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Epistaxis and oral anticoagulant therapy*

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SUMMARY

Epistaxis in the anticoagulated patient poses a complicated management problem, which requires interdisciplinary collaboration. The aetiology of the majority of cases of epistaxis remains idiopathic, but an ageing population and the prevalence of ischaemic heart disease and peripheral vascular disease has meant that there are increasing numbers of patients on long term oral anticoagulant therapy. This has led to a concomitant increase in the incidence of complications experienced.

We have reviewed the available relevant literature and guidelines in the current management practice in this scenario. In light of this, we propose a more standardised algorithm for the management of epistaxis in this challenging group of patients.

Key words: epistaxis, anticoagulation, warfarin, aspirin, therapy

INTRODUCTION

Epistaxis is the commonest emergency to present to an Ear, Nose and Throat (ENT) department, and will affect approximately 60% of the population at some stage of their lives. 6% of these people will require professional medical treatment (Elahi et al., 1995). Epistaxis has a number of local and systemic aetiological factors, but 85% of cases are said to be idiopathic – in the remainder anticoagulation therapy is one of the most commonly documented causes (Kotecha et al., 1996). The effects of local factors such as trauma, inflammation and neoplasia are accentuated in the patient on anticoagulant therapy. However, the association between epistaxis and hypertension is still disputed (Temmel et al., 2001). Hypertension is commonly said not to be related to increased incidence of epistaxis (Weiss, 1972; Fuchs et al., 2003). Hypertension is, however, commonly reported to contribute to episodes of refractory bleeding, and Jackson and Jackson noted it to be the most prevalent comorbidity in this scenario (Jackson and Jackson, 1988). Many authors empirically attribute the elevated blood pressure to the apprehension caused by the bleeding, but it would seem more likely that the generalised atherosclerosis limits the ability of the affected vasculature to relax due to the associated loss of elasticity.

Many different forms of drug therapy have been implicated in causing epistaxis. The commonest are warfarin, aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Other drugs implicated in causing epistaxis include selective serotonin reuptake inhibitors (Leung and Shore, 1996), cytotoxic chemotherapy (Kumar et al., 1996), antifungal agents (Grunwald and Amichai, 1998), fluoroquinolone antibiotics (Gales and Sulak, 2000), sodium chloride eye drops (Kushner, 1987), sildenafil for erectile dysfunction (Hicklin et al., 2002), valproic acid for epilepsy (Serdaroglu et al., 2002) and the oral contraceptive pill (Man and Segal, 1981).

There is no doubt of the benefit and cost effectiveness in treating high risk vascular patients with daily aspirin (Antiplatelets Trialists' Collaboration - Part I, 1994) but these benefits need to be weighed against the potential risks such as epistaxis. Intracranial haemorrhage and gastrointestinal bleeding have received widespread recognition as a complication of aspirin and other NSAID therapy, with one report suggesting up to one third of elderly patients with bleeding peptic ulcers taking these drugs (Faulkner et al., 1998). Interestingly, one study carried out in Finland has also shown a history of epistaxis in patients who have used aspirin or other NSAIDs to be an independent risk factor for intracerebral haemorrhage (Saloheimo et al., 2001).

Clearly, doctors and patients need to be made more aware of the possible risk of epistaxis associated with aspirin and NSAIDs, and the self medicating public need to be educated of their potential life threatening side effects.

The role of routine coagulation studies in patients with epistaxis remains unclear. In the majority of cases there is no discernable dysfunction of the normal haemostatic mechanism. However, current practices in the use of clotting screens are very variable. Holland et al. evaluated the use of coagulation studies in patients admitted with epistaxis (Holland et al.,

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1999). Their results showed that the majority of consultants (70%) did not request routine coagulation studies but there did not appear to be any consensus between the junior staff, with 51% routinely checking the coagulation status. Thaha et al. carried out a study to assess the necessity of such tests in patients admitted with epistaxis. Their results showed that abnormal coagulation studies (INR/APTT) were only identified in those patients taking warfarin or a combination of warfarin and aspirin. They therefore advocated that these haematological tests should be limited to those patients with recurrent or persistent bleeding despite adequate medical therapy, patients on anticoagulation therapy, or those with a history suggestive of an underlying bleeding diathesis (Thaha et al., 2000).

The management of epistaxis in the anticoagulated patient poses a potentially difficult management problem. There is limited consensus in the literature regarding their most efficient and cost effective management. We therefore have proposed a more standardised algorithm to provide some clinical guidelines for the management of epistaxis in this patient group.

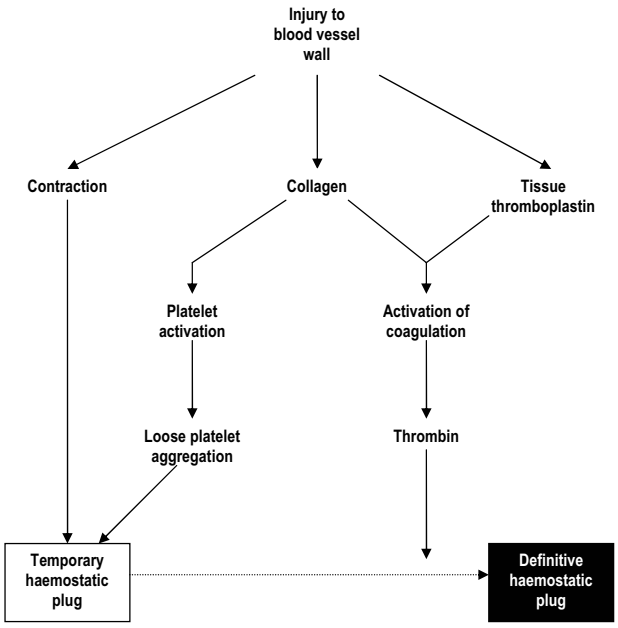


Figure 1. Summary of reactions involved in haemostasis.

Pathogenesis

In the normal clotting mechanism the primary response to bleeding is an interaction between the blood vessel and circulating platelets. Following vascular injury the vessel goes into spasm and there is a release of tissue factors that result in local platelet adherence and aggregation, thereby forming a platelet plug (Figure 1). The secondary response is activation of the clotting cascade via the intrinsic and extrinsic pathways, resulting in formation of a fibrin clot (Figure 2).

Aspirin and other NSAIDs prolong the bleeding time by affecting platelet function. This is by their alteration of arachidonic acid metabolism via inhibition of cyclo-oxygenase, resulting in inhibition of prostaglandin and thromboxane synthesis (Weiss, 1978).

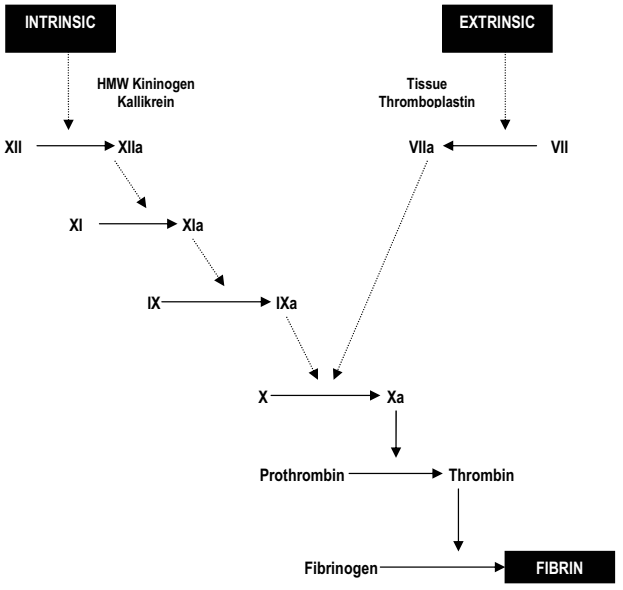


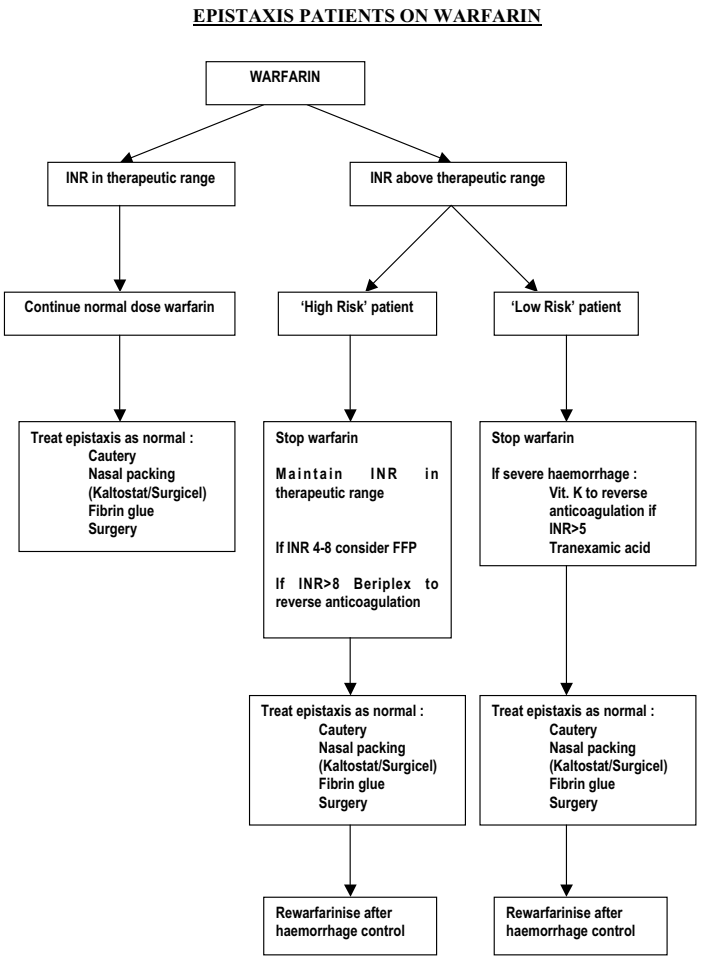
Figure 2. The clotting mechanism. (a is the active form of clotting factor).

The action of warfarin sodium is by inhibition of vitamin K synthesis in the liver. This results in deficiencies of vitamin K dependant clotting factors, namely factors II, VII, IX and X. Its action is therefore primarily in inhibiting the extrinsic pathway of the clotting cascade.

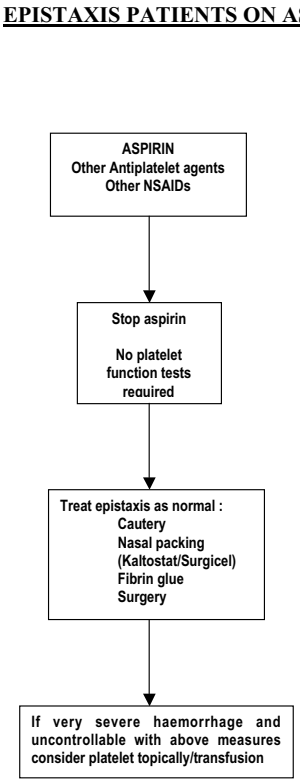
Aspirin induced epistaxis

A significant number of elderly patients in the community are prescribed aspirin prophylactically to decrease the incidence of myocardial infarction, stroke, venous thromboembolism and peripheral vascular graft failures (Antiplatelets Trialists' Collaboration - Part I, II and III, 1994). There are also a wide variety of commercially available NSAIDs, which are commonly self-administered for degenerative joint disorders and musculoskeletal complaints.

Aspirin irreversibly interferes with platelet function and hence its effects last for 5-7days i.e the life of the platelet. In contrast, other NSAIDs have a reversible but variable effect on the cyclo-oxygenase pathway. Although the use of aspirin has been clearly implicated in contributing to epistaxis, the effect of other NSAIDs remains unclear. Tay et al. showed a significant association between aspirin exposure and hospital admissions for epistaxis but no significant association between exposure to other NSAIDs and epistaxis (Tay et al., 1998). They suggested that the difference in effect between aspirin and other NSAIDs is perhaps due to the potency and qualitative difference in platelet dysfunction between these two groups of drugs. However, in contrast, Watson and Shenoi did show a statistically significant correlation between other NSAID therapy and epistaxis in their case control study (Watson and Shenoi, 1990).



ALGORITHM 1. Management of epistaxis in patients on warfarin.



ALGORITHM 2. Management of epistaxis in patients on aspirin.

Warfarin induced epistaxis

The use of warfarin is widespread in patients with prosthetic valves, a history of atrial fibrillation and previous thromboembolic events, to protect against future thrombotic events.

Warfarin requires highly individualised dosing, titration and monitoring, as there are many other drugs and disease states including chronic liver disease and malabsorption syndromes, which can interact with warfarin, altering its clinical effects. The activity of warfarin can be monitored by measuring the international normalised ratio (INR). This needs to be regulated in patients on long-term warfarin to ensure that the anticoagulation therapy is maintained in the desired therapeutic range. Thaha et al. showed that nearly one third of their patients admitted with epistaxis on warfarin were found to have an INR above the upper limit of their therapeutic range (Thaha et al., 2000). The number of patients on warfarin who are admitted to hospital with epistaxis has been reported to be as high as 17% (Srinivasan et al., 1997).

Guidelines in management of epistaxis in the anticoagulated patient

Epistaxis in the anticoagulated population can vary in severity from a minor nuisance bleed to life threatening haemorrhage. Despite this, Lavy showed that 40% attending the anticoagulation clinic were unable to recall a single first aid measure to control a nose bleed, even though a quarter of the group he studied had experienced at least one episode (Lavy, 1996).

The mainstay first line treatment for epistaxis in patients on anticoagulants is no different from the management of epistaxis in general. This involves the use of vasoconstrictors, electro or chemical cautery and anterior and posterior nasal packs. If these conservative measures fail, examination under anaesthetic will usually involve selective vessel ligation of the terminal arterial supply of the nasal mucosa (Sharp et al., 1997). Also, argon plasma coagulation has been described as a useful alternative for the treatment of bleeding telangectasia in the nasal mucosa, particularly in patients with hereditary haemorrhagic telangectasia (Bergler, 2003).

A review of the literature has highlighted that there is little consensus in managing epistaxis in the anticoagulated patient. There are specific factors that warrant consideration in the presence of a coagulopathy. The need to reverse oral anticoagulation is disputed. One report has shown that warfarin can be safely continued in patients with epistaxis if the INR is within the therapeutic range (Srinivasan et al., 1997). In their group, they had no additional bleeding complications due to continu-

ation of warfarin. Continuation of warfarin through the acute episode would clearly save time in re-establishing anticoagulation (which often involves prolonged hospitalisation), and avoid the risk of thromboembolic complications.

In cases of bleeding patients who are overanticoagulated, there have been a number of methods employed to reverse the anticoagulation. These include the use of fresh frozen plasma, vitamin K administration and the use of clotting factor concentrates. One group have described their use of clotting factor concentrates to restore normal haemostasis in patients with bleeding episodes, including epistaxis, due to overanticoagulation with warfarin (Nitu et al., 1998). Although it has been described as a safe, rapid and effective means of reversal, its expense at approximately £1300/patient/reversal is undoubtedly a limiting factor.

Vitamin K is a cofactor necessary for synthesis of coagulation factors II, VII, IX and X. Warfarin decreases the availability of vitamin K in the hepatocytes by acting as a competitive inhibitor. If the INR is grossly prolonged and bleeding is severe, vitamin K can be administered, but should be used with caution. Its effect does not begin for at least 6 hours and its use is associated with a delay of about 1 week in resuming effective anticoagulation once the warfarin is restarted. These may be limiting factors for its effective use in a patient with acute epistaxis who requires anticoagulation following haemorrhage control, prior to discharge. In contrast, fresh frozen plasma (FFP) has a much faster onset of action and avoids problems with re-establishing anticoagulation.

Tranexamic acid is an antifibrinolytic agent which exerts its effect by inhibiting the interaction of plasminogen and plasmin. It has no effect on blood coagulation parameters but may reduce blood loss and transfusion requirements. Its use has been widely described in managing severe epistaxis in hereditary haemorrhagic telangectasia (Klepfish et al., 2001, Lozano, 2002). Its use has also been described after oral surgery in anticoagulated patients, in the form of a mouthwash, which has significantly reduced post-operative bleeding (Dunn and Goa, 1999). It may therefore also have a role as a topical as well as systemic agent in anticoagulated epistaxis patients.

Alternative local management options have been proposed. Local administration of platelets in patients with thrombocytopenia has been described in those with epistaxis unresponsive to platelet transfusions (Kumonsky and Zylberman, 1997). This would provide a local concentration of platelets to set off the normal primary platelet response at the site of bleeding.

Fibrin glue has also been used to arrest epistaxis in the presence of a coagulopathy (Walshe et al., 2001, Vaiman et al., 2002). Fibrin is the final product of the clotting cascade, which can be topically applied to the nasal mucosa over the bleeding site via a custom made syringe. It has been found to be at least as effective as cautery and foam nasal packing. In addition, the patients' systemic anticoagulation status can be maintained thereby avoiding any increased risk of potential thrombosis and emboli.

As an alternative to more traumatic tamponade materials used, haemostatic gel-tamponades are available, which are covered with an active platelet aggregating material (RapidRhino®). These expand on application, but are extremely soft and have the added advantage of possible enhancement of the normal haemostatic mechanisms (Rieman, 2002).

In our own experience, we have found the use of Kaltostat® (a fibrous fleece of alginic acid) and Surgicel® (oxidised cellulose) to be very effective in aborting cases of epistaxis associated with anticoagulation. These are atraumatic to insert, do not require removal, and in association with the correction of the underlying haemostatic deficiency, often obviate the need for any additional nasal packing with the associated possible trauma to the nasal mucosa. A newer topical haemostatic sealant material, namely FloSealTM Matrix® which is a gelatin-thrombin based haemostat, has been shown to be effective in controlling intra-operative bleeding in vascular surgery (Weaver et al., 2002). Its use has not yet been reported in treating epistaxis, but there may be a place for exploring its use in this scenario.

Epistaxis in patients on warfarin (in therapeutic range)

The dose and indication in patients taking warfarin must be carefully noted. It should be routine practice to check a clotting screen in these patients on admission. If the INR is within the desired therapeutic range the patients can continue their normal dose of warfarin and the acute episode of epistaxis treated in the normal conventional way with nasal cautery or nasal packing. The use of merocel or BIPP packs should ideally be avoided in anticoagulated patients, as they are traumatic to insert and may potentiate further bleeding in this group of patients. We therefore advocate the use of Kaltostat® or Surgicel® to be applied either over a localised bleeding point or rolled into the shape of a nasal tampon which can then be inserted like a conventional nasal pack in cases of diffuse or posterior bleeding. If these simple measures fail, one may need to consider the topical use of fibrin glue for localised bleeding or surgery for selective vessel ligation if required. The key is that this particular group of patients whose clotting status is in therapeutic range can be essentially managed in the same way as all other uncomplicated cases of epistaxis, without the need for reversal of anticoagulation.

Epistaxis in 'high risk' overanticoagulated patients on warfarin

The indication and dose of warfarin must again be noted. If a routine clotting screen highlights that the patient is overanticoagulated, their subsequent management in terms of reversal of anticoagulation is dependant on 2 factors; 1) the extent of overanticoagulation and 2) the therapeutic indication for taking warfarin.

Patients on warfarin for mechanical heart valves and recurrent deep vein thromboses or pulmonary emboli are considered 'high risk' for future thromboembolic events. These patients therefore need to be managed aiming to maintain their antico-

agulation status within the therapeutic range. The degree of reversal must be carefully titrated and the choice of reversal agent is dependant on the extent of overanticoagulation on admission.

For high risk patients, if the INR <4, the warfarin may need to be stopped. The INR should be closely monitored to maintain anticoagulation at the lower end of the therapeutic range, and the epistaxis should be dealt with as above. One group have even suggested that anticoagulated patients with prosthetic heart valves undergoing minor oral surgery can continue their anticoagulation regime peri-operatively if the INR is less than 4 (Webster and Wilde, 2000). This would support the idea that epistaxis in such patients with INR<4 is unlikely to be significantly contributable to warfarinisation. Therefore provided local haemostatic measures can control the bleeding, the anticoagulation may not need to be greatly modified.

If the INR 4-8, the warfarin should be stopped and the INR may need to be reduced with use of Fresh Frozen Plasma (FFP). However, its necessity is determined by how high the INR is on admission and how quickly it falls after stopping the warfarin. Its use should be guided by monitoring the INR, aiming to lower this towards <4.

If the INR>8, the warfarin should be stopped and the overanticoagulation can be reversed in cases of very severe haemorrhage with the use of Beriplex®. This is a plasma derived concentrate of factors II, VII, IX, and X or Prothrombin complex. In high risk patients, the use of Beriplex should also be accompanied by the administration of heparin in order to prevent thrombosis. Beriplex® is said to be safer to use with respect to the risk of transmission of infective agents as compared with other blood products such as FFP, as there are more stringent controls applied to the selection of donors and in addition, the products are heat treated to eliminate and inactivate any virus activity. However, administration of Beriplex® has been reported to be associated with thromboembolic complications and myocardial infarction. Therefore in patients with a history of coronary heart disease, one must exercise caution and weigh up potential benefits of treatment with Beriplex® against the potential risk of such complications. In high risk patients, the administration of antithrombin III prior to the administration of prothrombin complex gives some protection against further thromboembolic events. This treatment regime with Beriplex® for reversal of anticoagulation should only be reserved for cases of refractory, intractable epistaxis, which fail to be controlled with routine measures.

Epistaxis in 'low risk' overanticoagulated patients on warfarin

In these patients the warfarin can be stopped and they do not require maintaining anticoagulation in the acute stage. Depending on the degree of overanticoagulation and the severity of bleeding, there may be a place for the use of tranexamic acid or vitamin K to enhance coagulation, whilst simultaneously controlling the epistaxis.

Epistaxis in patients on aspirin / other antiplatelet agents

All patients with epistaxis who are on prophylactic aspirin for vascular disease or a single deep vein thrombosis can safely stop taking their aspirin. There are also many patients taking other NSAIDs for musculoskeletal pain and a variety of newer antiplatelet agents, such as clopidogrel for secondary prevention of coronary heart disease. These also irreversibly inhibit platelet aggregation and may contribute to persistent bleeding in epistaxis patients. All such drugs can safely be stopped as the antiplatelet effect lasts for 5-7 days. Despite this, we feel that it is still advisable to stop these medications as this will allow some platelet regeneration and therefore a theoretical increase in platelet activity which may aid clotting. However, a recent survey of vascular surgeons suggested there was a consensus of opinion against the cessation of antiplatelet drugs peri-operatively, although interestingly it was suggested by a number of correspondents that they would stop clopidogrel, due to their concerns over its enhanced antiplatelet activity (Smout and Stansby, 2003).

There is no indication for any routine platelet function tests in patients on any of these drugs as these can be expected to be abnormal for up to 10 days after discontinuation.

The epistaxis should again be managed as normal and the antiplatelet agent may be recommenced when the epistaxis is controlled, which in the vast majority of cases will be within the 7-10 day 'window'.

In rare cases of severe haemorrhage which may be resistant to control with conservative and surgical measures, one may need to consider platelet administration either topically or as a transfusion, after liasing with the local haematologists.

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