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Review Article

Patient Reversal with Oral Anticoagulant Therapy in Maxillofacial Trauma in Emergency Room

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Abstract

Introduction: Approximately one third of patients with hemorrhagic trauma present coagulopathy. Anticoagulation adds additional complexity to the evaluation and treatment of the trauma patient. You must act quickly to determine the types of medications, complexity of the injury, coagulation status, and most appropriate reversal strategy. The objective of this review is to establish the emergency management with reversal of patients on oral anticoagulants who present with maxillofacial trauma.

Methods: Search for articles indexed in PubMed and EBSCO using a combination of keywords and the Boolean terms "Anticoagulation" AND "reversal" AND "trauma" AND "emergency" published between April 2014 and 2024.

Results: For patients on oral anticoagulants, it is of utmost importance to know the characteristics of the drug, and they must be recognized by the treatment to avoid complications and control bleeding. A patient with poor control of their underlying pathology increases the risk of bleeding, implying a high risk of morbidity.

Conclusion: Assess the patient with coagulopathies according to metabolic status, type of hemorrhage, and hemorrhage control. All necessary hemostatic measures and control surgeries should be considered. It is important to mention that the reversal of therapeutic anticoagulation will differ according to specific health systems and countries.

Keywords: *Anticoagulant; Emergency; Bleeding; Trauma*

Introduction

Trauma remains a leading cause of death, affecting more than 5 million people and causing death worldwide each year, and this number is expected to rise to more than 8 million.[1]

Approximately one-third of hemorrhagic trauma patients have been reported to have coagulopathy.[1]

Anticoagulation adds additional complexity to the evaluation and treatment of the trauma patient. Move quickly to determine the patient's medication types, injury complexity, coagulation status, and the most appropriate reversal strategy.[2]

Hemorrhages in the craniomaxillofacial region are usually an indicator of serious injuries such as craniomaxillofacial fractures that have a fatal risk for the patient if they are not treated.

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Oral anticoagulants are mainly used in the prevention of thromboembolic events and cerebrovascular accidents (CVA) in patients with atrial fibrillation and heart valves, patients with pulmonary embolism, as well as in the prevention of venous thromboembolism.[3]

Profuse bleeding can be fatal in case of over-anticoagulation or anticoagulation, this can be challenging for the treating physician in the emergency department, because more and more patients are on anticoagulant treatment. It is estimated that around 1-2% of the population in Western countries receives long-term anticoagulation.[4]

Warfarin is a vitamin K antagonist anticoagulant (VKA), it was the pioneer oral anticoagulant drug and is still used.

Warfarin is a VKA that inhibits the synthesis of factors II, VII, IX, X and anticoagulant proteins C and S.[3]

New oral anticoagulants (NOACs) have recently been implemented in anticoagulation therapy.

There are two types of NOACs: The direct thrombin inhibitor, dabigatran, and factor Xa inhibitors: rivaroxaban, apixaban, edoxaban and betrixaban[5]

Due to their safety, efficacy and predictable effect, NOACs have had a rapid expansion of their therapeutic indications.[6]

Since dabigatran was approved by the FDA in 2010, DOACs have surpassed VKAs in prescription.[7]

The NOAC prescription rate increased to 43-71% in patients with atrial fibrillation in recent years.[8]

The progressive development of antidotes for these new drugs will allow better management in a safe and rapid manner, allowing the reversal of their anticoagulant effect effectively.

This review aims to provide updated information on the emergency department management of patients on oral anticoagulant therapy with maxillofacial trauma.

Methods

A manual literature review search was performed in the PubMed and EBSCO databases by two researchers independently, using a combination of keywords and the Boolean terms “Anticoagulation” AND “reversal” AND “trauma” AND “emergency”. Regarding the inclusion criteria, bibliographic reviews, observational studies, clinical trials, clinical guidelines, systematic reviews and meta-analyses published between April 2014 and 2024, in English or Spanish were considered. Animal studies and letters to the editor were excluded. Finally, 30 articles were included in this review.

Search algorithm: ((Anticoagulation) AND (reversal)) AND (trauma)) AND (emergency)

Discussion

Coagulation cascade

The coagulation cascade consists of two: intrinsic and extrinsic. The extrinsic coagulation system consists of tissue factor and factor VII. The common pathway of the coagulation system consists of factors X, V, and II and fibrinogen.[9]

The intrinsic pathway is activated by contact with blood, converting factor XII to factor XIIa (activated), which catalyzes the conversion of factor XI to factor XIa, which in turn cleaves factor IX to factor IXa. Factor XIIa also converts prekallikrein to kallikrein to generate more factor XIIa in a positive feedback loop. Factor IXa then binds to its cofactor, factor VIII, and this complex will activate factor X to Xa, which is the beginning of the common pathway. Factor Xa then binds to its cofactor factor V to convert prothrombin (factor II) to thrombin (factor IIa). Thrombin eventually converts fibrinogen to fibrin to begin clot formation.[10]

The extrinsic pathway requires the addition of tissue factor, phospholipids, and calcium. Factor VII is activated by VIIa, which binds to tissue factor, and the resulting complex will convert factor.[11]

Reversers have different mechanisms of action. Factor Xa inhibitors (rivaroxaban and apixaban) act as reversible competitive antagonists of Xa. The direct thrombin inhibitor (dabigatran) is a reversible competitive antagonist of thrombin, which converts fibrinogen to fibrin.[12]

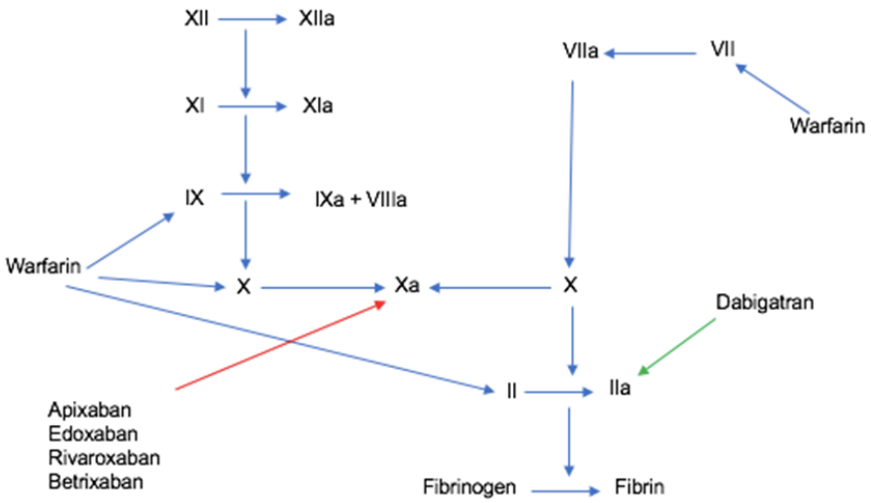

Figure 1. *Coagulation cascade and mechanism of action of anticoagulants.*

Laboratory exams

Laboratory tests are of utmost importance, they help the clinician guide the management of patients during emergencies by detecting and quantifying the remaining anticoagulant activity and are essential to evaluate hemostasis before any procedure. These evaluations should include coagulation status, blood cell count, blood group, and liver and kidney function. Abnormal kidney and liver functions affect drug metabolism and elimination.

At the same time, the exams help us plan the patient's reversal strategy given their coagulation status and take the corresponding measures to carry out an effective and safe procedure.

Prothrombin time

Prothrombin time (PT) evaluates extrinsic and common pathways. They provide the status of AVK activity.[13]

It is performed by adding the patient's plasma, anticoagulated with sodium citrate, to a reagent containing thromboplastin and calcium chloride. Calcium initiates coagulation and clot formation is measured using higher impedance or turbidity, or lower optical clarity, and is expressed in seconds.[10]

Activated partial thromboplastin time

Activated partial thromboplastin time (aPTT) reflects the function of the intrinsic and common pathways. It is carried out by activating coagulation by contact with a negatively charged surface, such as kaolin, silica or celite, together with the addition of phospholipids and calcium chloride. The time until coagulation formation is measured in seconds.[10]

INR

International normalized index is obtained by dividing the patient's PT with the PT of a normal control.[14]

The therapeutic INR ranges from 2.0 to 3.0 for most indications, although patients with mechanical heart valves may have higher targets ranging from 2.5 to 3.5.[10]

Fibrinogen function tests

Tests of fibrinogen function include thrombin clotting time (TCT) and the coagulable fibrinogen assay (Claus assay). Both tests add thrombin to the patient's plasma to directly catalyze the conversion of fibrinogen to fibrin. The TCT measures clot formation in seconds, while the Clauss assay estimates the amount of functional fibrinogen.[10]

Table 1. Common laboratory studies in patients on oral anticoagulants.

Anticoagulants	TP	aPTT	INR	Factor Xa
Warfarin	**Normal**	**+**	**++**	**Without effect**
Dabigratan	**+**	**+**	**++**	**Minimal effect**
Apixaban	**+**	**+**	**++**	**Marked effect**
Betrixaban	**+**	**+**	**++**	**Marked effect**
Edoxaban	**+**	**+**	**++**	**Marked effect**
Rivaroxaban	**+**	**+**	**++**	**Marked effect**

+ Extended

++ High

TP: Prothrombin time

aPTT: Activated partial thromboplastin time

INR: international normalized ratio

Generalities of Anticoagulants

Warfarin

A vitamin K antagonist anticoagulant, it has been widely used as an oral anticoagulant since the 1960s. Pharmacologically, warfarin competitively inhibits vitamin K epoxide reductase and blocks the conversion of oxidized vitamin K. vitamin K to its reduced form, which limits its availability for subsequent g-carboxylation of procoagulant factors II, VII, IX and X, as well as anticoagulant proteins C and S.[15]

Warfarin has very high and long-lasting bioavailability and its elimination is almost entirely through hepatic metabolism.[3]

Its use requires periodic controls with the international normalized blood index (NR) to maintain an adequate and safe therapeutic range. At the same time, it has many pharmacological and dietary interactions that can prolong or accelerate its effect.[16]

Some indications for which warfarin is prescribed are atrial fibrillation, presence of a metal valve or ventricular assistance device, deep vein thrombosis and pulmonary embolism.[2]

New oral anticoagulants (NOACs)

Its predictable pharmacokinetics and pharmacodynamics allow for fixed dosing and rapid onset of the anticoagulant effect. This also allows for less frequent laboratory monitoring and less variability in the therapeutic effect of nutritional intake and drug interactions.[10]

Xa inhibitors

Apixaban

Apixaban is a factor inhibitor Xa used to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), prevention of deep vein thrombosis (DVT) and pulmonary embolism in people suffering from had undergone hip joint surgery.[17]

Apixaban is a selective factor who has undergone hip joint surgery. Its excretion is mainly 75% hepatic and 25% renal, reaching a half-life between 8-15 hours.[15]

Betrixaban

Betrixaban is a selective factor Xa inhibitor and is the most recent NOAC to hit the market; it was approved for use in 2017. Peak concentrations can be observed between 3 and 4 hours after oral administration, with a half-life of 19 to 27 hours and its effect will last at least 72 hours from the last dose. The bioavailability of Betrixaban is 34% when administered orally.[18]

The main form of excretion is feces (85%) rather than renal (11%).[19]

Its use is mainly indicated for patients for the prevention of venous thromboembolism (VTE) with systemic involvement.[17]

Edoxaban

Edoxaban is a selective factor Xa inhibitor, which inhibits the conversion of prothrombin to thrombin.It is indicated for patients to reduce the risk of stroke, pulmonary embolism, non-valvular atrial fibrillation (NVAF).[5]

It is rapidly absorbed, reaching a maximum plasma concentration between 1-3 hours and has an oral bioavailability of 62%. The half-life of the drug is 10 to 14 hours and it is metabolized in both the kidney and the liver.[19]

Rivaroxaban

Rivaroxaban acts by reversibly and competitively inhibiting activated factor 80-100%, and has a rapid absorption rate, reaching a maximum plasma concentration between 2-4 hours.[19] It has a half-life between 7 to 13 hours.[15]

It is primarily used as prophylaxis against venous thromboembolic events (VTE) and non-valvular atrial fibrillation.[20]

Direct thrombin inhibitors

Dabigatran

Dabigatran was the first NOAC to be developed for anticoagulant therapy and is the only oral direct thrombin inhibitor currently available. Its way of acting is by competitively binding to thrombin but reversibly.[16]

It is used to prevent cerebrovascular accidents (CVA), in patients with atrial fibrillation, prevent deep vein thrombosis and pulmonary embolisms.[21]

It reaches its plasma peak after 2 to 4 hours after oral ingestion, with a half-life of 10.3 hours. Its elimination is mainly through the kidneys, so altered kidney function can increase the half-life and predisposes to an increased risk of bleeding.[18]

Reversal agents

Patients who present with traumatic injuries or critical illnesses requiring emergency surgery often require immediate reversal of their anticoagulation so that the medical-surgical team can safely perform the intervention.

Reversal of anticoagulation is performed with pharmacological agents and/or blood products. All depending on whether the clinical situation requires reversal, it is of utmost importance to evaluate whether the anticoagulant is the cause of the bleeding and/or is exacerbating the bleeding.[13]

Hemorrhage is a major source of mortality and morbidity in this population, and the risk is amplified by anticoagulation.

This process depends on the pharmacokinetic properties of the anticoagulant and abnormalities in laboratory tests. In a patient with hemorrhage, it is useful to evaluate the level of anticoagulant activity.[13]

Reversal of anticoagulated patients within the first 2 hours after trauma could decrease mortality rates by up to 38%.[21]

General Considerations for Warfarin Reversers

Vitamin K

Vitamin K is useful in treating warfarin-induced hemorrhage, but fails to completely normalize the INR when used as a sole agent in an emergency setting. The response to vitamin K is much slower than the response to PFC, taking at least 2 to 6 hours, but more often up to 24 hours.[21]

The use of Vitamin K with other complexes such as prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) is recommended.

The usual dose of vitamin K for reversal varies from 5 to 10 mg intravenously (IV), and combined with PCC.[3]

Prothrombin complex concentrate (PCC)

The PCC has important advantages, one of which is that administration is faster (it is not necessary to thaw or type the blood) and at the same time there is no risk of volume overload.[12]

There are two types of PCCs available: So-called 3-factor PCCs contain coagulation factors II, IX, and X, and 4-factor PCCs also contain substantial amounts of factor VII.[22]

Comparative studies have suggested that 4-factor PCC corrects INR more reliably than 3-factor PCC in reversing anticoagulation.[22]

Other studies compare the use of fresh frozen plasma (FFP) with PCC. The conclusion was that PCC causes less than half of the adverse events and a significantly faster reversal of coagulopathy.[21]

4-factor PCC in warfarin reversal is superior to that of PFC in patients taking VKAs and achieves more rapid homeostasis in patients requiring reversal for surgical interventions.[3]

Fresh frozen plasma (FFP)

Fresh frozen plasma (FFP) rapidly replenishes clotting factors, leading to warfarin reversal.

It is typically administered empirically in increments of 2 to 4 IU and may also be administered at 10 to 20 mL/kg to achieve reversal.[15]

One of the disadvantages is that it requires large volumes of PFC, which exposes patients to the risk of volume overload causing lung problems, microvascular damage that may require ventilation and lead to death. Another disadvantage is that since it is frozen, you have to wait for it to reach the appropriate temperature for administration to the patient.[12]

Recombinant factor VIIa

Activated factor (FVIIa) is a hemostatic agent that increases thrombin generation by activating factor X at the site of vascular injury.[3]

This clotting factor has rapidly gained popularity because its fast-acting properties have substantially less potential for volume overload and lack the risk of bloodborne pathogens in plasma.[21]

General considerations of NACO reverters

Direct oral factor Xa antagonists are increasingly preferred over warfarin due to their efficacy and safety profile demonstrating a 50% reduction in the risk of major bleeding compared to warfarin.[23]

Idarucizumab

Idarucizumab is the first effective humanized monoclonal antibody fragment developed specifically as a reversal agent for direct thrombin inhibitors, in this case dabigatran, a direct oral anticoagulant.[24]

Reversal studies demonstrated that idarucizumab was able to reduce clotting time, thrombin dilution time, and free dabigatran levels in patients with severe bleeding or who required an emergency procedure.[25]

Its mechanism of action is by binding to free dabigatran and thrombin-bound dabigatran, generally prescribed in a dose of 5 g IV (2.5/50 ml administered 15 minutes apart).[16]

Andexanet alfa

Studies demonstrated the effects of administering andexanet alfa, an anti-factor Xa decoy protein, to healthy volunteers taking apixaban or rivaroxaban and was found to rapidly reverse anticoagulation.[26]

Its mechanism of action is by binding to the active site of the Xa inhibitors. High doses are indicated: 800 mg IV followed by 8 mg/min for 120 min or low doses: 400 mg IV followed by 4 mg/min for 120 min.[16]

The onset of action is less than five minutes, and the half-life is approximately six hours.[16]

The International Forum on Anticoagulation also recommends andexanet as first line in bleeding related to direct oral factor Xa antagonist.[23]

One of the disadvantages is the pharmacodynamics of andexanet alfa, as hemostasis is short-lived between 1 to 2 hours with significant rebound effects thereafter, another disadvantage is its high cost.[8]

Table 2. Anticoagulant reversals and their mechanism.

Medicament	Warfarin	Rivaroxaban	Apixaban	Edoxaban	Betrixaban	Dabigatran
Action	Vitamin K dependent factors	Factor Xa	Factor Xa	Factor Xa	Factor Xa	Thrombin
Bioavailability	79-100%	63-79%	66%	50%	34%	3-7 %
Half life	36-42 hrs	7-13 hrs	8-15 hrs	9-11 hrs	19 a 27hrs	12-17 hrs
Reversal agents	Vitamin K PCC, FFP, Factor VIIa	Andexanet alfa, PCC	Andexanet alfa, PCC	Andexanet alfa, PCC	Andexanet alfa, PCC	Idarucizumab PCC

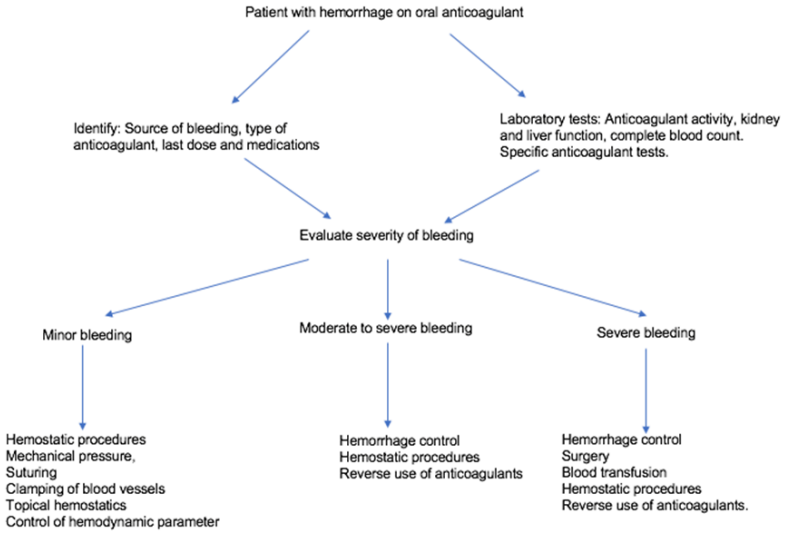

Figure 2. *Emergency treatment in a patient with bleeding with oral anticoagulants.*

Conclusion

As the population ages and more patients receive long-term anticoagulation, the use of warfarin and NOACs are becoming more frequent. Lately there has been a drastic increase in NOAC prescriptions due to their properties without the need for routine monitoring.

The patient with coagulopathies should be evaluated according to the patient's metabolic status, type of hemorrhage, and hemorrhage control. All necessary hemostatic measures and control surgeries should be considered.

It is important to mention that reversal of therapeutic anticoagulation will differ depending on health systems and specific countries.

The use of reversals depends greatly on their cost and availability, limiting their use in daily practice.

Conflict of Interest

The authors declare no conflict of interest.

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