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Oral anticoagulation in surgical procedures: risks and recommendations

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Summary. Surgery in anticoagulated patients is problematic. Coumarin therapy is often discontinued or reversed to reduce the perioperative bleeding risk. Meanwhile, the thromboembolic risk is enhanced. We sought to determine the frequency of bleeding and thromboembolism in anticoagulated patients undergoing routine surgery and to investigate the role of patient characteristics and the level of anticoagulation. We studied patients who attended the Leiden Anticoagulation Clinic for treatment relating to mechanical heart valve prostheses, atrial fibrillation or myocardial infarction and underwent surgery at the Leiden University Medical Centre between 1994 and 1998. Outcome events were bleeding and thromboembolism in the perioperative period. Seventy-two complications occurred in 603 interventions, yielding an overall frequency of 11·9% [95% confidence interval (CI): 9·3–14·9], 9·5% ($n = 57$) for haemorrhage and 2·5% ($n = 15$) for thromboembolism. Younger patients tended to have more complications [odds ratio (OR) for >65 years of age: 0·5, 95% CI 0·3–1·0] as did patients with atrial fibrillation (OR for atrial fibrillation *versus* mechanical heart valve prostheses: 1·8, 95% CI 0·8–4·2). High postoperative levels of anticoagulation were associated with a slightly increased risk of complications [OR international normalized ratio (INR) > 3 vs. INR < 2: 1·3, 95% CI 0·6–3·0]. We conclude that routine surgery in anticoagulated patients yields a high perioperative bleeding and thromboembolic risk. While neither patient characteristics nor the level of anticoagulation appeared to play a major role in the occurrence of complications, the risk was clearly associated to the type of surgery, with the highest risk in thoracic surgery.

Keywords: anticoagulation, surgery, risk, haemorrhage, thromboembolism.

Over recent decades, oral anticoagulant therapy with coumarin derivatives has proved to be effective in the prevention of arterial and venous thromboembolism. Nowadays, coumarins are recommended for the prevention of stroke in patients with atrial fibrillation (Albers *et al*, 2001), heart valve disease and mechanical heart valve prostheses (Stein *et al*, 2001) as well as for the primary and secondary prevention of deep vein thrombosis and pulmonary embolism (Hyers *et al*, 2001). Moreover, oral anticoagulation has been shown to be effective in the prevention of stroke and recurrent myocardial infarction in patients with ischaemic heart disease (ASPECT Research Group, 1994; Smith *et al*, 1990). In particular, patients with a high risk of arterial thromboembolism are often treated with anticoagulants for a longer period, sometimes even for life, which leads to several clinical dilemmas. This report focuses on anticoagulant policy in relation to surgery.

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In day-to-day practice, oral anticoagulant treatment is often discontinued or reversed in case of a surgical or medical procedure to reduce the risk of haemorrhage during and shortly after the intervention. This practice increases the risk of thromboembolism with added risk from the surgical procedure itself. Because of the lack of data, physicians have limited other guidelines for the management of anticoagulant therapy than personal clinical experience (Douketis *et al*, 1999, 2000).

A few attempts have been made to describe the occurrence of haemorrhage and thromboembolism in relation to surgery. These studies, however, were limited to specific surgical procedures (Chakravarti & MacDermott, 1998; Morris & Elder, 2000), to a limited number of events (Caliendo *et al*, 1999) or to one particular complication (Limburg *et al*, 1998). Recent review articles have presented recommendations that are mainly based on theoretical argumentation (Kearon & Hirsh, 1997; Heit, 2001). We felt that additional clinical data were needed to evaluate the overall effect of oral anticoagulation on the occurrence of untoward events related to surgery. Therefore, we determined the frequency of complications in anticoagulated

patients undergoing surgery at the Leiden University Medical Centre and investigated the role of patient characteristics and the level of anticoagulation

METHODS

Patients In the period between 1994 and 1998, we performed a prospective study among 4200 patients of the Leiden Anticoagulation Clinic to determine the optimal level of oral anticoagulation in patients with potential cardiac sources of embolism atrial fibrillation, mechanical heart valve prostheses and myocardial infarction Because of the extensive follow-up of the anticoagulation clinic we were able to register over 3200 hospital admissions during the time-window of the study We collected discharge letters for these admissions and selected all 603 admissions to the Leiden University Medical Centre during which a medical or surgical intervention had been carried out for which oral anticoagulation is usually interrupted We studied the discharge letters and checked whether a bleeding or thromboembolic complication was mentioned If such an event had occurred, we studied the full medical chart An overview of the interventions is provided in Table I

Cases and controls In the group of patients with interventions we calculated the frequencies of bleeding and thromboembolic events Moreover, we performed a nested case–control study to investigate in detail the factors which contributed to the occurrence of complications

All patients who had a bleeding or thromboembolic event in the perioperative period (from 2 days prior to the intervention until 3 weeks afterwards) were included as cases For every case we randomly chose two controls from the group of patients who also had surgery at our hospital but had not suffered any complication Each patient was included as a case (at the first complication that occurred during follow-up) or control only once As the risk of complications is obviously related to the type of intervention we matched cases and controls as a group according to the category of the intervention

Data collection We included the following information from the computerized records of the Leiden Anticoagulation Clinic date of birth sex and the indications for oral anticoagulant therapy and hospital admission The date of the surgical intervention was retrieved from the medical chart along with results of the blood tests for the level of oral anticoagulation before and after the intervention These levels as measured by prothrombin times were expressed in international normalized ratio (INR) which is the international standard (International Committee for Standardization in Hematology International Committee on Thrombosis and Hemostasis 1982) For each case we also registered the date of the complication and relevant results of laboratory tests X rays computed tomography (CT) scans and autopsy reports As we studied the role of the achieved level of anticoagulation on the day of the complication we used for the controls the INR value on the day the matching case had his complication

There is a wide range of clinical practice towards the preoperative discontinuation of anticoagulants Therefore we chose to disregard the methods that were applied to lower the anticoagulation level and studied only the INRs that were achieved In our hospital no intravenous heparin is administered in anticoagulated patients prior to surgical interventions except in rare cases and then only in those with artifical heart valves

Table I Classification of interventions

Category	Number of interventions
Abdominal surgery	
Aneurysma aortae	9
Digestive tract	16
Blatter/prostate	7
Other	4
Thoracic surgery	
Coronary artery bypass graft	55
Heart valve surgery	42
Lobectomy	6
Other	1
Orthopaedic surgery	
Hip	7
Knee	2
Shoulder	3
Other	5
Eye surgery	
Cataract	38
Ablatio retinea	3
Eyelid	5
Other	7
Major surgery other	
Amputations	14
Neurosurgery	11
Urology hernia inguinalis	21
Vascular	22
Other	8
Minor surgery other	
Pacemaker	63
Biopsy mediastinoscopy drains	17
Skin tendon	12
Other	30
Angiography	
Coronary	110
Peripheral	39
Endoscopy	
Digestive tract	28
Pulmonary	13
Other	5

Complications Haemorrhages (intracranial spinal and extracranial) and thromboembolic complications (ischaemic stroke myocardial infarction and arterial peripheral embolism) that occurred in the perioperative phase were the events of interest The incidence of venous thromboembolism was not studied All complications were reviewed by an expert panel of physicians who were blinded to the INR according to the following definitions

Intracranial and spinal haemorrhage was defined as a neurological deficit of sudden or subacute onset confirmed by surgery autopsy or CT scan Extracranial haemorrhage

was defined as severe blood loss, leading to prolonged hospital admission, blood transfusion, additional diagnostic or therapeutic interventions or death. Ischaemic stroke was included as a neurological deficit of acute onset, proved by autopsy or CT scan. Strokes that could not be categorized were registered as 'unclassified stroke'. Myocardial infarction was defined by two or more of the following: history of chest discomfort, typical rise of specific cardiac enzymes or the development of new Q waves on electrocardiogram. The diagnosis of arterial peripheral embolism required sudden peripheral ischaemia, proved by duplex scanning, angiography, surgery or autopsy.

Analysis

Frequencies and their 95% confidence interval (CI) were derived by standard calculations, based on the assumption of a Poisson distribution of the number of events. To assess the effect of patient characteristics and the level of anticoagulation on the occurrence of complications, we calculated odds ratios (OR) as a measure of the relative risk by means of logistic regression models. As cases and controls were matched on the type of surgery, the category of the intervention remained a variable in the applied logistic model at all times.

RESULTS

Complications

Seventy-two complications occurred among the 603 medical and surgical interventions in the Leiden University Medical Centre. As only first events were taken into account for the nested case–control study, 70 complications remained for this purpose. We selected two controls per case for all interventions except thoracic surgery, as only 63 controls were available in this category.

Incidence rates of complications per intervention category are given in Table II. The overall frequency of bleeding and thromboembolic events related to surgery was 11·9% (95% CI 9·3–14·9), 9·5% ($n = 57$) for haemorrhage and 2·5% ($n = 15$) for thromboembolism. Frequencies varied between the intervention categories, from a minimum of zero (eye and orthopaedic surgery) to 34 per 100 procedures (thoracic surgery). Two-thirds of all events occurred within 48 h after the intervention, at a range of −1 to 20 days, as shown in Fig 1.

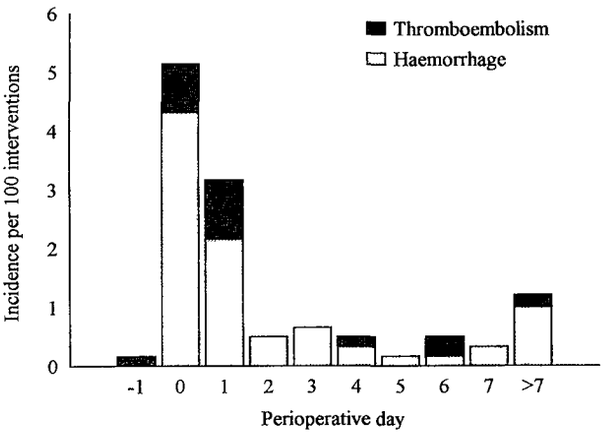

Fig 1. Frequency of complications according to perioperative day

More detailed information on the complications is presented in Table III. Fifty of the 57 bleeding events were located at the operation site. Six of the other seven haemorrhages had a gastrointestinal origin whereas one patient died from a retroperitoneal bleed after coronary bypass surgery. Fifteen thromboembolic events occurred. Eight patients had a myocardial infarction and five ischaemic stroke, all but one in the postoperative phase. One patient had a thrombosis of the renal artery 4 days after cardiac catheterization. We also registered a transient ischaemic attack during coronary angiography. As no CT scanning was performed, this complication was registered as unclassified stroke although the signs and symptoms pointed towards a thromboembolic event. The patient made a full recovery, as did the five patients with a proven cerebral infarction.

Risk estimates of patient characteristics

Table IV gives the results of the nested case–control study we performed on patient characteristics by comparing 70 patients with a perioperative event to 135 controls.

Table II. Frequencies of complications.

Category	Number ($n = 603$)	All events ($n = 72$)	Haemorrhage ($n = 57$)	Thrombosis ($n = 15$)	Overall frequency [% (95% CI)]
Abdominal surgery	36	4	4	0	11·1 (2·8–25·0)
Thoracic surgery	104	35	31	4	33·7 (23·2–46·0)
Orthopaedic surgery	17	0	–	–	–
Eye surgery	53	0	–	–	–
Major surgery, other	76	11	8	3	14·5 (7·1–24·5)
Minor surgery, other	122	4	4	0	3·3 (0·8–7·4)
Angiography	149	15	9	6	10·1 (5·5–15·9)
Endoscopy	46	3	1	2	6·5 (1·2–16·2)

Categories are defined in Table I.

Table III. Detailed information on perioperative events

	Number (n = 72)	Frequency % (95% CI)
Bleeding		
Fatal		
At the operation site	3	0 5
Other	1	0 2
Non-fatal		
At the operation site	47	7 8
Other	6	1 0
Total	57	9 5 (7 1–12 1)
Thromboembolism		
Fatal		
Myocardial infarction	1	0 2
Non fatal		
Myocardial infarction	7	1 2
Peripheral embolism	1	0 2
Ischaemic stroke	5	0 8
Unclassified stroke	1	0 2
Total	15	2 5 (1 4–3 9)

None of the patient characteristics examined – age, sex and the indication for anticoagulant therapy – was strongly associated with the occurrence of complications However, younger patients (≤ 65 years of age) tended to have more untoward events compared with the elderly (OR 1 6, 95% CI 0 9–2 9), whereas patients with atrial fibrillation appeared to have a higher risk compared with those treated because of a mechanical heart valve (OR 1 5, 95% CI 0 7–3 4) Both effects were mainly caused by an increased thromboembolic risk Multivariate analysis, in which the odds ratios were adjusted for the other patient characteristics, made the univariate outcomes more explicit

Risk estimates of the level of anticoagulation

We studied the role of the achieved levels of oral anticoagulation on the day of the intervention, at the time the complication occurred and over the period between the day of surgery and the complication The results are presented in Table V

On the day of surgery, the INR levels of the cases varied between 1 2 and 4 9 INR (mean 2 2 INR) Fifty-four per cent of the intensities were ≤2 0 INR, which is the target ceiling for many interventions The level of anticoagulation on the day of the intervention was not related to the occurrence of

Table IV. Risk factors odds ratios for patient characteristics

	Cases (n)	Controls (n)	Crude OR (95% CI)*	Adjusted OR (95% CI)†
Age				
All events				
≤65 years	32	47	1 0	1 0
>65 years	38	88	0 6 (0 3–1 1)	0 5 (0 3–1 0)
Bleeding				
≤65 years	24	47	1 0	1 0
>65 years	31	88	0 7 (0 4–1 3)	0 6 (0 3–1 3)
Thromboembolism				
≤65 years	8	47	1 0	1 0
>65 years	7	88	0 4 (0 1–1 3)	0 3 (0 1–1 1)
Sex				
Male	53	99	1 0	1 0
Female	17	36	0 9 (0 4–1 7)	0 9 (0 4–1 8)
Indication				
All events				
MHV	16	36	1 0	1 0
MI	29	60	1 1 (0 5–2 3)	1 1 (0 5–2 4)
AF	25	39	1 5 (0 7 3 4)	1 8 (0 8–4 2)
Bleeding				
MHV	14	36	1 0	1 0
MI	23	60	1 0 (0 5–2 3)	1 1 (0 5–2 4)
AF	18	39	1 3 (0 5–3 0)	1 5 (0 6–3 7)
Thromboembolism				
MHV	2	36	1 0	1 0
MI	6	60	2 0 (0 3–12 8)	2 2 (0 3–15 4)
AF	7	39	3 4 (0 6–21 1)	5 3 (0 7–38 9)

*Odds ratios adjusted for the category of the intervention only

†Odds ratios adjusted for the category of the intervention as well as for age sex and indication

MHV mechanical heart valve MI myocardial infarction AF atrial fibrillation

Table V. Risk factors odds ratios for different intensities of anticoagulation

	Cases (*n*)	Controls (*n*)	Crude OR (95% CI)*	Adjusted OR (95% CI)†
INR on the day of surgery				
All events				
<2	27	55	1 0	1 0
2–3	20	38	1 0 (0 5–2 2)	1 0 (0 5–2 1)
>3	12	26	0 9 (0 4–2 3)	0 9 (0 4–2 3)
Bleeding				
<2	19	55	1 0	1 0
2–3	15	38	1 1 (0 5–2 4)	1 0 (0 5–2 4)
>3	11	26	1 1 (0 4–2 9)	1 1 (0 4–2 9)
Thromboembolism				
<2	8	55	1 0	1 0
2–3	5	38	1 0 (0 3–3 6)	0 7 (0 2–2 9)
>3	1	26	0 3 (0 0–3 1)	0 3 (0 0–2 5)
INR on the day of the complication				
All events				
<2	23	42	1 0	1 0
2–3	20	38	1 0 (0 5–2 2)	1 0 (0 4–2 1)
>3	16	30	1 1 (0 5–2 4)	1 1 (0 5–2 6)
Bleeding				
<2	15	42	1 0	1 0
2–3	15	38	1 2 (0 5–2 8)	1 1 (0 5–2 7)
>3	15	30	1 4 (0 6–3 4)	1 3 (0 5–3 4)
Thromboembolism				
<2	8	42	1 0	1 0
2–3	5	38	0 8 (0 2–2 7)	0 5 (0 1–2 2)
>3	1	30	0 3 (0 0–2 3)	0 2 (0 0–1 9)
Highest achieved INR until the day of the complication				
All events				
<2	15	36	1 0	1 0
2–3	16	39	1 0 (0 4–2 3)	0 9 (0 4–2 2)
>3	33	60	1 4 (0 6–3 1)	1 3 (0 6–3 0)
Bleeding				
<2	10	36	1 0	1 0
2–3	13	39	1 2 (0 5–3 3)	1 1 (0 4–3 0)
>3	26	60	1 7 (0 7–4 1)	1 6 (0 6–4 0)
Thromboembolism				
<2	5	36	1 0	1 0
2–3	3	39	0 5 (0 1–2 5)	0 5 (0 1–2 6)
>3	7	60	1 0 (0 7–4 1)	0 7 (0 2–2 9)

INR international normalized ratio
*Odds ratios adjusted for the category of the intervention only
†Odds ratios adjusted for the category of the intervention, as well as for age, sex and indication

a complication afterwards, as shown by odds ratios of 1 0 (95% CI 0 5–2 2) for levels between 2 and 3 INR and 0 9 (95% CI 0 4–2 3) for INR values >3

The anticoagulation levels on the day of the complication varied between 1 1 and 12 0 INR (mean 2 6 INR) Sixty-one per cent of the INR values were 2 0 or higher Twenty-seven per cent was even higher than 3 0 INR However, patients without a complication had no different INRs than the patients with a complication had on the days of the complication 62% INR >2 0, 27% INR >3 0 Thus, INR values on the day of the complication did not differ between cases and controls for all complications combined (OR 1 0, 95% CI 0 5–2 2 for INR 2–3, OR 1 1, 95% CI 0 5–2 4 for INR >3) Higher anticoagulation levels (INR > 3) tended to be associated with bleeding events (OR 1 4, 95% 0 6–3 4) whereas at the same time thromboembolism was prevented (OR 0 3, 95% CI 0 0–2 3)

As we studied the influence of the highest achieved intensity level over a longer period – from the day before the intervention until the day the complication occurred, with a maximum of 1 week – only the highest values (INR > 3) seemed to be associated with a slightly increased risk of complications (OR 1 4, 95% CI 0 6–3 1) As very few individuals had INRs over 5 (five of 64 patients, nine of 135 controls), we could not estimate the risk during high INRs

Multivariate analysis, in which we adjusted the effects of the INR values for age, sex and the indication for treatment, did not alter the outcomes essentially as shown in the last line of Table V.

DISCUSSION

Anticoagulant therapy in non-routine situations such as surgery raises clinical questions as how to minimize the risk of postoperative haemorrhage without compromising the prevention of thromboembolic events. As so little is known about the risks of surgery in anticoagulated patients, we decided to investigate the frequency of perioperative complications and study potential risk factors for events. The frequency of major haemorrhage and thromboembolism was high in the perioperative period (11·9 events per 100 interventions, 95% CI 9·3–14·9), especially in chest surgery. Bleeding complications occurred most frequently (9·5 per 100 events, 95% CI 7·1–12·1) and these were most frequently located at the operation site or in the gastrointestinal tract. Two-thirds of all events occurred within 48 h after the intervention. Neither patient characteristics – sex, age and the indication for anticoagulant therapy – nor the level of anticoagulation in the perioperative phase appeared to play a major role in the occurrence of complications.

Frequency of haemorrhage and thromboembolism

The frequency of perioperative complications varied between the different categories of interventions. Eye surgery and orthopaedic interventions appeared to have a low risk of complications where as many as one-third of all patients undergoing thoracic surgery suffered an untoward event. These differences can, for the greater part, be explained by the nature of the interventions and the applied anticoagulant treatment.

Most eye surgery is performed in the relative absence of blood vessels, which makes haemorrhage an uncommon complication (Gainey *et al*, 1989). Moreover, oral anticoagulation on the day of surgery was reduced to levels below 2·0 INR for all 53 interventions (mean 1·4 INR). In the orthopaedic patients, the average anticoagulation level on the day of surgery was 1·6 INR and in the first postoperative week the INR was 2·2.

Thoracic surgery, which mainly consisted of coronary bypass and heart valve surgery, is characterized by extensive (micro) vascular surgery and a high proportion of acute interventions. The need for extracorporeal circulation induces platelet dysfunction and firm anticoagulation is applied to keep grafts open and avoid valve thrombosis as illustrated by an average INR of 2·6 on the day of surgery and a mean INR of 3·3 in the first postoperative week. All these qualities might have contributed to the high risk of postoperative complications in this category.

The overall frequency of perioperative complications was 11·9% over 24 days, which is equivalent to an incidence of 181 events per 100 patient-years. As the average annual risk of all combined untoward events in our patient group was 4–7% (ASPECT Research Group, 1994; Atrial Fibrillation Investigators, 1994; Cannegieter *et al*, 1995), surgery increased this risk 25–45-fold. Even when thoracic surgery, with its extreme complication rate, was set aside, the frequency of untoward events remained high (7·4 per 100 interventions, 95% CI 5·2–10·1). We therefore conclude that routine surgery in anticoagulated patients yields a high risk, of which physicians must be aware.

Risks

Patient characteristics. The patient characteristics we examined did not much influence the risk of complications. The higher frequency among patients treated for atrial fibrillation might be the result of the fact that atrial fibrillation is often related to other cardiac diseases, such as impaired left ventricular function, valve disease or cardiac ischaemia. Hence, the vulnerability to thromboembolism in these patients is increased. The different complication rates between the three patient groups in our study were mainly caused by an increased risk of thromboembolic events whereas the bleeding risk remained constant, which supports this hypothesis.

A considerable cardiovascular burden might also account for the high complication risk among younger patients. As patients suffer from cardiovascular disease at a relatively young age, their disease might follow a more malignant course that makes them more susceptible to thromboembolic events.

Level of anticoagulation. The achieved level of oral anticoagulation in the perioperative period appeared to play only a minor role in the causal mechanism leading to the overall risk of complications in relation to surgery. However, when bleeding and thromboembolic events were studied separately, higher anticoagulation levels tended to be associated with bleeding whereas lower INR values favoured thromboembolism.

We found that INR on the day of the intervention did not predict the occurrence of a complication, indicating that local factors are of much more importance at this stage. This observation was confirmed by the finding that patients who actually experienced their untoward event in the first 24 h had similar levels of anticoagulation as the controls. Our data suggest an effect of the highest anticoagulation levels in the period preceeding a complication: INR values over 3·0 seemed to be related to a higher risk of events (OR 1·4, 95% CI 0·6–3·1).

A shortcoming of our study was that we could not identify those patients who received intravenous heparin in the perioperative phase. However, the general practice in the Leiden University Medical Centre is to refrain from treatment with heparin when oral anticoagulation is reversed. Exceptions to this practice are few and are mainly limited to patients who underwent heart valve surgery and did not reach an adequate postoperative INR level in time. We therefore do not believe that the outcomes of our study were essentially altered by the lack of data on heparin use. A reliable comparison of the high bleeding risk in our study to the average perioperative bleeding risk was prohibited by the wide variety of surgical procedures we studied.

Recommendations

We conclude that one in 10 medical or surgical interventions in anticoagulated patients is complicated by a haemorrhagic or thromboembolic event. Although the level of anticoagulation appeared to be just a small part of the causal mechanism that leads to the occurrence of complications, high perioperative levels (INR > 3) should be avoided, in which the days following surgery are at least as important as the day of the intervention itself In particular, patients with atrial fibrillation are highly prone to experience a thromboembolic event and should be anticoagulated with the utmost consideration

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