with a reduced risk of gastro-intestinal bleeding. It can be used in conjunction with aspirin (synergistic activity) for unstable angina and after the insertion of a coronary artery stent, although this is an unlicensed indication.<sup>7</sup>

It is used as an adjunct to oral anticoagulation for prophylaxis of thrombo-embolism associated with prosthetic heart valves. Modified release preparations can be used for secondary prevention of ischaemic stroke and transient ischaemic attacks. It can also be used in conjunction with low dose aspirin for occlusive vascular events in those who have had a previous stroke.

These drugs can have some effect on APTT and therefore post-operative bleeding. On cessation, platelet function recovers fully after 2 days.

#### Dental considerations

Patients on single drug antiplatelet medication can be dentally managed using local measures when teeth are extracted (Table 2).

According to UKMI guidelines,<sup>7</sup> patients taking antiplatelet medication with the following medical problems should be referred to a specialist service/secondary care.<sup>8</sup>

- Dual antiplatelet therapy;
- Liver impairment and/or alcoholism;
- Renal failure;
- Thrombocytopenia or other haemostasis disorders;
- Patients receiving a course of

cytotoxic medication.

These patients have an increased tendency for prolonged bleeding which will be discussed later in this paper and in paper 3.

### Anticoagulants

The most commonly used anticoagulants are coumarins which include warfarin, followed by heparin. Their uses vary widely (Figure 1) but they are used most frequently for the prevention and treatment of thrombo-embolism.

#### Warfarin

Warfarin is the most commonly used coumarin oral anticoagulant and has been approved for use since the 1950s. The British Heart Foundation<sup>9</sup> estimates that there are 60,000 people in the UK on warfarin, that's approximately 0.1% of the UK population. It was initially marketed as a pesticide against rodents and is still used for this purpose. It is a synthetic derivative of coumarin, a chemical which is naturally found in plants. It is termed as a vitamin K antagonist as it inhibits biosynthesis of vitamin K dependent coagulation proteins VII, IX, X and II (prothrombin). Therefore, it inhibits coagulation and prolongs both prothrombin time (PT) and activated partial thromboplastin time (APTT).

Effects begin in 8–12 hours, persist for 72 hours, with maximal effect at 36 hours. The activity of warfarin is expressed using the international normalized ratio (INR), which is the PT ratio. For an individual not taking warfarin, the INR would be 1.0. Warfarin is reversed by the administration of vitamin K.

One of its main shortcomings is that it interacts with many foods and drugs, necessitating frequent blood monitoring each month. Metabolism varies greatly between patients.

Examples of drugs that can interact with warfarin are:

- Antibiotics – especially erythromycin, tetracycline, metronidazole;
- Antifungals – especially miconazole, ketoconazole, fluconazole;
- Analgesics – especially aspirin and NSAIDs;

- Antidiabetic drugs – especially Chlorpropamide;
- Antiepileptic drugs – especially Phenytoin;
- Homeopathic medications such as St John's Wort (Table 3);
- Some foods such as grapefruit juice.

Highly protein-bound drugs can displace warfarin from serum albumin and can cause an increase in INR.<sup>10</sup> This is true with statin drugs such as Simvastatin, aspirin and NSAIDs.

Antibiotics such as metronidazole, and especially macrolides such as erythromycin, potentiate the effect of warfarin by decreasing its metabolism. Some broad spectrum antibiotics can decrease the amount of bacterial flora in the gut, increasing vitamin K absorption and hence decreasing the effect of warfarin. Certain foods, such as green leafy vegetables, reduce the effect of warfarin as they contain vitamin K. Foods such as grapefruit juice can increase the effect of warfarin owing to inhibition of the liver enzyme cytochrome p450.

Hyperthyroidism which is not well controlled can also increase the effect of warfarin. The proposed mechanism seems to be the change in metabolism rate of clotting factors and warfarin.<sup>11</sup>

Herbal interactions should also be considered. Patients taking herbal medications that are known to interfere with coagulation (Table 3) should be advised to stop them two weeks prior to an invasive dental procedure.<sup>12</sup>

#### Dental considerations

Discontinuing warfarin for a few days prior to dental surgery is no longer recommended as this increases the risk of thrombo-embolic events.<sup>13</sup>

Risk of thrombo-embolism to patients taking warfarin for atrial fibrillation is 1.4% per year, whereas the risk of thrombo-embolism for the same group of patients not on warfarin is 5% per year.<sup>14</sup>

A study by Wahl looked at 950 patients who had 2400 invasive dental procedures, without stopping warfarin, and found the incidence of post-operative bleeding requiring intervention to be 1.4%. The same study looked at 526 patients who stopped warfarin, of which 5

suffered embolic complications and 4 died.<sup>15</sup>

A chart produced by the National Patient Safety Agency,<sup>16</sup> British Dental Association<sup>17</sup> and British Society for Haematology,<sup>18</sup> and summarized by UKMI,<sup>19</sup> advises that, if a patient on warfarin has an INR of 4.0 or below, dental treatment can be carried out without altering his/her anticoagulant regime. If a patient has an INR above this, a consultation is required with the patient's clinician responsible for the anticoagulation, who can then adjust the warfarin if needed. Any patients with an erratic or fluctuant INR may need to be referred to a dental hospital.

Minor surgical procedures include extractions of up to 3 teeth at a time, crown and bridge work, gingival surgery, and dental scaling. Local anaesthetic regional block injections may also be a bleeding hazard.<sup>20</sup>

The INR should be measured ideally within 24 hours of procedure, but for patients with a stable INR, it can be measured within 72 hours. The timing of the procedure should be considered and planned ideally in the morning and at the beginning of the week so as to allow more time to deal with delayed bleeding episodes.

Local haemostatic measures should always be used where possible (Table 2).

#### Heparin

Heparin is a natural sulphated glycosaminoglycan found in mast cells. It is a catalyst for plasma antithrombin III (ATIII) which regulates coagulation by inactivating activated coagulation proteases such as thrombin and factor Xa, and also decreases platelet aggregation<sup>21</sup> (Table 4).

Some heparins are used for immunosuppression effects.<sup>22</sup> Heparin is given intravenously or subcutaneously. The dose is adjusted in accordance with APTT levels. Heparin is available as standard unfractionated heparin or low molecular weight (LMW) heparin. Standard heparin has a half life of 1–2 hours and can be monitored by APTT (activated partial thromboplastin time – see paper 1 for definitions). Any effects on clotting are lost within 6 hours of stopping heparin, therefore it is important to schedule dental procedures which may induce bleeding

after the effects of heparin have worn off.<sup>20</sup>

Withdrawal of heparin is usually adequate to reverse its anticoagulation effects. Low molecular weight (LMW) heparins, such as Certoparin, Dalteparin, Enoxaprin, Riviparin and Tinzaparin, interact mostly with factor Xa. They have a longer half life of 2–4 hours and do not routinely affect standard blood results like APTT. Their main uses are for:

- Long-term outpatient prophylaxis for pregnancy;
- Patients intolerant to warfarin;
- Prophylaxis for patients with lupus anticoagulant factor.

Newer oral anticoagulants, such as Dabigatran, Rivaroxaban and Apixaban are being trialled and are gaining popularity as successors to warfarin. These drugs also act mainly on

factor Xa but have the obvious advantage of oral administration as opposed to parenteral.<sup>23</sup>

These drugs, like the LMW heparins, do not affect standard blood results and so may pose difficulties in assessing bleeding tendencies prior to invasive dental procedures. Liaison with the patient's haematologist is advisable. Development of clear guidelines is needed to aid management of patients on these newer drugs that require invasive dental procedures.

#### Dental considerations

As heparin has a shorter half life than warfarin, patients receiving heparin can usually be scheduled for simple dental extractions the day after its administration. All local measures described (Table 2) should be taken. Consultation with the patient's haematologist or general

<p><b>1. Local Anaesthetic</b></p> <ul style="list-style-type: none"> <li>■ Use local anaesthetic with a vasoconstrictor;</li> <li>■ Avoid regional nerve blocks where possible. If necessary, then ensure an aspirating syringe is always used.<sup>26</sup></li> </ul>
<p><b>2. Minimize Trauma</b></p> <ul style="list-style-type: none"> <li>■ As with all extractions the aim is to minimize trauma as much as possible.</li> </ul>
<p><b>3. Haemostatic Agents</b></p> <ul style="list-style-type: none"> <li>■ Consider the use of a haemostatic resorbable dressing following an extraction such as oxidized regenerated cellulose (Surgicel®), synthetic collagen or gelatine sponge to promote and stabilize clot formation by providing a mechanical matrix.<sup>27</sup></li> </ul>
<p><b>4. Suture</b></p> <ul style="list-style-type: none"> <li>■ Suture the socket with resorbable sutures to achieve primary closure where possible and then apply pressure to socket with a gauze pack until haemostasis is achieved.</li> </ul>
<p><b>5. Post-operative Instructions</b></p> <ul style="list-style-type: none"> <li>■ Give clear post-operative instructions to the patient, both verbal and written.</li> </ul>
<p><b>6. Tranexamic Acid Mouthwash</b></p> <ul style="list-style-type: none"> <li>■ The use of tranexamic acid mouthwash post-operatively is not routinely advocated in patients on warfarin as it is expensive, difficult to obtain and, when used in combination with other haemostatic measures, provides little additional reduction in post-operative bleeding.<sup>19</sup></li> <li>■ However, tranexamic acid mouthwash may be useful as an antifibrinolytic agent for patients with congenital and other acquired bleeding disorders.</li> </ul>

**Table 2.** Local haemostatic measures.

Herbal Medicine	Possible Indication for Use	Effect on INR	Effect on Platelets
Ginger	Nausea	Increase	
Garlic	Decrease cholesterol	Increase	Inhibit platelet adhesion and aggregation <sup>12</sup>
Ginseng	Increase energy levels	Increase	Inhibit platelet adhesion and aggregation
Gingko	Increase cerebral blood flow therefore improving memory and decreasing dementia	Increase	Inhibit platelet adhesion and aggregation
St John's Wort	Depression	Decrease	

**Table 3.** Interactions of herbal medicines with warfarin.

- Atrial fibrillation;
- Prophylaxis and treatment of peripheral arterial emboli;
- Prevention of clotting;
- Prevention of clotting during arterial heart surgery;
- Acute thrombo-embolic episodes;
- Prevention of deep vein thrombosis and pulmonary emboli after surgery;
- IV renal haemodialysis patients to prevent thrombosis in the pumps;
- Prophylactic prevention of thrombosis after a myocardial infarct.

**Table 4.** Indications for use of heparin.

practitioner is advisable to decide when the heparin should be resumed again. This will depend on the complexity of the extraction and the patient's thrombo-embolic risk. Patients on renal haemodialysis, who are also on heparin, will be discussed further under renal disorders.<sup>24</sup>

### Corticosteroids

Corticosteroids are involved in a wide range of physiological processes regulating stress response, immune response, inflammation, metabolism of carbohydrates, protein catabolism, as well as regulating blood electrolyte levels.

Corticosteroids are potent anti-inflammatories as they suppress phospholipase A2 and therefore inhibit main products of inflammation. They also inhibit thromboxane A2, a known platelet aggregant. There are widespread indications for corticosteroid use (Table 5).

Patients on corticosteroid therapy may experience prolonged

bleeding due to:

- A decrease in platelet function as a result of inhibition of thromboxane A2;
- Effects on the vessel wall, therefore interfering with the initial haemostatic interactions between vessel wall, platelets and clotting factors;<sup>25</sup>
- Immunosuppression leading to an increased chance of infections and therefore increased fibrinolysis.

#### Dental considerations

Medical advice should be sought prior to the dental treatment of these patients and local haemostatic measures used.

### Chemotherapy

Chemotherapy generally refers to targeting neoplastic cells. The aim of chemotherapy is to destroy rapidly dividing cancer cells, although this function is non-specific, therefore cells that divide rapidly under normal circumstances are also harmed. This includes the cells in the bone marrow resulting

in myelo-suppression and hence a reduction in platelet number. As chemotherapy affects cell division, tumours with high growth fractions, such as lymphomas including Hodgkin's disease, are more sensitive to chemotherapy as a large proportion of the targeted cells are undergoing cell division at any time.

Chemotherapy may be given as curative or palliative treatment in order to prolong life or palliate symptoms.

Other uses of chemotherapy include the treatment of autoimmune disorders, such as rheumatoid arthritis or multiple sclerosis.

One cycle of chemotherapy usually lasts for approximately six weeks, with a six week rest in-between chemotherapy cycles. The lifespan of platelets is 7–10 days, whilst the lifespan of leucocytes is 4 weeks. Therefore, dental procedures need to be scheduled around week 4 to allow optimal healing and haemostasis before the start of the next cycle.

#### Dental considerations

Medical advice should be sought prior to carrying out invasive dental procedures. It is important to liaise with the patient's oncologist or haematologist to establish the most appropriate window for treatment.

### Conclusion

As we live in a society where medical interventions are continually advancing, people are living longer and

- Adrenal insufficiency in Addison's disease;
- Suppression of various allergic reactions, eg asthma, dermatitis;
- Suppression of inflammatory conditions, eg arthritis, inflammatory bowel disease, Crohn's disease or ulcerative colitis, temporal arteritis;
- Suppression of auto-immune disorders such as systemic lupus erythematosus, sarcoidosis;
- As post-transplant immunosuppressants;
- Graft versus host disease to prevent transplant rejection;
- Chemotherapy.

**Table 5.** Indications for corticosteroid use.

medical conditions are extremely diverse, it is important for the dental clinician to be able to recognize medical conditions and treatments that may cause bleeding complications following dental treatment. This paper outlines the main drugs that can interfere with haemostasis that patients may be taking when they present for treatment in the dental practice. Through understanding the conditions and drugs that can cause prolonged bleeding, the dental practitioner is able to risk assess each patient and manage the patient accordingly.

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