

Bleeding during Oral Anticoagulant Therapy: Warning Against a Greater Hazard

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Abstract

Background: Bleeding is one of the main concerns in patients undergoing oral anticoagulation therapy.

Objective: To investigate the determinant causes of bleeding in patients undergoing oral anticoagulant therapy.

Methods: A total of 360 patients with atrial fibrillation (AF) undergoing oral anticoagulant (ACo) therapy, with a target INR of 2.0-3.5, were followed prospectively for a period of 48 ± 7.2 months. The patients were evaluated on average every 30 days and were investigated regarding the presence of associated pathology that could lead to bleeding.

Results: A total of 338 patients participated in the present study. Of these, 210 (62.13%) were females. Mitral stenosis was present in 218 patients (64.4%), a mitral biological prosthesis in 64 (18.9%) and mitral valve failure in 56 (16.5%) patients. Bleeding occurred in 65 patients (19.2%), being severe in 7 (10%) patients. In 38/65 patients, a new associated disease was identified, which facilitated bleeding. An associated disease was identified in 100% of the patients with bleeding within the therapeutic range, against 49.05% of associated disease diagnosis in those with an INR > 3.5 ($p=0.001$).

Conclusion: The diagnosis of a local disease associated to the bleeding was frequent among those patients undergoing oral anticoagulant therapy (58.5%). There was an association between bleeding with an INR within the therapeutic range (INR=2.0-3.5) and the diagnosis of a pathology predisposing to bleeding ($p<0.001$). It is mandatory to investigate the cause of bleeding in patients undergoing oral anticoagulant therapy, especially if the INR is within the therapeutic range. (Arq Bras Cardiol 2009; 93(2):163-167)

Key Words: Hemorrhage; anticoagulants; mitral valve stenosis; atrial fibrillation.

Introduction

The possibility of occurrence of a thromboembolic event in patients with atrial fibrillation and rheumatic valvular disease is high¹.

Several studies, such as the Framingham study², showed that the probability of thromboembolism in patients with an atrial fibrillation (AF) rhythm is 17.5-fold higher than in the general population, without arrhythmia. Thus, the antithrombotic prevention becomes mandatory for this special group of patients. Warfarin is the most commonly used oral anticoagulant agent worldwide³. Bleeding is one of the most feared side effects during Warfarin use⁴.

In patients with a native valve or bioprosthesis that maintain an AF rhythm, the recommended therapeutic range for the prevention of thrombogenesis is found with the international normalized ratio (INR) between 2 and 3. In patients with a mechanical prosthesis, regardless

of the cardiac rhythm, this range increases to 2.5 -3.5. INR values that are higher than the programmed ones expose patients to the undesirable risks of bleeding. But, would the anticoagulant action be the only responsible for the bleeding, by reducing the formation of vitamin K-dependent procoagulant factors or would there be other occult pathologies, unknown to the patient, favoring the hemorrhage?

The present study aimed at analyzing possible clinical causes associated to the oral anticoagulation therapy that could contribute to the hemorrhagic event.

Methods

A total of 360 patients of both sexes, who had been using oral anticoagulant therapy for more than 60 days and had rheumatic valvular disease with a native valve or biological prosthesis associated to atrial fibrillation were followed prospectively for 48 ± 7.2 months.

The inclusion criteria were: age ≥ 18 years; to reside in the city of Sao Paulo, SP, not very far from the hospital where the study was carried out; to have a telephone and cognitive level to understand the complex treatment with oral anticoagulation.

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Manuscript received January 9, 2008; revised manuscript received March 19, 2008; accepted April 07, 2008.

Patient inclusion was carried out sequentially, at the moment when the analysis of the prothrombin time was being carried out at the Outpatient Clinic of our institution, which is used to assess the need for medication adjustment. We aimed at maintaining the INR between the target values of 2.0 and 3.5, with a mean of 2.5. In order to do that, patients were assessed periodically, on average every 30 days. Any bleeding was to be communicated to the medical research team by telephone or at the emergency department (ED), where patients should go in case of hemorrhagic events. For the present study, bleeding was considered as blood losses that would cause the patient to seek medical attention, either by telephone communication or by going to the ED of our institution. Thus, minor bleedings such as small bruises and gum bleeding were excluded.

All patients that presented bleeding had their INR calculated at the moment of this clinical event. The investigations were carried out by complementary imaging assessments, indicated according to the clinical suspicion or the type of bleeding and by the hematological method to quantify, through a complete blood count, the effects of the blood loss. All patients with bleeding identified as originating in the gastrointestinal tract underwent at least high digestive endoscopy and colonoscopy. The female patients with gynecological hemorrhages with INR at target values or a little higher ($\text{INR} \geq 3.5$) were referred to specialized evaluation. The patients of fertile age with bleeding outside the menstrual period were also referred for assessment.

During the bleeding, the oral anticoagulant therapy was withdrawn. The hemorrhages were quantified from mild to moderate when the procedure was restricted to clinical observation. When the bleeding was defined as severe, there was the need for blood replacement due to the decrease in hemoglobin of up to 5 points, with hemodynamic instability.

Results

Of the 360 selected patients, 22 were lost to follow-up. Of the 338 patients that were followed, there was a predominance of females (62.13%) and age < 65 years (86.8%) (Table 1).

Of the valvular disorders, mitral stenosis was present in more than half of the studied population (64.4%), the mitral biological prosthesis failure was present in 18.9% and of the native mitral valve in 16.5% (Table 1).

Only 50.1% of the INR examinations presented results that were within the recommended values (Chart 1).

There were 65 patients (19.2%, incidence of 4.8% a year) with hemorrhagic events, of which 53 (81.54%) with $\text{INR} \geq 3.5$ and 12 with $\text{INR} < 3.5$. Therefore, elevated INR values were significantly associated with bleeding ($p = 0.0001$ OR = 7.17 (3.69 – 13.92) (Table 2). The occult cause of the bleeding was identified in 38 (58.46%) of the patients that bled.

In all the 12 patients (100%) that presented bleeding with INR within the therapeutic range ($\text{INR} < 3.5$), the associated pathology was identified. In those patients with bleeding and $\text{INR} \geq 3.5$, pathologies associated with bleeding were identified in 26 (49%). Thus, the bleeding that occurred when the INR values were within the recommended therapeutic range was significantly associated ($p = 0.0001$, relative risk = 2.03 (1.45 – 2.3)) to the diagnosis of diseases that predispose to bleeding. Thus, the diagnosis of an associated pathology was two-fold more frequent in patients with bleeding within the therapeutic range (Table 3).

There was a two-fold higher incidence of bleeding among the elderly (older than 65 years), $p = 0.001$ (Table 1). We observed a non-significant tendency ($p = 0.058$) to a more frequent diagnosis of associated diseases in patients younger than 65 years (Table 3).

The female genital system was the most frequent site where the bleeding associated to the presence of a pathology predisposing to hemorrhagic event was identified (76.6%), followed by the gastrointestinal (50%) and the urinary tract (55.5) (Table 4). Some patients had more than one associated pathology. Bleeding was identified more often in the female group (47 patients) associated to an occult pathology present at higher proportion (61.70%) ($p = 0.41$; Table 3). In cases

Table 1 – Characteristics of the studied population and the bleeding.

Variable	Cohort			Bleeding				p	
	N	%	Age	Present	%	Absent	%		
Sex	Female	210	62.13	43 ± 6	47	22.38	163	77.6	0.06 ¹
	Male	128	37.7	55 ± 8	18	14.06	110	85.9	
	Total	338			65	19.23	273		
Age	< 65 yrs	293	86.8		45	15.35	248	84.65	0.001 ²
	≥ 65 yrs	45	13.2		20	44.45	25	55.55	
	Total	338			65		273		
Valvulopathy	Mitral stenosis	218	64.4		39	17.88	179	82.11	
	Mitral biological prosthesis	64	18.9		21	32.81	43	67.18	
	Mitral failure	56	16.5		5	8.92	51	91.07	
	Total	338			65		273		

¹ Fisher's Exact Test. ² Chi-square.

with gynecological bleeding with INR-target, the patient was referred to specialized evaluation.

The hemorrhagic events diagnosed as severe were observed in 7 patients (10% of the patients that presented bleeding); in 5 of them, the presence of an associated pathology was identified. Thus, the presence of severe bleeding did not constitute a risk factor for the diagnosis of associated disease ($p = 0.69$) (Table 2). Additionally, we did not observe any association between values of $INR \geq 3.5$ ($p = 0.604$ – Fisher – Table 5).

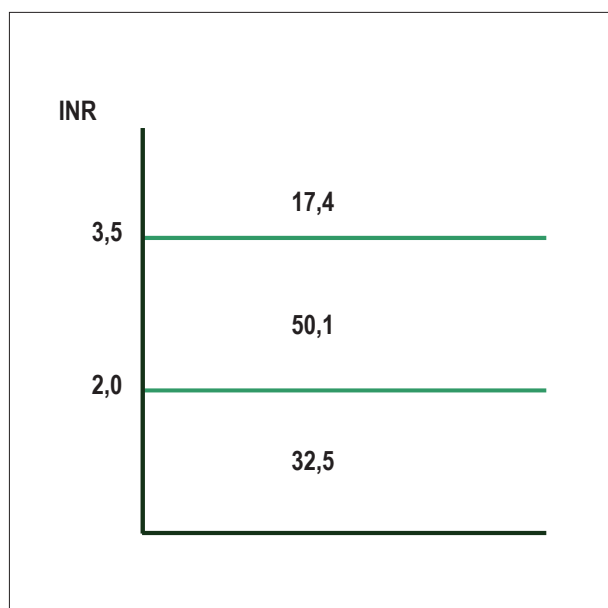


Chart 1 – Percentage of the INR values.
INR: International Normalized Ratio

No deaths caused by bleeding were identified, either for those that presented an occult pathology or the ones that did not.

Of the complementary imaging examinations, the colonoscopy and high digestive endoscopy were the most useful ones in the identification of the associated disease according to the bleeding site.

Discussion

It is well established the idea of using oral anticoagulant therapy in patients with rheumatic valvular disease associated to atrial fibrillation (AF)⁵. For decades, conclusions from well-documented studies showed that in this patient population, the probability of thromboembolic events is high, being up to 7-fold higher when compared to that of the general population⁶. The thromboembolic phenomenon can also significantly modify the natural history of the rheumatic valvular disease. Once installed, there are no efficient means to revert it and the patient is then exposed to its consequences. However, there are means of prevention that decrease, although they do not completely eliminate, the thromboembolic phenomena⁷. The thromboembolism prevention must be always present during

Table 2 – Bleeding and INR values.

	INR	Bleeding		Total	p
		Present	Absent		
	≥ 3.5	53	104	53	
	< 3.5	12	169	12	
	Total	65	273	65	$< 0.001^1$

¹Chi-square test

Table 3 – Characteristics of the patients that presented bleeding.

		Pathology		Total	p
		Present	Absent		
INR	≥ 3.6	26	27	53	
	< 3.5	12	0	12	
	Total	38	27	65	$< 0.001^1$
Mild / Moderate		33	25	58	
	Severe	5	2	7	
	Total	38	27	65	0.69 ¹
Age	> 65 yrs.	8	12	20	0.058 ¹
	≤ 65 yrs.	30	15	45	
Sex	Male	9	9	18	
	Female	29	18	47	0.414 ¹
	Total	38	27	65	

¹ Fisher's Exact Test

Table 4 – Association between bleeding and INR values.

	≥ 3.6	< 3.5	Total	P
Mild/ moderate	48	10	58	0.604 ¹
Severe	5	2	7	
Total	53	12	65	

¹Fisher's Exact Test.

Table 5 – Pathology identified according to the bleeding site.

Pathology	N	%
<i>Present</i>	5	55.5
- Bladder polyps	2 (22.2%)	
- Neoplasia		
- Bladder	1 (11.1%)	
- Prostate	1 (11.1%)	
- Renal calculi	1 (11.1%)	
<i>Absent</i>	4	44.4
Total	9	100.0
Pathology	N	%
<i>Epistaxis</i>		
- Present	6	
- Absent	6	
Total	12	
Pathology	N	%
<i>Gynecological Bleeding</i>	23	76.67
- Neoplasia	2 (6.67%)	
- Menopause	8 (26.6%)	
- Climaterium	7 (23.33%)	
- Uterine myoma	6 (20.0%)	
<i>Absent</i>	7	23.33
Total	30	100.0
Pathology	N	%
<i>Present</i>	10	50.0
- Neoplasia		
- Hemorrhoid	4 (20.0%)	
- Diverticulum	2 (10.0%)	
- Polyps	1 (5.0%)	
- Gastric ulcer	3 (15.0%)	
<i>Absent</i>	10	50.0
Total	30	100.0

the follow-up of the valvular pathology evolution, particularly in the presence of AF⁸.

The oral anticoagulant therapy of choice is Warfarin, which, although has been used in medical practice for more than 50 years, is difficult to be managed, with toxic concentrations that are very close to the effective doses. Several external situations can disrupt these limits, which justifies the difficulty of the treatment and the complexity of the norms to be followed by those submitted to it⁹.

The laboratory control to reach the effective dose of Warfarin is based on the International Normalized Ratio (INR), a standardization criterion that has been proposed by the World Health Organization (WHO) since 1982¹⁰. The effort of the medical team warning the studied population regarding the factors that can influence the intensity of the drug effects was not enough to prevent the fact that only approximately 50% of the INR values were within the target-values. The same difficulty was demonstrated in the literature when carrying out the adequacy of the outcomes concerning the anticoagulation¹¹. Despite the frequent dose adjustments, 17.4% of the INR measurements were above the values considered to be safe, which reflects excessive doses of the medication, exposing the patients to the risk of bleeding.

Hylek et al¹² demonstrated that the risk of bleeding was associated with the INR values. The probability of bleeding increases as the INR increases¹², a fact that was well demonstrated in the present study, in which the probability of bleeding among those who reached INR values > 3.5 was 7-fold higher when compared to the group with target-INR (Table 2)¹³.

In the present study, the hemorrhagic events occurred when the INR values were within the therapeutic range cannot be attributed to the use of oral anticoagulation therapy, as the presence of subclinical diseases that predisposed to bleeding was verified in all patients with INR between 2.0 and 3.5.

The complexity of the treatment with vitamin-K inhibitors was documented when we verified that the patients in whom the presence of a disease with bleeding potential was identified were exposed to a 2-fold higher incidence of presenting some blood loss, regardless of the adjustment of the Warfarin dose. It can be deduced that certain diseases in patients undergoing oral anticoagulant therapy become isolated risk factors for hemorrhagic events (Table 2).

All the patients that constituted the cohort of the present study were unaware of the associated disease. Therefore, the diagnosis of the occult lesion was only possible after they were submitted to a clinical and imaging assessment, which were complemented by hematological tests.

As the associated organic anomalies were unknown and did not have clinical manifestations, it can be inferred that they probably would not be identified at an early stage if not for the bleeding. In many patients, the bleeding led to an early diagnosis of neoplasias.

In order to establish a correlation between the bleeding and INR values, the study participants were carefully advised to seek the emergency department of the institution and to communicate by telephone with the medical team in the event

of any bleeding episode, which made possible to know the INR value at the moment of the event.

Some authors call the attention to a higher sensitivity to Warfarin presented by some elderly patients, which would put them into a higher risk for bleeding¹⁴. Our data are in agreement with those in the literature, as we found a 2-fold higher incidence of bleeding among elderly patients (older than 65 years) (Table 1). We observed a non-significant tendency ($p = 0.058$) to a more frequent diagnosis of associated diseases in patients younger than 65 years. Such finding might be explained by the high percentage of relatively young women in our sample, which led to frequent gynecological hemorrhagic events triggered by climacterium and menopause.

It was observed that the female population was predominant in the sample, a justification for the prevalence mitral valve stenosis and rheumatic fever sequelae, which more often affects the female sex¹⁵. The mean age of the studied female population was 52.44 years. The 30 women that presented metrorrhage were referred to gynecological assessment. Hormonal disorder due to hypoestrogenism due to ovarian failure was identified in 15 of them. As these women were menopausal, they used estrogen, a fact that exposed them to a lower action of plasminogen activator inhibitor-1 (PAI-1) and increase in fibrinolysis. Thus, the occurrence of uterine bleeding was favored by the presence of the anti-vitamin K drug.

All patients that presented bleeding followed the established rules, by immediately seeking the emergency department. This attitude facilitated the success of the correction of the cause of hemorrhage. This is the reason, perhaps, why only

7 of the 65 patients that presented bleeding needed volemic replacement.

Recalling an old saying, "A blessing in disguise", the feared bleeding events, once their cause was identified and promptly corrected, helped to identify organic defects before their devastating consequences arose.

Conclusion

- All the patients that presented bleeding with INR values within the therapeutic range (INR 2.0-3.5) in the present study had a diagnosis of associated pathology that predisposed to bleeding.
- The patients with bleeding and therapeutic INR values presented a 2-fold higher probability of presenting an associated pathology that predisposed to bleeding.
- The finding of an associated disease that predisposes to bleeding in patients undergoing oral anticoagulation therapy is a frequent one (58% in the present study).

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

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