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The Patient Needs Emergency Surgery and is Under Treatment with Non-vitamin K Antagonist Oral Anticoagulants: What Shall We Do?

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Abstract

Introduction: A characteristic feature of emergency surgery is its limitation in patient preparation. It is difficult, and often impossible, to eliminate certain patient-dependent factors to reduce the operative risk. The effects of certain drugs in use by the patient, such as anticoagulant drugs, may be important in this respect. Among these anticoagulant drugs are the non-vitamin K antagonist oral anticoagulants (NOACs).

Methods: In preparation for a lecture presentation in the XVII European Congress of Trauma and Emergency Surgery (Vienna, April 2016), the authors performed an Internet search using the terms "NOAC," "new oral anticoagulant," "direct oral anticoagulant," and "emergency surgery" to gather scientific evidence with which to establish a collection of suggestions for the management of patients under anticoagulation with NOACs in the emergency setting.

Conclusion: Data on the management of patients in the emergency setting undergoing treatment with anticoagulants are scarce and mainly based on information regarding routine preoperative approaches. Therefore, more scientific evidence is needed to establish appropriate guidelines that favor patients and are easy for caregivers to understand. The one consensus throughout the literature is that the reversal of NOACs is to be carried out with the administration of PCC.

Keywords: Direct antithrombin; Factor Xa inhibitors; Coumarin; Emergency surgery; NOAC

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Introduction

One of the specific characteristics of emergency surgery is its limitation in patient preparation. The elimination of certain patient-related factors to lower the operative risk is difficult and often impossible [1]. The effects of some drugs being used by patients in the emergency setting, such as anticoagulant drugs, may therefore raise important issues [2,3]. The introduction of anticoagulant drugs represented a major breakthrough in the treatment and prophylaxis of some cardiovascular diseases. Similarly, the possibility of safe oral administration allowed the patients to treat themselves in the comfort of their homes. Therefore, the introduction of oral anticoagulant drugs to the pharmacopoeia was welcomed by both patients and clinicians. Initially used as a pesticide, especially in the control of mice, warfarin was first used for clinical purposes in 1954 and remains the most widely prescribed anticoagulant in the United States today [4]. Despite its success, its use is not without disadvantages. Warfarin has a highly variable pharmacokinetic profile, which is associated with its unreliable absorption and interaction with many common drugs. Its serum concentration thus varies widely; the patient has a high risk of thromboembolic complications when the serum warfarin concentration is low and a high risk of bleeding when the serum warfarin concentration is high [4-6]. Therefore, tight laboratory control is mandatory to reduce the likelihood of adverse effects [6]. Non-vitamin K antagonist oral anticoagulants (NOACs) recently became available with the promise of being more reliable than dicoumarinic drugs [6-9]. BIBR 953 compound, now known as dabigatran or dabigatran etexilate [10], was the first available NOAC. It became available for use in 2008 and was approved by the Food and Drug Administration (FDA) in 2010 [11]. The acronym "NOAC" originally referred to new or novel oral anticoagulants, but as investigations progressed and new molecules were identified, the acronym no longer made sense [8]. However, the widespread use of the NOAC designation in the literature was already substantial, and its preservation was important for database search purposes. Since then, the meaning of NOAC has changed to "non-vitamin K antagonist oral anticoagulants," which comprises all molecules with

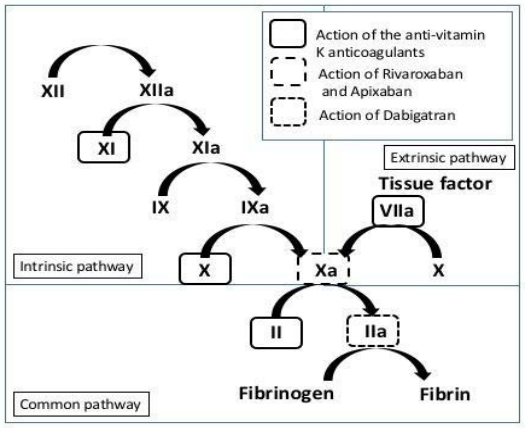

Figure 1: Action of different oral anticoagulants in the clotting cascade.

a direct inhibitory effect on coagulation factors [8]. Despite their reliability, these drugs have not reduced surgeons' concern regarding the management of patients in need of emergency surgery or with a traumatic or spontaneous bleeding event. In fact, these drugs do not enjoy a good reputation because their anticoagulant effect is difficult to gauge with the classic coagulation tests, namely the prothrombin time (PT) and activated partial thromboplastin time (APTT) [12,13]; moreover, no antidote is widely available [14]. For the aforementioned reasons, NOACS are known in the medical media as "the cardiologist's darling, the intensivist's headache, and the trauma surgeon's nightmare" [15]. Despite their beneficial effects for countless cardiovascular patients, these drugs represent a disaster waiting to happen for the general surgeon, particularly the emergency surgeon. While vitamin K antagonists have established guidelines and suggested actions for both their laboratorial control and effect reversal [16,17], no widespread data are available for NOACs because their specific antidote remains unknown [14]. This hinders the action of surgeons, who develop an aversion to these drugs, particularly surgeons working in the emergency setting [15]. This review aims to summarize the basic knowledge about the use of NOACs in patients in need of emergency surgery. Data on the preoperative period were compiled because of the lack of information regarding emergency surgery. The main goal of this review is to assist the general and emergency surgeon in the decision-making process when treating an acute surgical patient undergoing treatment with oral NOACs. This paper was drafted based on the lecture of the same title given by the first author at the XVII European Congress of Trauma and Emergency Surgery, April 2016 in Vienna.

NOACs

Treatment with NOACs and oral anticoagulants in general, is a source of concern for the surgeon treating patients in need of emergency surgery because of the increased associated morbidity, particularly with respect to bleeding complications [18]. The belief that NOACs are associated with more severe and frequent bleeding complications than other anticoagulants is widespread within the medical profession, especially among surgeons, and is probably strengthened by the difficult laboratory control and absence of a specific antidote. However, this belief is unfounded because there is no scientific support of a higher risk of bleeding complications in the literature. In fact, quite the opposite evidence is available [9,18]. The currently available NOACs are dabigatran, rivaroxaban, and

Table 1: Comparative pharmacokinetics of AVKs and NOACs.

	AVK	NOACs
Onset of action	Days	2-3 hours
Duration of action	Long	Short
Laboratory control	Mandatory	No need
Food interaction	Yes	No
Drug interaction	Yes	Few

AVK: Anti-vitamin K Anticoagulants; NOACs: Non-vitamin K Antagonist Oral Anticoagulants

apixaban. Although a few more drugs have recently become available, these three have the most widespread global approval. All drugs in this class directly inhibit the activity of clotting factors in the clotting cascade. Dabigatran inhibits the action of thrombin on clot formation, and the others inhibit the action of factor Xa [6,19] (Figure 1). This mechanism of action results in an anticoagulant effect that is more predictable and dose-related than other anticoagulants. Moreover, NOACs have a brief onset of action (2–3 h), a short duration of action with a half-life of about 12 h, reduced drug and food interactions, and no requirement for routine laboratory control [6,20] (Table 1). The major disadvantage, which may be resolved in the near future, is the absence of a specific antidote [14]. These features make these drugs considerably more attractive than the classic vitamin K antagonist anticoagulants, and the predicted trend is that NOACs will replace them. However, the use of warfarin is widely established, and this drug is still being used in a broad range of situations. The only indications for NOACs, as endorsed by pharmaceutical control organizations such as the FDA and verified in clinical studies, are the prevention of thromboembolic events associated with non-valvular atrial fibrillation and the treatment and prophylaxis of deep vein thrombosis and pulmonary embolism [6]. Some countries have extended indications such as adjunctive treatment of various acute coronary syndromes or thromboprophylaxis in certain orthopedic surgeries; however, these indications are not widespread [6]. The use of NOACs in patients with mechanical heart valves has been shown to be associated with increased morbidity and is actually a contraindication to their use [21]. This indication profile results in the frequent use of NOACs in older patients with significant cardiovascular morbidities. Their inherent surgical risk is already high, and the use of NOACs adds a bleeding risk due to the pharmacological effects of these drugs.

Increased Risk of Bleeding

Despite the more favorable pharmacological profile of NOACs than vitamin K antagonists, the risk of bleeding complications persists [22]. According to the published studies, the rate of major bleeding complications associated with NOACs ranges from 2.1% to 3.6% per year [22]. Some of these published studies include the RE-COVER study of dabigatran [23], the Einstein study of rivaroxaban [24], and the AMPLIFY study of apixaban [25]. All studies reported favorable results of NOACs when compared with vitamin K antagonists [9,23-25]. Only the subset of patients with gastrointestinal bleeding did not show an advantage associated with the use of NOACs [9] because of the higher frequency of events in this group. However, there was a trend toward less use of surgery to treat bleeding events in patients receiving NOACs. Hirschl et al. [26] conducted a meta-analysis of major studies involving NOACs and concluded that their effectiveness is not inferior to and that they are safer than the classic oral anticoagulants. The forthcoming development of specific antidotes is welcome as an added safety factor and will result in the further widespread use of NOACs [9,18,26]. The ideal oral anticoagulant must be safe and effectively administered orally with predictable

Table 2: HAS-BLED score risk factors.

Hypertension
Abnormal renal function
Abnormal hepatic function
Stroke
Bleeding history or predisposition
Labile INR
Elderly (over 75 years)
Drugs (antiplatelet or NSAID) or alcohol use

INR: International Normalized Ratio; NSAID: Non-steroidal Anti-inflammatory Drug; each risk factor sums 1 point

Table 3: HEMORR2HAGES score.

Hepatic or renal function disorder
Ethanol abuse
Malignancy
Old age (over 75)
Reduced platelet count or function
Re-bleeding risk (prior bleed)
Hypertension (uncontrolled)
Anaemia
Genetic factors (CYP2C9 variant)
Excessive fall risk
Stroke

Each risk factor sums 1 point except re-bleeding that adds 2 points

pharmacokinetics [9]. It should be easy to reverse, preferably with a specific antagonist with a rapid onset of action, in case of urgent need. NOACs come very close to these ideals, but it is still too early to claim that. Issues concerning cost, cost-effectiveness, and the effects of long-term use are not fully understood [7,9,26]. NOACs are new, expensive drugs, and although they are very attractive, they still raise some questions that only further research will answer.

What to do in Urgent Cases?

As for vitamin K antagonists, the management strategy for NOACs in the preoperative period must be defined. The increased bleeding risk is real and is mainly apparent in the emergency setting. The optimal strategy with which to handle this bleeding risk is critical. Approximately 10% to 20% of patients undergoing treatment with NOACs will be exposed to surgery or invasive procedures in an emergency setting sometime in their lives [27]. Although multiple publications have addressed the risk of bleeding in patients undergoing treatment with NOACs, and although some of these publications have focused on the preoperative period, none specifically addresses the emergency setting. Thus, it is only possible to extrapolate the existing data to emergency situations. The answers to some specific questions would be helpful in defining a management plan, as described below.

What is the bleeding risk?

The bleeding risk is not related solely to the fact that the patient is undergoing treatment with NOACs. Some investigation groups have used risk scores such as the HAS-BLED [3,28-30] or HEMORR2HAGES [29,30] to estimate the arterial bleeding risk in patients undergoing treatment with anticoagulant drugs. These scores include patient-related variables such as hypertension, renal function, and age, which are added to the use of agents that act on the coagulation cascade or affect platelet aggregation (Tables 2 and 3). Another significant portion of bleeding risk is related to the intervention being performed. Several methodologies are used to calculate this risk. Most of these methodologies stratify the risk into three classes according to the degree of invasiveness and complexity of the intervention (Table 4) [20]. These stratification methods are usually used for elective procedures and are not directly adaptable to the emergency setting. In such cases, one must admit a higher degree

Table 4: Surgical bleeding risk stratification.

Bleeding risk	Intervention
Minimal risk	Non-complex dental intervention Ophthalmology Digestive endoscopy Superficial surgery Wound revision
Low risk	Endoscopy with biopsy Complex dental intervention Prostate or bladder biopsy Pacemaker implantation Hernia repair
High risk	Open pelvic, abdominal and cardiothoracic surgery Urology Intracranial neurosurgery Major Orthopaedic or Trauma surgery Major Vascular surgery Posterior chamber eye surgery

of severity. Most emergent surgical cases include procedures involving cavities and the handling of non-compressible vascular beds; thus, a high risk of bleeding must be assumed [20,27]. Furthermore, these patients are under treatment with NOACs because of the high thrombotic risk associated with their illnesses. This fact may not be relevant in the preoperative period but will be crucial in the recovery period, when the patient must resume their anticoagulant medication [2,3,18].

When was the last administration?

Considering the short half-life of NOACs (around 12 h for most of them), it is important to know when the drug was last administered. After two half-lives, the patient is expected to have a reduced risk of bleeding if an operation is performed. This occurs 24 to 36 h following the last administration [2,27,29]. Patients in the emergency setting have often undergone prolonged fasting for various reasons; they are sometimes awaiting medical evaluation in the emergency department and may be able to undergo an intervention without a significant risk of bleeding and without any other action depending on their last NOAC intake.

How is the renal function?

Dabigatran [2,18,20,27,29,31] has almost exclusive renal excretion, and its pharmacokinetics thus change in the presence of renal dysfunction. Other NOACs, despite previous hepatic metabolism, may also undergo alteration of their serum concentrations when renal function is impaired. In fact, renal dysfunction is a contraindication to the use of NOACs in some countries.

How is the liver function?

Similar to kidney function impairment, liver function impairment also disturbs the pharmacokinetics of NOACs [2,18,27,29,31]. Rivaroxaban and apixaban are eliminated after enzymatic metabolism in the liver, and severe hepatic dysfunction can influence their serum concentrations.

Is the patient taking other drugs?

Despite the fact that few drugs interact with NOACs, some agents compete with the same enzymatic complex and metabolic pathways in the liver and could alter the elimination of NOACS or their breakdown into inactive metabolites [2,18,27,29,31]. Some examples of these agents are ketoconazole and rifampicin; more importantly, however, amiodarone and verapamil are drugs with cardiovascular effects that can be prescribed simultaneously with NOACs or other anticoagulants. Antiplatelet drugs can also influence the action of NOACs, enhancing the bleeding risk [32,33].

Laboratory control

As previously mentioned, routine laboratory control is not necessary for patients undergoing treatment with NOACs. However, some particular situations require determination of the plasma levels or anticoagulant activity of NOACs. These situations include trauma, spontaneous bleeding, suspected overdose, persistent thrombotic disease despite continued drug administration, and the need for emergency surgery [20]. Although the general belief is that conventional tests are useless, this belief is unfounded. The results of these tests, mainly measurement of the PT and APTT, are changed in a somewhat predictable manner by NOACs; this makes them useful in guiding further management [13,34]. However, more appropriate tests are available. For drugs that inhibit factor Xa, the most appropriate test would be measurement of the plasma anti-factor Xa activity. For dabigatran, a direct thrombin inhibitor, the most frequently used tests are the ecarin clotting time and the diluted thrombin time. These tests are sensitive enough to serve as a good surrogate to the plasma concentration of the drug [12,13]. However, most hospitals do not have these recently developed tests in either routine practice or the emergency setting. These hospitals must instead rely on the results of the classic tests. The combination of the APTT and PT can be vital in decision-making. The APTT is most useful for estimating the activity of dabigatran, and the PT is most useful for estimating the activity of factor Xa inhibitors [13]. Despite their low sensitivity, normal results of these tests assure that the patient's coagulation function is adequate to proceed with surgery [27]. However, the results of these classic tests can be changed by factors other than NOACs. Moreover, reversal of the anticoagulation activity of NOACs using procoagulant drugs may not result in a return to a normal APTT and PT [27]. Several recent papers have described the use of thromboelastometry to determine the activity of NOACs. Apparently, their applicability in the emergency setting and, above all, in assessing anticoagulation reversal may be valuable in the near future. At this time, their use is still experimental [35-37].

Do antidotes exist?

In recent years, antidotes have been developed for almost all currently available NOACs [14]. However, only idarucizumab has been approved [38]. Idarucizumab is a monoclonal antibody with no effect on coagulation that binds specifically to dabigatran, inactivating it. It is currently the only NOAC antidote commercially available and was approved by the FDA in October 2015 [38]. Other drugs also have antagonist effects against NOACs. Some are drug-specific while others are active against multiple drugs, but all are still in the testing phase and are not ready for current practice. The main use for these drugs is to reverse the effects of NOACs in case of severe bleeding or the need for urgent or emergent procedures [14,18,38] and should be included in protocols. Unfortunately, Idarucizumab is not available in most Hospitals around the world, yet.

Protocols in Use

Many protocols for the use of NOACs have been established. However, all are meant for use in the perioperative period, especially in routine practice [39]. As stated above, there are no specific guidelines for the use of NOACs in emergency surgery. A common feature of all NOAC protocols is laboratory control. Knowledge and integration of the patient's coagulation status is essential for proper decision-making [18,27,29,31]. As mentioned previously, tests that are able to express the serum concentrations of the drugs are preferred, but their availability is not widespread. Thus, many hospital clinicians must rely on the results of the classic tests. Patients present for emergency treatment with varying degrees of urgency. Some patients may wait a few hours for normalization or improvement of their coagulation status, considering the short half-life of NOACs. In most situations, waiting two half-lives (up to 24 hours) may reduce the drug levels enough for safe performance of the intervention. This may be the case in some patients with acute appendicitis or acute cholecystitis. This is not warranted in some other patients, however, such as those with hepatic failure or those who have renal failure and are under treatment with dabigatran because of the almost exclusive renal elimination of this drug. We should expect a slower reduction of the plasma concentrations in these circumstances, which requires a more proactive approach [27,31]. Tables 5 and 6 present a suggested management scheme according to the coagulation test results, based on the proposals of the Working Group on Perioperative Haemostasis [27]. Because its renal elimination, hemodialysis is an alternative method for elimination of dabigatran; however, it is rather impractical in the emergency setting [18,29]. Gastric lavage with activated charcoal, another way to reduce the plasma concentration of NOACs, must only be performed when the last administration of the NOAC was in the previous 2 hours, thus preventing its absorption [18,27,29]. Hemofiltration with charcoal filters can also be used to eliminate these drugs, but again, it is not very useful in the emergency setting [18,29]. There are circumstances in which the patient cannot wait to undergo surgery. Such patients usually present with severe sepsis or acute bleeding (trauma, digestive, etc.) and require prompt treatment. In these cases, if the patient is not bleeding, appropriate intervention should be performed without the prophylactic administration of procoagulant drugs [27]. These drugs should only be used in the event of hemorrhagic complications, whether intraoperative or postoperative. For actively bleeding patients, as for patients who have sustained trauma [2,5,40], resuscitation should be performed according to the principles of Advanced Trauma

Table 5: Management of patients undergoing emergency surgery while taking dabigatran.

Dabigatran <30 ng/ml APTT<1.2	Operate
Dabigatran >30 ng/ml<200 ng/ml APTT>1.2<1.5	Wait 12 hours and obtain new test If emergent, operate and antagonize anticoagulant effect as needed
Dabigatran >200 ng/ml APTT>1.5	Wait 12 hours and obtain new test Delay surgery as much as possible Discuss Haemodialysis, especially if Creatinine clearance less than 50 ml/min If emergent, operate and antagonize anticoagulant effect as needed
Dabigatran >400 ng/ml	Major haemorrhagic risk Haemodialysis

APTT: Activated Partial Thromboplastin Time

Table 6: Management of patients undergoing emergency surgery while taking rivaroxaban.

Rivaroxaban <30 ng/ml APTT<1.2 and PT<1.2	Operate
Rivaroxaban >30 ng/ml<200 ng/ml APTT>1.2<1.5 and PT>1.2	Wait 12 hours and obtain new test If emergent, operate and antagonize anticoagulant effect as needed
Rivaroxaban >200 ng/ml APTT>1.5	Wait 12 hours and obtain new test Delay surgery as much as possible If emergent, operate and antagonize anticoagulant effect as needed
Rivaroxaban >400 ng/ml	Major haemorrhagic risk

APTT: Activated Partial Thromboplastin Time; PT: Prothrombin Time

Life Support [41] (or other approved protocols) and an operation carried out to control bleeding, with previous activation of a massive transfusion protocol. Procoagulant drugs can and should be added to reverse the anticoagulation effects of NOACs at the beginning of resuscitation [18]. The consensus in the literature is that the reversal of anticoagulation produced by NOACs should be accomplished by the administration of prothrombin complex concentrate (PCC) at a dose of 25 to 50 U/kg body weight, which can be repeated in case of failure of the first dose [2,19,27,31,42]. This drug is readily available, easily prepared, and quick to administer without excess volume, and it has no increased risk of disease transmission [19,29,42]. Alternatively, fresh frozen plasma could be used, but this adds a large volume load and is only available after thawing, which takes at least 30 mins. The use of recombinant factor VIIa is not recommended because of its dangerous prothrombotic potential [29]. The literature describes factor VIIa as a last resort, with some anecdotal reports but without adequate results published. Activated PCC does not seem to be more favorable than simple PCC and may have a higher thrombotic risk. However, some authors state that it is a better agent for reversal of dabigatran. Regardless, activated PCC is not widely available [29]. PCC itself may comprise three or four components. Four-component PCC contains factor VII, making it theoretically more effective [29].

Resumption of anticoagulation is important, especially in patients with an increased risk of thromboembolic events. To determine the optimal time point at which to resume administration of NOACs, it is important to weigh the thrombotic risk of the patients' cardiovascular disease and the bleeding risk of the intervention. In patients with a low hemorrhagic risk, it is possible to resume NOACs 6 to 8 h after the intervention. In patients with a high bleeding risk, the administration must be postponed. In patients at low thromboembolic risk, NOACs may be resumed 48 to 72 h after the procedure. In higher-risk patients, it is advisable to start a bridging therapy. Most researchers recommend starting low-molecular-weight heparin in the immediate postoperative period, after 6 to 8 h, and only resume NOACs after 48 h and always 12 h after the last dose of low-molecular-weight heparin [2,18,43].

Conclusion

Discussion around the emergency surgical management of patients undergoing treatment with NOACs is far from over. It will continue as long as opinions regarding the indications for and management of NOACs remain so diverse and numerous. More scientific evidence is needed to establish appropriate guidelines that favor patients and are easy for caregivers to understand. There is also a need to generalize a more comprehensive and sensitive package of tests that allow for a better understanding of the behavior of NOACs in plasma. The one consensus throughout the literature is that the reversal of NOACs is to be carried out with the administration of PCC.

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