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# Effect of Warfarin in patients undergoing oral

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***ABSTRACT:***
***Background:*** *The most common indications for warfarin therapy are atrial fibrillation, presence of mechanical heart valves and venous thromboembolism. Oral surgical procedures in patients with warfarin present a problem, because the interruption of anticoagulant therapy increases the risk of thromboembolism. Bleeding is the main complication associated in oral surgery, in patients with anticoagulants. The risk of bleeding is influenced by the intensity of anticoagulant therapy, which is indicated by INR. Fundamental to the surgical treatment of patients taking warfarin is the monitoring of the international normalised ratio (INR) before and after operation. A postoperative rise in INR was observed to be more common than a postoperative fall.*
***Conclusion:*** *It is common practice to reduce or discontinue the anticoagulant medication to minimize the risk of bleeding. But this is still controversial. The aim of this study is to highlight the areas of major concern and protocols to be followed for managing these patients in a dental operatory or patients who have to undergo minor oral surgical procedures.*

***Keywords:-*** *Warfarin; Oral surgery; Anticoagulants; INR.*

## I. INTRODUCTION AND IMPACT OF THE PROBLEM

Approximately 1.4% of the adult population requires continuous oral anticoagulation, and this percentage may increase in the future.[1] Moreover, at least 10% of this population faces the possibility of a surgical intervention every year. Maintaining the anticoagulation effect until the time of surgery or during the procedure may result in excess bleeding;[2] on the other hand, interrupting the treatment during the perioperative period increases the risk of thromboembolic events.[3] In order to overcome the problem, warfarin is usually interrupted several days prior to the intervention and replaced with the temporary use of anticoagulants of shorter action in order to minimize the time without anticoagulation effect. This bridging practice has been based traditionally on the use of unfractionated heparin (UH) as an intravenous infusion; however, this involves unnecessary hospitalizations and additional costs for patients, institutions and health systems alike.

Management during oral surgical procedures of patients who are taking anticoagulants has changed drastically during the past decade, but there are still differences in the approaches of oral and maxillofacial surgeons.[4] The balance between reduction in the dose of oral anticoagulants on the one hand, and excessive bleeding during surgery in therapeutically anticoagulated patients on the other, is a major problem, particularly with outpatient procedures.[5] Several protocols have been proposed for such patients,[6] and can be summarised as: temporary discontinuation or a reduction in dose of oral anticoagulants to obtain a subtherapeutic international normalised ratio (INR); replacement of oral anticoagulation with heparin or low-molecular weight heparins; or continuation of oral anticoagulation.[7] However, the latest recommendations emphasise that the risk of serious bleeding in patients with therapeutic INR is small. It has therefore been suggested that the dose of oral anticoagulant should not be discontinued or changed.

## II. GENERAL POINTS

Anticoagulants present management problems in oral surgery mainly because of prolonged intraoperative and postoperative bleeding. However, about 90% of postextraction hemorrhage is from other causes, including the following:[8]

- Excessive operative trauma, particularly to oral soft tissues;
- Poor compliance with postoperative instructions;
- Interference with the extraction socket or operation site
- Inflammation at the extraction or operation site, with resultant fibrinolysis;
- Inappropriate use of analgesia with aspirin or other nonsteroidal antiinflammatory drugs, which, by interfering with platelet function, induce a bleeding tendency;
- Uncontrolled hypertension.

The following general points should be considered in patients for oral surgery on anticoagulant therapy:

1. Dental preventive care is especially important to minimize the need for surgical intervention.[9]
2. Systemic conditions that may aggravate the bleeding tendency can be present.[8]
3. Drugs that cause increased bleeding tendency (eg, aspirin and other nonsteroidal antiinflammatory drugs) should be avoided.[10]
4. Any surgical intervention can cause problems; thus, the possibility of alternatives to surgery should always be considered. The patients should be warned in advance of the procedure of the increased risk of intraoperative and postoperative bleeding and intraoral/extraoral bruising. If the bleeding tendency is great, dental extractions, other surgical procedures, and some local analgesic injections (regional blocks) can cause serious problems.
5. Other interventions to avoid, if possible, include regional local analgesic injections (may bleed into fascial spaces of neck and obstruct airway; intraligamentary or intrapapillary injections are far safer) and intramuscular injections.[8]

## III. WARFARIN (COUMARIN)

Coumarins are used in the treatment and prophylaxis of thromboembolic disorders. Warfarin (also used as rat poison) is the common one used. Warfarin is highly water soluble and rapidly absorbed from the stomach and the upper gastrointestinal tract; its plasma concentrations peak 60 to 90 minutes after oral administration. It binds to the enzyme vitamin K 2,3-epoxide reductase in liver microsomes, antagonizing the vitamin K–dependent synthesis of several coagulation factors, especially factors II, VII, IX, and X and proteins C, S, and Z, so that prothrombin time (PT) and activated partial thromboplastin times (APTT) are prolonged.[11]

Coumarin anticoagulant therapy should maintain PT of 1.5 to 2.5 times the control.8 Warfarin effects are delayed for 8 to 12 hours and maximal at 36 hours but persist for 72 hours. The plasma half-life of warfarin is about 37 hours and Warfarin is metabolized mainly in the liver and by the cytochrome p450 complex, and its effect is reversible with vitamin K.[11]

## IV. THROMBOEMBOLIC EVENTS VS POST OPERATIVE BLEEDING

It has been common in primary care dental practice to discontinue warfarin treatment for a few days prior to dental surgery in order to limit bleeding problems. It has been assumed that stopping warfarin for short period presents a negligible risk to the patient. However, data from trials and published case reports do not support this conclusion.

Wahl reviewed[6] 542 documented cases involving 493 patients in whom anticoagulation was withdrawn prior to variety of dental procedures. He reported that:

- 4 patients experienced fatal thromboembolic events (2 cerebral thromboses, 1 myocardial infarction, 1 embolus - type not specified).
- 1 patient experienced two non-fatal thromboembolic complications (1 cerebral embolus, 1 brachial artery embolus).
- The majority of patients had no adverse effects.

This gives an incidence of serious thromboembolic complications of 1%. There has been criticism of this finding as length of time that the anticoagulant was stopped was either longer than normal practice (range 5-19 days) or unknown.[12] In addition, although the data suggest that stopping anticoagulant therapy caused the thromboembolic events, this cannot be assumed.

The risk of thromboembolic events associated with the perioperative withdrawal of oral anticoagulants is also relevant to non-dental procedures. One survey among American dermatologists calculated that following withdrawal of warfarin for between two and seven days, one thromboembolic event occurred for every 6219 cutaneous excisions (0.02%) conducted.[13]

A study looking at risk of stroke in anticoagulated patients with atrial fibrillation undergoing endoscopy found that of 987 patients (1137 procedures) in whom the anticoagulant was adjusted, 12 patients suffered a stroke within 30 days of the procedure, 9 of these were within 7 days of the procedure. In 438 patients (457 procedures) in whom the anticoagulant was not adjusted none suffered a stroke. The authors calculated the risk of stroke as 0.79% in 7 days after the procedure and 1.06% in the 30 days after the procedure. Patients with more complex procedures and those with co-morbid illnesses were at an increased risk. [14]

The estimated risk of thromboembolic events if warfarin is discontinued prior to surgical procedures therefore varies considerably between studies. For minor procedures such as dental surgery, the risk appears to vary from 0.02% to 1%.

Clinically significant postoperative bleeding has been defined[16] as that which;

1. Continues beyond 12 hours, or
2. Causes the patient to call or return to the dental practice or accident and emergency department, or
3. Results in the development of a large haematoma or ecchymosis within the oral soft tissues, or
4. Requires a blood transfusion.

Wahl estimated the incidence of serious bleeding problems in 950 patients receiving anticoagulation undergoing 2400 individual dental procedures.[17] Only 12 patients (<1.3%) experienced bleeding uncontrolled by local measures and none of the patients were reported to have experienced serious harm. Of these 12 patients:

- 7 had higher than recommended anticoagulation levels

- 3 of these were given a course of postoperative antibiotics, which may have interacted with the warfarin.

- 2 were started on a placebo mouthwash four times a day immediately after the procedure, which is contrary to standard advice to avoid rinsing for the first 24 hours.

Increased postoperative bleeding must be balanced against the consequences of thromboembolism.

## V. INTERNATIONAL NORMALIZED RATIO

The activity of warfarin is expressed using the international normalised ratio (INR). For an individual not taking warfarin a normal coagulation profile is an INR of 1.0.
UK guidelines[18] recommend the following target INRs:

| Indication | UK INR target | Acceptable range |
|---|---|---|
| Pulmonary embolus (PE) | 2.5 | 2.0-3.0 |
| Deep vein thrombosis (DVT) | 2.5 | 2.0-3.0 |
| Atrial fibrillation | 2.5 | 2.0-3.0 |
| Recurrence of embolism - no longer on warfarin | 2.5 | 2.0-3.0 |
| Recurrence of embolism on warfarin | 3.5 | 3.0-4.0 |
| Mechanical prosthetic heart valves | 3.5 | 3.0-4.0 |
| Antiphospholipid syndrome | 3.5 | 3.0-4.0 |

In theory all patients will have an INR below 4.0.

Of the literature, one stated that minor dental surgical procedures could be carried out with the INR ≤4.5, [19] six limited the INR to ≤4.0,[20,28] one just stated ≥3.5 (23 patients included with INRs ≥3.5),[21] one limited the INR to ≤3.0[22] and one trial stated no limits but included patients with INRs up to 3.0. Results suggest that limiting the INR to ≤4.0 enables procedures to be carried out safely without excessive postoperative bleeding.

Reviews discussing the continuation of oral anticoagulation during minor dental surgical procedures have advocated that procedures can safely be carried out with the INR within the therapeutic range (2.0 – 4.0) when local haemostatic measures are used to control bleeding.[6,15] Others have advocated upper limits of 3.5[24,26] or 3.0.[25]

The INR is valid only for patients who have stable anticoagulant therapy. Patients presenting with an INR much higher than their normal value, even if it is less than 4.0, should have their procedure postponed and should be referred back to the clinician maintaining their anticoagulant therapy.

Patients who have an INR greater than 4.0 should not undergo any form of surgical procedure without consultation with the clinician who is responsible for maintaining their anticoagulation (this may be the GP or the hospital anticoagulant clinic haematologist). The warfarin dose will need to be adjusted prior to the procedure. Patients who are maintained with an INR >4.0 or who have very erratic control may need to be referred to a dental hospital or hospital based oral/maxillofacial surgeon.

The following medical problems may affect coagulation and clotting:[20,24,29]

- liver impairment and/or alcoholism
- renal failure
- thrombocytopenia, haemophilia or other disorder of haemostasis
- those currently receiving a course of cytotoxic medication.

Patients with any of these conditions who also take warfarin should not be treated in primary care but referred to a dental hospital or hospital based dental clinic. Patients requiring major surgery are unlikely to be treated in the primary care setting.

## VI. MANAGEMENT

### a) Timing

Think about the timing of the surgery. Planned surgery should ideally be:

- At the beginning of the day - this allows more time to deal with immediate re-bleeding problems.
- Early in the week- this allows for delayed re-bleeding episodes occurring after 24–48 hours to be dealt with during the working week. A Tuesday morning procedure allows the patient to have their INR measured on Monday.[26]

### b) Local anaesthetic

A local anaesthetic containing a vasoconstrictor should be administered by infiltration or by intraligamentary injection wherever practical.[16] Regional nerve blocks should be avoided when possible. However, if there is no alternative, local anaesthetic should be administered cautiously using an aspirating syringe. [16,21,26,19] Local vasoconstriction may be encouraged by infiltrating a small amount of local anaesthetic containing adrenaline (epinephrine) close to the site of surgery.[25]

### c) Local haemostasis

Sockets should be gently packed with an absorbable haemostatic dressing [16,29,26] e.g. oxidised cellulose (Surgicel ), collagen sponge (Haemocollagen ) or resorbable gelatin sponge (Spongostan ), then carefully sutured. Trials in patients who have continued anticoagulant therapy throughout the perioperative period have used resorbable (catgut or synthetic – Vicryl polyglactin) or non-resorbable (silk, polyamide, polypropylene) sutures. Resorbable sutures are preferable as they attract less plaque.[26] If non-resorbable sutures are used they should be removed after 4 -7 days.[26] Following closure, pressure should be applied to the socket(s) by using a gauze pad that the patient bites down on for 20 minutes.

Efforts should be made to make the procedure as atraumatic as possible and any bleeding should be managed using local measures. The use of tranexamic acid mouthwash, which acts as a local antifibrinolytic agent, has been investigated but is not recommended routinely in primary care.

**d) Post operative management**

Patients should be given clear instructions on the management of the clot in the postoperative period and advised:[8]

- to look after the initial clot by resting while the local anaesthetic wears off and the clot fully forms (2-3 hours)
- to avoid rinsing the mouth for 24 hours
- not to suck hard or disturb the socket with the tongue or any foreign object
- to avoid hot liquids and hard foods for the rest of the day
- to avoid chewing on the affected side until it is clear that a stable clot has formed. Care should then be taken to avoid dislodging the clot
- if bleeding continues or restarts to apply pressure over the socket using a folded clean handkerchief or gauze pad. Place the pad over the socket and bite down firmly for 20 minutes. If bleeding does not stop, the dentist should be contacted; repacking and resuturing of the socket may be required

who to contact if they have excessive or prolonged postoperative bleeding. The surgery and out of hours/on call dentist's name/number should be provided. There should be a facility for the patient to be reviewed and treated immediately by a dentist if a bleeding problem occurs. If it is not possible for the patient to be seen immediately by a dentist then the patient should be referred to their local Accident and Emergency department

**e) Postoperative pain control**

Patients should follow the advice of their anticoagulant clinic with regard to the choice of analgesia for short term mild to moderate pain. Generally paracetamol is considered the safest simple analgesic for patients taking warfarin and it may be taken in normal doses if pain control is needed and no contraindication exists. Patients should be advised **not** to take aspirin, aspirin containing compound analgesic preparations or non-steroidal anti-inflammatory drugs (NSAIDs) e.g. ibuprofen, which are considered less safe than paracetamol, in patients taking warfarin.

If prescribed analgesia is to be provided additional options include;

- **Rofecoxib –** a cyclo-oxygenase-2 (COX-2) inhibitor. The COX-2 inhibitors are as effective as standard NSAIDs and have a similar side effect profile, however, the risk of gastro-intestinal bleeding is lower
- **Dihydrocodeine –** an opioid analgesic with similar analgesic efficacy to codeine. It is suitable for mild to moderate pain. It has no anti-inflammatory activity and is of limited value in pain of dental origin.

**f) Drug interactions with warfarin**

**Amoxicillin -** There are anecdotal reports that amoxicillin interacts with warfarin causing increased prothrombin time and/or bleeding but documented cases of an interaction are relatively rare.[27] However, a single 3 gram dose given for endocarditis prophylaxis has not been shown to produce a clinically relevant interaction. Prophylactic antibiotics do not appear to affect the bleeding risk postoperatively.[28] Patients requiring a course of amoxicillin should be advised to be vigilant for any signs of increased bleeding.

**Clindamycin -** Clindamycin does not interact with warfarin when given as a single dose for endocarditis prophylaxis. Prophylactic antibiotics do not appear to affect the bleeding risk postoperatively.[28] Clindamycin is restricted to specialist use for treatment and should not be used routinely for dental infections due to its serious side effects.[29] There is a single case report of an

interaction between warfarin and a course of clindamycin.[27]

**Metronidazole -** *CAUTION* metronidazole interacts with warfarin and should be avoided wherever possible. If it cannot be avoided the warfarin dose may need to be reduced by a third to a half by the GP or anticoagulant clinic.[27]

**Erythromycin -** Erythromycin interacts with warfarin unpredictably by only affecting certain individuals. Most are unlikely to develop a clinically important interaction. Patients should be advised to be vigilant for any signs of increased bleeding.[27]

**Paracetamol –** The anticoagulant effect of warfarin is normally not affected, or only increased by a small amount, by occasional doses of paracetamol.[27] Paracetamol is considered to be safer than aspirin as an analgesic in patients taking warfarin and is the analgesic advised by anticoagulant clinics and the patient held 'Anticoagulant therapy booklet'. The anticoagulant effect of warfarin may be enhanced by prolonged regular use of paracetamol.

**Aspirin –** *AVOID* use as an analgesic and anti-inflammatory agent. Concurrent aspirin increases the likelihood of bleeding by 3-5 times, increases the bleeding time and may damage the stomach lining.[27] The interaction is well documented and clinically important.

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) -** *AVOID* NSAIDs e.g. ibuprofen, diclofenac. Care should be taken when using NSAIDs in patients on anticoagulant therapy due to the increased risk of bleeding from the gastro-intestinal tract.[27]

**Rofecoxib (COX-2 inhibitor) –** Patients should be closely monitored if rofecoxib is used. In patients on chronic warfarin therapy treatment with rofecoxib has been associated with an increase in INR values. Although rofecoxib can increase the risk of gastro- intestinal bleeding, this risk is less than with standard NSAIDs and rofecoxib may be considered a safer option. Close monitoring is important in the first few days of rofecoxib therapy and patients should be advised to be vigilant for signs of increased bleeding.[30]

## VII. STRATEGIES FOR REDUCING THE PREOPERATIVE RISK OF THROMBOEMBOLISM

After a recent venous thromboembolic event, the risk of recurrence drops dramatically during the first three months, hence the suggestion by some authors of deferring nonpriority surgeries for at least 1 month, ideally 3 months. This suggestion could be extended to recent arterial or cardioembolic events.[31] The placement of a temporary caval filter is a possibility to consider in very recent DVT and in nondeferrable major surgery.[32]

Regarding the true usefulness of perioperative bridging, there are no prospective, randomized or placebo-controlled studies to date showing reliable information about its efficacy, safety, dose or comparative differences between potential drugs and regimes. The existing evidence is derived from good-quality studies, but there is a tendency to extrapolate it to the perioperative setting from non-surgical situations and lower quality studies (purely observational). In non-surgical areas, there is good-quality evidence supporting the usefulness of LMWH for the management of DVT-PTE, and for reducing the risk of recurrence after an event. They have been shown to lend themselves to outpatient management because of their safety profile, and they have even been shown to be better than UFH.[32] The evidence supporting the use of LMWH for the control of arterial or cardioembolic events is less strong, although there is indirect evidence suggesting its usefulness in the management of chronic AF,[33] subacute ischemic stroke,[34] and also in cases of prosthetic valves, this is a more controversial issue.[35] In the perioperative setting, there are no randomized controlled trials providing reliable evidence on the usefulness of bridging with LMWH; however, there are multiple descriptive prospective cohort studies showing a low mean rate of thromboembolic events (1%) and major bleeding (3%). In prosthetic valves, there are at least 14 studies with 1,300 patients showing an overall rate of thromboembolic events of 0.83%; in chronic AF, 10 studies with 1,400 patients show a

rate of 0.57%; and in DVT-PTE, 9 studies with 500 patients show an overall rate of 0.6%. The data were consolidated in a recent review by the ACCP.9 There are two ongoing good-quality studies that are expected to provide more reliable information by 2014.[36] The usefulness of unfractionated heparin (UFH) as a perioperative bridging agent is also supported by a smaller number of purely observational studies. A multi-center prospective non-randomized cohort study comparing perioperative bridging with UFH versus LMWH did not show significant differences in terms of thromboembolism or bleeding rates.[37] Although no differences were found in a subgroup analysis of prosthetic valves,[38] some cardiology societies still express their reservations regarding the use of LMWH in high-risk prosthetic valves.[39]

Regarding the bridging dose of LMWH, evidence-based guidelines.[40] are consistent in suggesting therapeutic doses of LMWH in high-risk groups, and prophylactic doses or no bridging in low-risk groups, although there are some inconsistencies in relation to the moderate risk of venous thromboembolism.

Out of simplicity and due to medical and legal reasons, an attempt should be made at unifying the recommendations around a more aggressive approach as that suggested by the best known guidelines: prophylactic doses for low-risk groups, and therapeutic doses for moderate and high-risk groups.[40]

## VIII. PRACTICAL PROTOCOL FOR PRE-OPERATIVE OUTPATIENT BRIDGING WITH LMWH

Based on pharmacological studies of these drugs,[42] clinical trials on perioperative bridging and the guidelines mentioned above, the following parameters could be suggested: warfarin interruption 4 to 5 days prior to surgery[40,41] (although a longer time period might be required in certain situations such as, an INR greater than 3, an elderly patient, decompensated heart failure and active cancer);[42] initiation of LMWH 24 to 36 hours after the last dose of warfarin (3 days before the procedure).[40,41]

A twice-daily dose is preferable over single daily dose regimes for therapeutic doses.[43] Prophylactic and therapeutic treatment must be interrupted 12 hours and 24 hours before the procedure or regional anesthesia, respectively.[40,41] Given the erratic clearance of warfarin, an INR lower than 1.5 must be documented before surgery; some authors suggest measuring the INR one day prior to surgery, in order to allow the possibility to correct an abnormal result with low-dose oral vitamin K (1-2.5 mg), thus avoiding the need to postpone surgery or the unwarranted administration of plasma.[44]

## IX. WARFARIN REVERSION IN EMERGENCY CASES

In cases of emergency surgery, a dose of 2.5-5 mg of vitamin K given orally or as a slow intravenous infusion may revert the anticoagulation effect of warfarin within 12 to 24 hours.[45] When the surgery is to be performed within a shorter period of time, it is important to consider, aside from vitamin K, a dose of 10 ml/kg-15ml/kg of fresh frozen plasma (FFP).[46] However, its processing and administration take time, and it is also associated with transfusion risks (transfusion acute lung injury or TRALI, excess fluid burden, risk of infection, anaphylactic reactions); moreover, it might be insufficient in reverting hyper-anticoagulation states. The use of prothrombin complex concentrate has been introduced recently at a dose of 25 IU/kg-50 IU/kg that appears quite promising, with comparative advantages over the use of FFP, it being faster, safer and more effective, and lacking the adverse effects associated with the use of FFP. However, its use is still limited because of its high cost and the scant evidence in the perioperative setting.[47]

## X. CONCLUSION

Concluding all above controversies and problems, Management of patients on warfarin needing oral surgery in dental clinics should be as under:-

1. Careful history taking including:
- Underlying medical condition (need of antibiotic prophylaxis?)
- Presence of increasing bleeding risk factors
- Previous bleeding experience in oral surgery procedures

- Habits (i.e., alcohol intake)
- Mental condition

2. Careful oral examination to determine:
- Degree of urgency of planned surgical procedure
- Extent of planned surgical procedure
- Gingival condition

3. Order INR

4. Decision of whether to treat or to refer with consideration of following factors:
- Result of history taken
- Result of oral examination
- Result of INR
- Logistical considerations: distance to hospital or emergency care facility
- Patient mobility

5. Referral always to hospital in presence of either one of following conditions:
- INR > 3.5
- Need of more than simple surgical procedure
- Presence of additional bleeding risk factors or logistic difficulties

6. Performance of surgery in office without INR provided:
- Need of surgery cannot be postponed
- History of stable INR up to 2.5
- Previous available INR value obtained within last week

7. If surgery to be performed in office, following materials should be used:
- Absorbable packing hemostatic agents
- Sutures
- Hemostatic mouthwashes.

**Conflict of Interest**

None declared.

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