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REVIEW ARTICLE

Basic concepts and common misconceptions about coagulation and the management of anticoagulation in the trauma patient

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Trauma is a common reason for seeking emergency care, and when a patient is on oral anticoagulants the management of trauma becomes more complex. Advances have been made steadily in relation to vitamin K agonists, but even though these drugs have been available for over 50 years there is great variability in the handling of reversion and complications. The introduction of new oral anticoagulants with significant advantages and more convenient dosing further complicates management; craniocerebral trauma is an area that poses special problems. Control of hemostasis and the safe reversion of anticoagulation are reviewed in this article. We believe that multidisciplinary management governed by protocol is necessary. Protocols should be based on the best available evidence and be certified by relevant scientific associations as we wait for guidelines supported by adequate evidence to become available. [Emergencias 2012;24:134-142]

Key words: Anticoagulation. Vitamin K antagonists. Craniocerebral trauma. Fresh frozen plasma. Prothrombin complexes. Activated recombinant factor VII.

Introduction

Traumatic injuries of different magnitudes are a frequent reason for consulting the emergency department (ED). In different types of trauma patients on oral anticoagulants, management is complicated and this is an area under constant review. A special group is elderly people suffering from traumatic head injury (THI)[1]. The need for proper management of hemostasis and rapid but safe reversal of anticoagulation in severe THI, the methods employed, the indication of a second CT scan in mild-moderate THI during observation[2-7] and algorithms to guide and better organize therapeutic measures are some of the aspects under recent review. In the absence of clinical trials, we believe a multidisciplinary management protocol is required, based on the best available evidence and endorsed by the different scientific societies involved. In this paper we briefly review basic concepts and some universal errors carried over from the past that must be corrected, and we present some proposals on management protocols.

Oral anticoagulants or anti-vitamin K?

Firstly, given the flood of new oral anticoagulants directed against thrombin or activated factor X[8], we believe it is more correct to start using the term vitamin K inhibitors or anti-vitamin K agents (AVK) to refer to classical oral anticoagulants. There are several AVKs on the market, each with their own half-life and dosage, and they are not interchangeable. Those with a longer half-life have a longer onset of action which requires, in some indications or circumstances, the use of bridge therapy or simultaneous heparin.

Apart from acenocoumarol (Sintrom® in

Table 1. Comparison of various characteristics of oral dicoumarol and other antithrombotic agents

Properties	Dicoumarol	Direct thrombin inhibitors	Activated Factor X inhibitors
Activity	Inhibits the synthesis of vitamin K dependent factors.	Acts directly on thrombin.	Inhibición directa del factor X activado.
Onset of action	Several days. At various times, depending on the compund: Slower for warfarin.	A few hours.	A few hours.
Type of action	Slow-acting anticoagulant, indirect decrease of vitamin K dependent factors.	Direct-acting anticoagulant.	Direct-acting anticoagulant.
Route of administration	Oral.	Oral (Dabigatran).	Oral.
Therapeutic stability	No.	Yes.	Yes.
Anticoagulant dose	Variable, depending on the patient, indication and the desired INR	Fijas según la indicación.	
Therapeutic level controlled by laboratory values	Yes.	No.	No.
Drug Interactions	Significant and common.	Minimum.	Little experience. Potent inhibitors of CYP3A4 and P-gp (eg; ketoconazole, itraconazole or inhibitors HIV protease) increase the concentration of rivaroxaban. Induce CYP3A4 (eg phenytoin, carbamazepine, rfampicina, phenobarbital) lower drug levels.
Interactions with food	Multiple.	No.	No.
Antidote	According to patient condition: Vitamin K, PFC, CP, rFVIIa (Novo Seven®).	There is no antidote at present.	There is no antidote at present.
Possibility of neutralization	Use of the antidote (vitamin K).	Not specific. By different compounds (PFC, PCC, rFVIIa).	Not specific. By different compunds (PFC, PCC, rFVIIa).
Effect of suspension	Moderate and progressive increase of K dependent factors, depending on the drug used.	The half-life is about 4-6 hours.	

FFP: fresh frozen plasma: PCC: prothrombin complex concentrate, rFVIIa: recombinant activated factor VII.

Spain), widely used in our setting, there is growing use of warfarin – predominant in Anglo-Saxon countries and taken by most of our tourists and foreign retirees living in Spain. Warfarin, with its longer half life, is the most widely distributed anticoagulant worldwide and the agent most documented in the international scientific literature.

It is useful to recall that AVKs not only inhibit coagulation factors, but also natural inhibitors such as protein C and protein S, and that the reduction of levels is not homogeneous. Also, their effectiveness and the response are influenced by the presence of genetic polymorphisms, liver function and possible interaction with other drugs or dietary supplements. It should also be noted that the presentations of vitamin K available on the market differ: there are at least two different commercial preparations, konakion® (phytomenadione) and kaergona® (menadione) (which we believe should be withdrawn), with different dosage, route of administration and effectiveness, so they are not interchangeable.

With the forthcoming introduction of new oral anticoagulants in routine clinical practice[8], direct inhibitors of thrombin (dabigatran) or activated factor X (rivaroxaban and apixaban) require review of our knowledge and certain possibly misleading notions (Table 1). Direct inhibitors of thrombin only act on thrombin. They offer, at a higher cost, the convenience of a single dose for the prophylaxis of thromboembolic disease (double in the case of other indications pending approval in Spain), no need for dose adjustment or periodic controls with (analytical) laboratory tests, with a better safety profile than low molecular weight heparin (LMWH) or anti-aggregants[9], but on the other hand no antidotes or reversal methods, and restricted use in dialysis patients or in the event of hemorrhage, and the administration of proactive drugs such as recombinant activated factor VII (rFVIIa) should be considered[10].

What is the ideal anticoagulant? The obvious answer is one with the following characteristics: effective, safe (reversible and possessing an antidote), with easy administration and compliance, high bioavailability, fast and direct action but appropriate half-life, no need for dose adjustment or

Table 2. Differences between currently approved anticoagulant agents

	Route	Action	Onset	Antidote	Need for monitoring	Pharmacological dose variability	Interaction
AVK (Sintrom®)	Oral	Indirect	Late	Yes	Yes	Yes	Yes
UFH	IV	Indirect	Immediate	Yes	Yes	*	(albumin)
LMWH	SC	Indirect	Fast	Yes	Yes**	*	No
Fondaparinux	SC	Direct	Fast	No	No	No	No
DTI	Oral	Direct	Fast	No	No	No***	No
Inh. F. Xa	Oral	Direct	Fast	No	No	No	Yes

AVK: anti-vitamin K; UFH: unfractionated heparin; LMWH: low molecular weight heparin; DTI: direct thrombin inhibitor; Inh. F Xa Inhibitors of activated factor X; IV: intravenous; SC: subcutaneous. * Adjusted for weight. ** platelets and hemoglobin level. *** Reduced dose in elderly and renal failure patients.

periodic controls with laboratory tests, and low cost or at least cost-efficient. Table 2 shows the characteristics of the main groups of anticoagulants.

Are analytical clotting studies useful?

Now in the second decade of the 21st century, we are still suffering the consequences of the academic theoretical model of the 1960s which explained the famous coagulation cascade in terms of an extrinsic pathway, an intrinsic pathway and a common or terminal pathway. It is now accepted that there is a single pathway of the coagulation cascade. This new model is hemostatic, based on initiation, amplification and propagation. The ultimate goal is the activation of prothrombin (factor II), so that its active form, thrombin, starts fibrin formation (factor I) from circulating fibrinogen (Figure 1). Thrombin plays a key role in thrombus formation. All anticoagulants exert their inhibiting effect directly or indirectly on thrombin.

The old academic model of two pathways, still taught in some medical schools, only serves to explain two analytical coagulation determinations developed primarily for monitoring treatment with classical anticoagulants: activated partial thromboplastin time (aPTT) for heparin, and prothrombin time (PT) for AVK. Then, in order to homogenize and reduce the variability of results of AVK monitoring, the standardized International Normalized Ratio (INR) was introduced. The INR was developed to standardize PT coagulation values obtained in each patient. Due to variations between different batches of manufacturer's tissue factor used in the reagent to perform the PT test, the results may present variations. For each batch of tissue factor, the manufacturer assigns an ISI value (International Index of safety) which indicates how a particular batch of tissue factor compares to an international reference tissue factor. The ISI is usually between 1.0 and 2.0. The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the batch used.

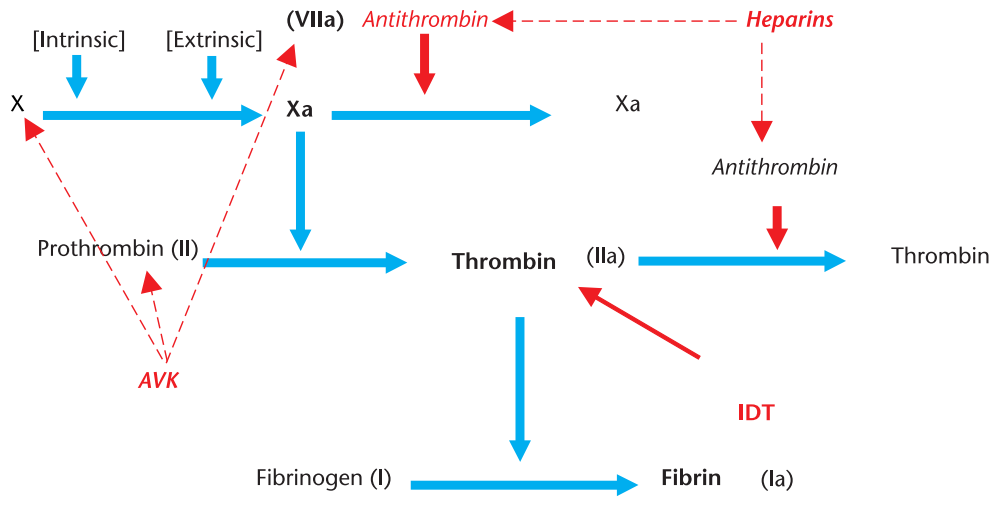

Figure 1. Common model of the coagulation cascade and sites of action of anticoagulant drugs. AVK: anti-vitamin K; DTI: direct thrombin inhibitors.

Table 3. Limitations of routine analytical studies of coagulation in clinical practice (Dizk 2007, amended)

1. The relationship between levels of coagulation factors and the values of PT or aPTT is not linear.
2. Slightly positive or abnormal coagulation test results may occur in patients with biologically normal clotting factor level.
3. INR and aPTT tests overestimate deficits at the top of the coagulation cascade and underestimate deficits at the bottom or end.
4. Tests may overestimate the degree of lack of a clotting factor if more than one factor is reduced.
5. INR and aPTT tests are useful for analyzing defects in patients with fibrin formation disorders, but they are not designed to predict the risk of bleeding.
6. More importantly, these tests are insufficient to assess overall hemostasis. The most widely used technique for the determination of fibrinogen is an indirect estimate, strongly influenced by the deficit or consumption of other factors, prolongation of aPTT or PT and affected by inflammation and proteins.

PT: Prothrombin time, aPTT: activated partial thromboplastin time.

However, these techniques have a number of limitations, beyond the scope of this review, but summarized in Table 3, and interested readers are referred to the authoritative text by Walter H. Dizk[11].

Such are their limitations and low predictive value, almost zero compared to the value of clinical interview and personal or family history, that the French Society of Anesthesia does not recommend analytical coagulation studies to detect preoperative risk of hemorrhagic or thrombotic events (Dr. N Rosencher, personal communication).

Hemotherapy: What is the utility of fresh frozen plasma?

Denomination and origin

Another important but poorly understood concept that requires better explanation is hemotherapy or the use of blood components or hemoderivatives[12]. Blood transfusion is one of the oldest and most widely accepted medical practices, but unfortunately it is largely not evidence-based. Common terms and concepts regarding plasma require clarification. First, in Spain fresh plasma is not generally available (only in some Nordic countries), but fresh frozen plasma (FFP) is used. Moreover, in our country the law requires that FFP be subjected to extra safety measures. It can be inactivated with different methods: methylene blue or psoralens; or after a quarantine period, when the donor repeats a donation and the negativity of serological and molecular studies of the screening tests are reconfirmed. This FFP does not have the same composition, or levels of coagulation factors, nor is it equally effective. Recently, a Spanish collaborative group, in a prospective observational study on the management of patients with thrombotic thrombocytopenic purpura, confirmed their previous findings on the lower efficiency of FFP inactivated with methylene blue – of predominant use in Spain – compared with quarantined FFP[13].

Safety

In contrast to popular opinion, the administration of FFP is not innocuous. In recent years numerous reviews have appeared on the effectiveness and safety of blood transfusion, particularly a consecutive series of monographs on hemotherapy published in the journal Lancet[14,15] and one in Blood[12]. At present the most frequently reported risks responsible for increased mortality in USA and several European countries are: transfusion associated circulation overload (TACO), and especially transfusion related acute lung injury (TRALI), and both with increased incidence are clearly associated with the administration of plasma[12].

Dose

The theoretical recommended dose of FFP is greater than 30 ml / kg of body weight, administered relatively fast. However, in practice we do not usually administer more than 7.5-10 ml / kg of body weight[16], and this is done slowly, because it is not possible to administer FPP as recommended in many of our patients due to access problems or poor hemodynamic tolerance. This slow rate of administration, sometimes even continuous infusion, results in a significant reduction of factor VI levels, which already tend to be lower in inactivated FFP than in fresh plasma[13]. One must remember that each of the clotting factors has a different half life and concentration, with clinical and therapeutic consequences. These half-lives range from 4-5 days for fibrinogen (factor I) or prothrombin (factor II), 8 hours for factor VIII or von Willebrand factor, to 4-6 hours for factor VII and as short as 1-2 hours for factors X and XII.

Lack of efficiency, effectiveness and efficiency of FFP

In addition, there is evidence that the administration of FFP at usual doses is not very useful[11,17,18]. The classic meta-analysis by Stanworth et al.[18] on the efficacy of FFP confirmed what several observational studies and a few clinical trials had reported: that administration of FFP before an invasive procedure does not correct the result of altered coagulation test. There is no evidence that the prophylactic administration of FFP shortens or corrects bleeding times more effectively than transfusions administered after a therapeutic procedure. Similarly, there is no evidence that prophylactic FFP transfusions before an invasive procedure reduce potentially increased bleeding more effectively than therapeutic FFP following an invasive procedure. A classic study carried out at Massachusetts General Hospital found that FFP transfusion only managed to normalize PT-INR values in 0.8% of patients and reduced the PT-INR value to half normalized values in only 15% of patients. The average reduction of PT was 0.20 seconds (mean decrease in INR of 0.07). Multivariate analysis showed no correlation between the amount of bleeding and the following: pre-transfusion PT-INR, aPTT, platelet count or creatinine values. The authors concluded that FFP transfusion managed to correct minor abnormalities in coagulation values in a minority of patients, while PT remained uncorrected in 99% of patients[19].

Alternatives to transfusion of fresh frozen plasma

Prothrombin complex concentrates?

Prothrombin complex concentrates (PCC) are of plasma origin and contain the four factors dependent on vitamin K for hepatic synthesis (II, VII, IX and X). They also contain two other proteins of hepatic origin with anticoagulant properties: protein C and protein S[20].

PCCs are known and were used from the 1950s. At the time they were used to reverse episodes of bleeding in patients with hemophilia B, and later in patients with hemophilia A. In the 1970's it became apparent that the effectiveness of PCCs was dependent on the amount of activated clotting factors present in the composition. From that moment the pharmaceutical industry developed so-called activated PCC, obtained by controlled activation of the coagulation factors they contain. Currently, due to these advantages, PCCs are particularly indicated to reverse the anticoagulant effects of AVK, to treat coagulation disorders in patients with liver disease and cases of bleeding due to clotting factor deficit[21].

PCCs currently available differ substantially in constitution[22], with different concentrations of coagulation factors, and some even incorporate low doses of heparin. They have a high safety profile regarding the risk of thrombosis and the transmission of viruses[23]. PCC can correct clotting times (which FFP has not been shown to do) by increasing some of the coagulation factors and their inhibitors altered by AVK[24]. Of course, it must be remembered that the correction is transient; once the effect is extinguished due to the different half-life of the components, the patient will be anticoagulated again.

A consensus document has recently been published on the proper use of PCC, endorsed by the Ministry of Health and the Medical Association, and by British guidelines[25], as well as a meta-analysis by Stanworth et al.[16]. The slowness with which conventional treatment corrects INR, the disputed use of vitamin K for its slow response, and especially FFP transfusion, have led to the recommendation that PCC be used as the first line of AVK reversal protocols. The British guidelines and other later European guidelines, as well as the Cochrane library, recommend first administration of PCC before FFP[25].

PCC offers clear advantages over other drugs used to reverse anticoagulation (Table 4): faster INR correction, faster and more efficient correction of plasma hemostasis (coagulation), with almost immediate normalization of coagulation times, and avoids all the side effects of hemoderivatives: especially volume overload associated with FFP, episodes of allergic and anaphylactic reactions, non-hemolytic febrile reactions, hemolytic blood group incompatibility reactions, TRALI (the main cause of transfusion-related death in the U.S. in 2005-2009) and is not associated with the risk of viral or prion transmission[26-28].

Furthermore, the use of PCC prevents or reduces progression of intracranial hemorrhage (ICH). There are still more benefits and other details of PCC versus FFP worth mentioning: infusion rate is much faster than for the FFP which usually requires up to 30 minutes for preparation and cross-matching; antiviral protection is more complete in preparations subjected to detergent (Lipid-enveloped viruses) and / or nanofiltration (viruses without a lipid envelope) and the cost of the pro-

Table 4. Comparison between the different measures available to reverse the effect of anti-vitamin K

Product parameter	FFP	PCC	rFVIIa	Vitamin K
Volume	Large	Small	Small	Small
Speed of administration	Slow	Fast	Fast	Bolus slow/perfusion fast
Availability	Delayed (around 30 minutes)	Immediate	Immediate	Immediate Late affect
Safety transmission of pathogens	Low (only 1 step for inactivation / viral removal and quarantine)	High (S / D, nano-filtration, two-step inactivation/ viral removal)	No risks described	Total
Support Group	Yes	No	No	No

FFP: fresh frozen plasma; PCC: prothrombin complex concentrate, S / D: Solvent / detergent; rFVIIa: Recombinant Factor VIIa.

duct (usually above 200€ per vial), should be weighed against that of FFP.

Regarding the supposedly higher cost of PCC, the cost of FFP is conveniently not mentioned. In Catalonia in 2009 the price of one unit of FFP inactivated with methylene blue was 66.6€ (€ 88.45 if purified). A patient weighing 80 kg would require between 1,600 and 3,000 mL of FFP (10-20 mL / kg) about 250-280 mL per unit, equivalent to between 5 and 12 units of FFP, i.e. between 333 and 1,061€.

Recombinant Factor VIIa?

The emergence of rFVIIa a few years ago was a transitional revolution and raised great hopes for the management of massive uncontrollable bleeding and even ICH[29]. Its use increased dramatically, as off label. At the University Hospital Miguel Servet in 2010, rFVIIa was the top drug for intensive care unit expenditure (personal communication). However, the few randomized clinical trials involving multi-trauma or ICH failed to demonstrate its effectiveness and there was some increase of thrombotic events in patients receiving rFVIIa. The Sevilla Document on alternatives to blood transfusion (ATSA)[30] recorded the following conclusions: "The administration of rFVIIa constitutes a particularly useful alternative to reduce bleeding and / or transfusion requirements in various medical or surgical procedures where patients present massive hemorrhage not controlled by conventional methods. The use of rFVIIa (80-120 mg / kg) may be indicated in these situations when other therapeutic measures have failed or are insufficient. For ICH, the recommended dose is 80 mg / kg, administered early. Another emerging indication is for prophylaxis in surgery with a high risk of bleeding, in which case the dose may be lower (20-60 mg / kg). In all cases, close monitoring of possible thrombotic complications is recommended. rFVIIa is contra-indicated in terminal patients, and after assessing the risks and benefits it should be used with caution in patients with a history of thromboembolic events."

Other authors found better results: rFVIIa shortened the time to surgical intervention in patients with coagulopathy and THI. In this case, the incidence of atherothrombotic was similar between the group receiving rFVIIa and that receiving plasma[31].

For proper and efficient use of rFVIIa, some authors suggest previous correction of possible alterations such as acidosis, hypothermia, thrombocytopenia and coagulopathy (hypofibrinogenemia), which would impair or annul the effect of rFVIIa. They also suggest early use as from initial stages of care, but only after correcting the preceding five factors. To be more effective, we must ensure a certain minimum number of platelets (> 50 x 10^9 / L), fibrinogen (> 15-20 g / L) and coagulation factors, and furthermore, we must prevent hypocalcemia[32].

Its usefulness in limiting or even stopping the progression of ICH should not be ruled out, although the need to review its role on a prospective basis has been suggested, frFVIIa was found safe and effective when used in patients with THI and coagulopathy that required craniotomy, even in the elderly[33]. Another study, which assessed rFVIIa use in an ED found a lower reversal of INR time in patients receiving rFVIIa: mean 4.8 hours versus 17.5 hours[34].

Different studies have developed possible algorithms to control the evolution of these patients and guide their observation with the aim of detecting complications early and at the same time optimizing hospital resources[35-40]. In many cases these algorithms can only be applied in centers with computed tomography (CT) imaging and the means to reverse anticoagulation, which complicates the possibility of their use in more hospitals. Only considering the means to reverse anticoagulation, we found it difficult to develop an algorithm which could be of use for the management of these patients[41-47].

Adjusted for the means of each hospital and the protocols of each ED regarding the management of this type of patient, Figure 2 shows a proposed algorithm[25,48]. As a general principal, for all patients receiving AVK we suggest: delaying surgery or invasive procedures until hemostatic control is achieved whenever possible, temporarily suspending AVK, and immediately requesting INR monitoring (in the ED itself, if possible, with a bedside device). In case of hemorrhage or moderate to severe THI, anticoagulation must be reversed rapidly with vitamin K (phytonadione INN) without waiting for the results of INR or imaging tests. In contrast, for trauma or mild THI, we should act on the results of CT scans and adjust the level of anticoagulation according to INR level and thrombotic risk factors or history of bleeding. Similarly, if anticoagulation is suspended or reversed, a high-risk prophylactic dose of LMWH should be administered as soon as the INR is ≤ 1.5, provided there are no contraindications. In contrast, in patients bearing metallic mitral valves with a history of peripheral thromboembolism, patients with antiphospholipid syndrome or those with a history of recent thromboembolic events (less than three months), the hematology department should be consulted to assess the reversal and possible administration of bridge of therapy with intravenous sodium heparin.

With all the information and ED resources available at present, new or adapted guidelines should be issued while we await evidence-based Recommendations by scientific societies backed by multicentre controlled randomized trials. This should be done in a collaborative and multidisciplinary way for each ED, involving the departments of hematology, transfusion, neurology and neurosurgery, to ensure that patients on oral anticoagulants with THI are safely attended in the context of effective utilization of resources. These guidelines should provide the information necessary to allow the early detection of warning signs and rapid changes in these patients, and apply the best possible corrective measures at lower cost.

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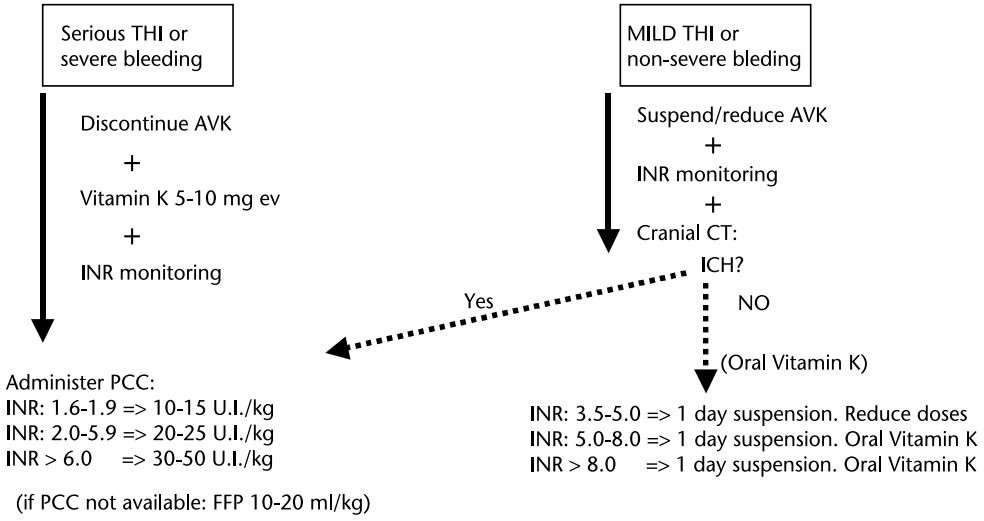

Figure 2. Algorithm for AVK reversal in trauma patients with major and minor bleeding. THI: traumatic head injury; AVK: anti-vitamin K, PCC: prothrombin complex concentrate; FFP: fresh frozen plasma, IU: international units. ICH: intracranial hemorrhage.

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Conceptos básicos y errores comunes sobre la coagulación y el manejo de la anticoagulación en el paciente con traumatismo

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Los traumatismos constituyen un motivo de consulta frecuente en los servicios de urgencias. Su asociación con el tratamiento anticoagulante oral agrega mayor complejidad. El tratamiento anticoagulante con fármacos antivitamina K (AVK) está en constante progresión. A pesar de su presencia hace más de cincuenta años, todavía existe una gran variabilidad en el manejo de su reversión y de sus complicaciones. La incorporación de nuevos anticoagulantes orales, que aportan importantes ventajas y comodidades, agrega más complejidad al tema. Una variedad especial son los traumatismos craneoencefálicos. El control de la hemostasia y la reversión de la anticoagulación de forma segura constituyen algunos de los aspectos en revisión. Consideramos necesario un manejo multidisciplinar, protocolizado, basado en la mejor evidencia disponible, avalada por las diferentes sociedades científicas implicadas hasta contar con guías y recomendaciones con adecuado nivel de evidencia. [Emergencias 2012;24:134-142]

Palabras clave: Anticoagulación. Antivitamina K. Trauma craneoencefálico. Plasma congelado. Complejo protrombínico. Factor VII recombinante activado.