Original Article

Documentation of various approaches and outcomes in patients on warfarin undergoing dental procedures: a review article

Fayez El Shaer, Ismael Raslan, Nora Al Osaimi, Ghada Bawazeer, Fhakr Alayobi, Tarek Alhogbani, Suliman Kharabsheh, Walid Al Habeeb

King Fahad Cardiac Center, Department of Cardiac Sciences, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Received December 13, 2015; Accepted August 19, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Appropriate management of patients with mechanical prosthetic valves on warfarin during dental procedures is crucial. If the patients continue warfarin, they might develop bleeding, while interruption of therapy can cause thromboembolic events. Bridging therapy (mostly heparin) is used in some patients, while others stop medications. There is no unifying protocol. Information on management of patients on warfarin undergoing dental procedures in Saudi Arabia is lacking. Therefore, the current study aimed to provide more insight into various approaches utilized by clinicians to deal with such patients at a large teaching hospital in Riyadh, and to evaluate the frequency and severity of bleeding and thromboembolic complications during different types of dental procedures in this population. This was a cohort study. Patient records were used to collect data on peri-procedural management of patients on warfarin, continuation or interruption of warfarin therapy, as well as bleeding and thromboembolic complications. Fifty medical records were reviewed from March to October 2012. Regarding management, 10% had no proper documentation, 74% underwent bridging therapy, 12% discontinued warfarin therapy, and 4% continued warfarin. Of the patients, 31% had minor bleeding (15% in patients on bridging therapy and 16% in patients continuing warfarin). Thromboembolic complications were documented in 4%, (2% in those on bridging therapy and 2% in those discontinuing warfarin). Patients on bridging therapy (heparin) were admitted to the hospital for a mean of five days, and none of the other patients were admitted. Adopting the protocol to continue warfarin caused bleeding tendency that was controlled with the usual measures, with more cost effectiveness, and no thromboembolic risks.

Keywords: Dental procedures, warfarin, bridging therapy, heparin, complications

Introduction

The role of anticoagulants in many cardiovascular disorders is well established, and their use as prophylaxis against stroke or thromboembolism is increasing. As a result, many patients undergoing elective surgery or invasive procedures may be regularly taking one of these agents. The correct management of anticoagulation therapy in such patients both before and after procedures is essential [1, 2].

Although continuation of anticoagulation therapy increases the risk of bleeding following invasive procedures, interruption of such therapy may increase the risk of thromboembolism [3-5]. Accordingly, individual circumstances should be carefully reviewed before an informed decision on modifying anticoagulation therapy is made in patients undergoing surgery or invasive procedures.

Several days are required for the anticoagulant effect to reduce after warfarin therapy is discontinued, which can potentially delay urgent surgery. Rebound hypercoagulability may occur following the abrupt cessation of anticoagulation therapy. Several days may be required after warfarin therapy is resumed to reestablish a therapeutic and adequate level of anticoagulation.

The importance of these issues varies in part with the indication for anticoagulation (e.g., prophylaxis for thromboembolism versus treatment for an acute thrombotic episode). Accord-
ingly, there is no general recommendation that can be applied to all patients undergoing elective surgery who take long-term anticoagulation therapy.

Systemic embolization (predominantly cerebrovascular events) occurs at a frequency of approximately 0.7% to 1.0% patients/year in patients with mechanical valves who are treated with warfarin, 2.2% patients/year in those treated with aspirin, and 4.0% in those not on anticoagulants. A major advantage of the bioprosthesis valve is freedom from anticoagulation after three months of treatment and low risk for systemic embolism thereafter [6].

Most patients can undergo low-risk surgical procedures (e.g., cataract surgery, coronary angiography, venography, joint aspiration, dental procedures such as tooth extraction and root canal, minor skin procedures, arthrocentesis, or bone marrow biopsy) without needing to change their anticoagulant regimen [7-9]. In such patients, oral anticoagulation with a vitamin K antagonist can be continued to achieve an international normalized ratio (INR) value at or below the low end of the therapeutic range (e.g., INR 1.7 to 2.3).

The risk of bleeding occurring with surgery in patients taking anticoagulant therapy depends on patient age, comorbid diseases (e.g., chronic renal disease), the type of surgery [10], the anticoagulant regimen (intensity and duration), the use of other drugs that affect hemostasis (e.g., heparin, aspirin, or antiplatelet agents), the stability of anticoagulation, and the degree of anticoagulation [3, 11, 12].

In patients undergoing dental extraction, anticoagulation with warfarin is associated with a minimal risk of serious bleeding if the INR is within the therapeutic range just prior to the planned surgery [13]. Tranexamic acid or amnocaproic acid mouthwash, if available (e.g., 4.8% to 5% aqueous solutions used four times per day for at least two days) can be used in patients on anticoagulants to limit gingival bleeding after dental procedures [13-18]. The use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or Cox-2 selective inhibitors for analgesia should be avoided.

There are documented cases of rare but serious embolic events when warfarin has been withdrawn prior to dental procedures. In a literature review of 542 documented cases in 493 patients in whom continuous anticoagulation was withdrawn for a dental procedure (without heparin bridging), serious embolic complications occurred in five case (0.9%) [19]. As with dental procedures, cessation of prophylactic anticoagulation (warfarin or antiplatelet therapy) has been associated with a small risk of thromboembolic events [20-22].

Anticoagulation is generally safe in patients undergoing minor skin procedures (e.g., skin cancer removal) if the INR is maintained within the therapeutic range [10, 20-22]. The risk of bleeding after the use of heparin is variable. A two- or three-day course of intravenous heparin before surgery, with cessation four hours before the procedure, is unlikely to result in peri- or intra-operative bleeding [12]. In the non-perioperative setting, the risk of bleeding associated with intravenous heparin therapy is less than 5% in patients with acute venous thromboembolism. However, in patients with deep vein thrombosis (DVT), who are judged to be at high risk for bleeding, the incidence of major bleeding is approximately 11% during the first five days of intravenous heparin therapy [11].

Interruption of warfarin usually takes two to three days for the INR to fall to below 2.0, and four to six days for it to normalize. One study prospectively evaluated 22 patients with a baseline INR of 2.6 in whom it was deemed safe to discontinue warfarin [23]. In these patients, the mean INR was 1.6 and 1.2 at 2.7 and 4.7 days after discontinuation of warfarin, respectively. The time required for the INR to normalize after stopping warfarin may be longer in patients receiving higher-intensity anticoagulation (INR: 2.5 to 3.5), and in elderly patients. Once the INR is 1.5 or below, surgery can be performed with relative safety in most cases, although a normalized INR is typically required in patients undergoing surgery associated with a high bleeding risk (e.g., intracranial, spinal, or urologic procedures) or if spinal anesthesia is to be used. Following surgery and after warfarin is restarted, it takes approximately five days for the INR to rise above 2.0. It is therefore estimated that if warfarin is withheld for five days before surgery and is restarted as soon as possible afterwards, patients...
would have a subtherapeutic INR for approximately four days before surgery and four days after surgery [24].

In theory, a slight elevation of the INR to approximately 1.5 around the time of surgery should provide partial protection against venous thromboembolism [25, 26]. However, there is no evidence that such low-intensity perioperative anticoagulation, for example that which is used for prevention of postoperative DVT, effectively prevents arterial thromboembolism.

If the patient has been adequately anticoagulated for some time prior to stopping warfarin, it is generally assumed that almost any preexisting thrombus would have either resolved or be endothelialized, thereby minimizing the risk of embolism [27]. Among patients with nonvalvular atrial fibrillation, for example, over 85% of thrombi resolve after four weeks of warfarin therapy as determined via transesophageal echocardiography [26].

Nevertheless, although the INR itself may not be a good guide to a reduced risk of thromboembolism, some patients have a significant reduction in their usual anticoagulant intensity during surgery, and a minor increase in the risk of thromboembolism is probably unavoidable [28].

Among patients with atrial fibrillation, chronic low-dose warfarin with aspirin is much less effective than adjusted-dose warfarin in preventing embolic events, demonstrating that lesser degrees of anticoagulation do not provide optimal protection [29].

The timing of interruption and reversal of warfarin and other vitamin K antagonists depends upon the amount of time available before the procedure, the elimination half-life of the vitamin K antagonist (i.e., 36 to 42 hours for warfarin; 8 to 12 hours for acenocoumarol; and 96 to 140 hours for phenprocoumon), as well as the estimated bleeding and thrombotic risk.

Timing of resumption of warfarin therapy should be within 12 to 24 hours after surgery, typically the evening after surgery, provided that surgical hemostasis has been achieved [13]. If warfarin is resumed alone, without heparin bridging, a full anticoagulant effect will take four to six days to occur, thereby allowing a more gradual re-anticoagulation, which may be preferable in patients undergoing surgery associated with substantial expected blood loss.

Rebound hypercoagulability may occur following the abrupt cessation of anticoagulation. Accordingly, alternative preoperative and/or postoperative prophylaxis against thromboembolism with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) should be considered in high-risk patients (e.g., a prosthetic valve in the mitral position, venous thromboembolism within the previous four weeks, or active malignancy) for the period during which the INR is less than 2.0 [30-32].

The clinical effects of rebound hypercoagulability after stopping warfarin are unclear. There is some biochemical evidence for this phenomenon; additionally, some investigators recommend that warfarin should be withdrawn gradually [33-35].

Surgery itself increases the risk of thromboembolism, as documented by changes in hemostatic markers that are part of the acute phase response and wound healing process [36]. High levels of hemostatic markers, such as fibrin or D-dimer, an index of intravascular thrombogenesis and fibrin turnover, are predictive of postoperative thrombosis [37]. Although there is evidence that surgery increases the risk of venous thromboembolism, there is no evidence that surgery itself increases the risk of arterial thromboembolism, apart from risks associated with particular procedures, such as carotid surgery [38].

Bridging anticoagulation can be defined as the administration of a short-acting anticoagulant, typically a LMWH, during the perioperative interruption of warfarin. Bridging can be used as an alternative to warfarin interruption. The intent of bridging is to minimize the time patients are not being anticoagulated, thereby minimizing patients’ risk for preoperative thromboembolism. The therapeutic benefit of bridging anticoagulation is not fully established in every patient population. Because of the lack of evidence-based information indicating whether or not bridging anticoagulation is warranted, there is considerable variation in the use of this modality [39-41]. Given this uncertainty, the decision about bridging anticoagulation should be based upon individual patient
and surgery-related factors. In general, bridging anticoagulation may be considered in patients with the following [1]: Prior stroke or systemic embolic event, mechanical mitral valve, mechanical aortic valve and additional stroke risk factors, atrial fibrillation and multiple stroke risk factors (e.g., CHADS \(_2 \geq 4\), CHA\(_2\)DS\(_2\)-VASc \(\geq 5\)), recent (within three months) venous thromboembolism, active coronary or peripheral vascular disease, previous thromboembolism during interruption of warfarin therapy, or major cardiac or vascular surgery.

Guidelines

The risk of significant bleeding in patients with a stable INR (of < 4) is minimal. Thrombosis risk may be increased in patients in whom oral anticoagulants are temporarily discontinued. Oral anticoagulants should not be discontinued in the majority of patients requiring outpatient dental surgery including dental extraction (grade A level Ib) Checking of the INR is recommended 72 hours prior to dental surgery for stably anticoagulated patients (class 1, level Ib). Patients taking warfarin should not be prescribed non-selective NSAIDs and COX-2 as analgesia following dental surgery (class11, level III). In patients who undergo minor dental procedures and receive vitamin K antagonists (VKAs), continuation of VKAs around the time of the procedure and co-administration of an oral prohemostatic agent (class 1B) is recommended [1].

Bleeding stratification

**Major bleeding**

Bleeding that requires transfusion of \(\geq 2\) U packed red blood cells (RBCs).

**Clinically relevant non-major bleeding**

Not major bleeding but requires medical attention (e.g., application of wound dressing or additional sutures).

**Minor bleeding**

Self-limiting, usually with pressure at the bleeding site, and does not require medical attention.

Aims of the study

**Primary objectives**

To describe current approaches to the management of patients taking warfarin and are undergoing dental procedures. To evaluate bleeding and thromboembolic complications in patients on chronic warfarin therapy during dental procedures.

**Secondary objectives**

To propose a management protocol for chronically anticoagulated patients who require a dental procedure. To calculate the cost associated with inappropriate management of anticoagulated patients.
Inclusion criteria

Inclusion criteria were Patients on warfarin for no less than three months, those undergoing dental procedures, and those with mechanical prosthetic valves, followed up in the cardiology clinic. Informed consent was obtained from all patients participating in the study for us to collect data from their files.

Exclusion criteria

Exclusion criteria were any patient with severe liver or renal disease, cancer, history of heparin-induced thrombocytopenia, pregnant patients, and those whose age was more than 65 years and less than 18 years.

Data analysis

The frequency was expressed as a percentage, and continuous variables were expressed as mean ± standard deviation. A Chi-square ($\chi^2$) test was used. A P-value of ≤ 0.05 was considered for significant differences. Statistical analysis was performed using SPSS for Windows (version 17, SPSS Inc., Chicago, USA).

Results

Fifty medical records were reviewed from March to October 2012. They were managed as follows: 10% of patients had no documentation, 74% underwent bridging therapy, 12% discontinued warfarin therapy, and 4% continued warfarin (Table 1). Of the patients, 31% had minor bleeding (15% in patients on bridging therapy and 16% in patients continuing warfarin) (Figure 1). Thromboembolic complications were documented in 4% of patients (2% of patients on bridging therapy and 2% of patients in those discontinuing warfarin) (Figure 2). Patients with heparin bridging therapy were admitted to the hospital for a mean of eight days; no other patients were admitted (Figure 3). Continuation of warfarin caused bleeding (Figure 4) that was easily controlled with the usual measures, with more cost-effectiveness and no thromboembolic risks (Figures 5, 6).

Discussion

The anticoagulant effect of warfarin is mediated through inhibition of the VKD gamma-carboxylation of coagulation factors II, VII, IX, and X [23]. The full anticoagulant effect of warfarin may be delayed for 36 to 72 hours after administration, until the normal clotting factors have been cleared from the patient’s circulation.

Upon initiation of therapy, warfarin can create a biochemical paradox by producing an antico-
Approaches and outcomes for patients on warfarin undergoing dental procedures

Agulant effect due to inhibition of procoagulants, while also producing a potentially thrombogenic effect by impairing the synthesis of naturally occurring inhibitors of coagulation, such as proteins C and S [23].

Warfarin is strongly protein-bound; any agent that binds to albumin may also displace warfarin and increase its biological activity.

The laboratory test most commonly used to monitor warfarin therapy is the one-stage prothrombin test (PT), which is sensitive to reduced activity of factors II, VII, and X. This test utilizes thromboplastin to activate clotting in blood specimens.

There are many different commercially available thromboplastins that are typically derived from extracts of lung, brain, or placenta. Different thromboplastins yield varied PT responses to warfarin-induced anticoagulation. Different makes and models of coagulation analyzers may also affect PT values. Consequently, PT values are often not consistent among various laboratories and are therefore not suitable for defining therapeutic ranges for warfarin therapy.

The INR was developed to standardize PT values so that test results from different thromboplastins and coagulation analyzers would be equivalent. Under the INR system, the thromboplastin is assigned an international sensitivity index (ISI) value. The ISI indicates the relative sensitivity of the thromboplastin compared to an international reference of the thromboplastin. The ISI, the patient’s PT, and the mean normal PT, which is a value derived in each laboratory by averaging at least 20 normal individuals, are used to calculate the INR.

There is no current consensus regarding the management of patients undergoing elective surgery while on long-term anticoagulation therapy. The primary concern associated with discontinuation of anticoagulation prior to surgery is the increased risk of thromboembolism and cerebrovascular accidents. There is also a concern regarding life-threatening rebound hypercoagulability following the abrupt cessation of anticoagulation [33, 35, 42]. These concerns need to be weighed against the potential for hemorrhagic complications that may occur during or following surgery.

A definitive, standardized protocol for the management of dental extractions in anticoagulat-
ed patients is still lacking. Recently published literature consistently suggests that there is no need to discontinue anticoagulation and that the application of local hemostatic measures is sufficient to prevent bleeding complications [35].

In one study of 19 patients, for example, thrombin and fibrin formation increased after abrupt cessation of warfarin therapy, but no patient had a thromboembolic event [35]. In another report, however, 32 patients were randomly assigned to receive abrupt or gradual withdrawal of warfarin [34]. Very high levels of thrombin activation were seen in a few patients treated with abrupt withdrawal, two of whom developed thrombotic events (one recurrent DVT and one thrombosis in a varicose vein).

In spite of this recent view on oral anticoagulant maintenance, many oral surgeons are still not adopting this approach [44]. In fact, the ideal local hemostatic measures to adopt in such patients (e.g. gelatin sponge, sutures or no sutures, or mouthwash with tranexamic acid) and the range of INR values for safe dental extraction are still matters of debate [45].

The number of bleeding complications was not statistically different between surgical extractions and non-surgical ones or according to the type of tooth extracted (molar, wisdom, or incisor). In contrast with the previous protocol, absorbable sutures were used as they cause less trauma than removal of non-absorbable sutures [46] (Figure 5).

Dental extractions in patients with an INR higher than 4 should not be performed. This value should be considered as the upper cut-off of the range for the procedure, and in patients not needing surgery for an emergency medical condition, the patient should be referred to their physician for an adjustment of oral anticoagulant dose [46].

All the procedures were performed in an outpatient setting, and none of the postoperative late bleeds required hospitalization, transfusions, or further drug prescription, as local measures were sufficient to stop the bleeding. The management procedures are more extensive and time-consuming than those routinely performed, but are nevertheless completely feasible and easily used in an ordinary dental office.

Indeed, the significance of this study is that it demonstrates that patients taking oral anticoagulants are safely and easily managed in a dental office, with the adoption of only a few, precise strategies.

The present study confirms that, in oral anticoagulant patients treated with local measures, no serious bleeding complications are expected after dental surgery. The incidence of bleeding complications was not statistically different between patients maintained with anticoagulant or bridging. In conclusion, dental extractions can be safely performed in anticoagulated patients on an outpatient basis, with cost reduction and less discomfort (Figure 3).

Conclusions

Better documentation of various approaches and outcomes of warfarin patients undergoing dental procedure is needed. The risk of clinically relevant bleeding after dental procedures appears to be low. Thorough risk assessment and further prospective studies are warranted. Efforts should be made to create a standard management protocol for patients on warfarin during dental procedures.

Acknowledgements

We wish to thank all dental clinic nurses and clerks for assistance and the patients for their cooperation. We also wish to acknowledge our statistician for their support and effort.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Fayez El Shaer, King Fahad Cardiac Center, Department of Cardiac Sciences, College of Medicine, King Saud University, 11472 Riyadh, PO 7805, Saudi Arabia. Tel: 4671161; Fax: 4671158; E-mail: felshaer@ksu.edu.sa

References


[2] Spyropoulos AC and Douketis JD. How I treat anticoagulated patients undergoing an elec-
Approaches and outcomes for patients on warfarin undergoing dental procedures

116

Approaches and outcomes for patients on warfarin undergoing dental procedures


