Factors affecting warfarin control in patients attending the warfarin clinic in the cardiac surgical center in Ahmed Ghasim hospital (2010)

By
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A thesis submitted in partial fulfillment for the requirements of the degree of M.D in clinical pathology

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Dedication

To my big family:
Dear father, dear mother and sisters

To my small family:
My husband Haytham, and sweet kid
Mohamed
Acknowledgment

After finishing my study, I would like to express my thanks to my supervisor, Dr. A/salam Ibrahim Bashir for his continuous effort in helping me in revision and discussion of my study.

I also thank Dr. Anwar A.Y. Kordafani for her ideas and her continuous encouragement.

I also thank staff of Ahmed Ghasim hospital for helping me in the analysis of the samples.

Lastly I thank my family who supported me and encouraged me to complete my study.
Abstract

Background

Warfarin is a commonly used medication with a narrow therapeutic index. The initiation of warfarin requires consideration of a variety of factors, which include reviewing the indications and contraindications for this agent, performing a thorough clinical assessment along with a risk-benefit analysis for anticoagulation, consideration of warfarin pharmacology, developing strategies to monitor the intensity of anticoagulation and for the detection of adverse events, and education of the patient.

Design:

Descriptive prospective cross sectional study.

Setting:

This study held at the cardiac surgery and renal transplant center in Ahmed Ghasim Hospital.

Objectives:

The different factors which affect proper warfarin control the level of knowledge, and the degree of control in one hundred patient were assessed.

Methodology:

Patient knowledge about the warfarin dose, the time of administration, the effect of diet, drug interaction with warfarin and the incidence of complication were studied using a direct questionnaire and the last INR was measured to identify the level of control.

Results:

The results were compared to the results of a similar Sudanese study which was conducted at 2000 in the same hospital in the same number
of patients. In our study 38% of the patients were properly controlled having an INR within the therapeutic range, in contrast to the previous study when the number is 34%, 20% of our patients had good level of education regarding warfarin, compared to 16% in the previous study. 60% of our patients did not received any education programme about warfarin, 71.4% of them were educated after starting the therapy. 60% of the patients were taking different medication with different interaction with warfarin. 88% of the patients knew the different interaction of warfarin with different types of diet. 70% of the population studied live far from the center outside Khartoum state. Only 2 of our patients were provided with the warfarin booklets, and they obtained it from another hospital, in the previous study 12 of the patients had the booklet and they obtained it from abroad. 36% of our patients suffered from bleeding, the commonest site was epistaxis, 36.2% from them had bleeding for several times, compared to 12% in the previous study this reflects the bad control as 33% of our patients had prolonged INR, compared to one patient in the previous study. Only 2 of our patients suffered from one attack of cerebral thrombosis in the form of cerebrovascular accident. School education did not seem to affect warfarin control since in both educated and illiterate patients, the percentage of those who had controlled INR are similar. The optimum maintainance dose was found to be 3-5mg.

Conclusion:

From this study it was concluded after 10 years that more than half of the patients were not well controlled having an INR outside the therapeutic range, the most significant causes of poor control were lack of full education about the drug and the far residence from hospital and laboratories and the high cost of the INR investigation. Bleeding endangered a large number of our patients life. Thrombosis still seemed to be a rare complication.
andex

خلفية

عقار الوارفرين هو عقار شائع الاستعمال له العديد من الفوائد والأضرار. يستجيب البدء في
اعطاء هذا العقار من قبل الطبيب موازنة الأسباب الملغومة لأعطائه مع الأسباب المانعة لأعطائه،
زائدًا الفحص السريري الشامل والمعرفة بفاموكلي العقار ووسائل المتابعة ومعرفة الأعراض
الجانية بالإضافة إلى توعية وارشاد المريض.

نوع الدراسة

دراسة مقطعية وصفية

المكان

مركز جراحة القلب والكلى مستشفى أحمد قاسم

الأهداف:

قياس معدل السيولة ودراسة العوامل المختلفة التي تؤثر عليه تم دراسة مدى معرفة المريض
بالعقار.

وسائل

تم دراسة مدى معرفة المريض بالجرعة، زمن اعطائها، نوعية الغذاء واستعمال العقارات
المختلفة ومعدل حدوث المضاعفات عن طريق السؤال المباشر. كما تم قياس معدل السيولة

النتائج

تم مقارنة النتائج مع نتائج دراسة سابقة أجريت في العام 2000 م في نفس المستشفى
على نفس العدد من المرضى. 38% من المرضى لديه فحص سيولة في المستوى المطلوب مقارنة
ب34% في الدراسة سابقة. 20% من المرضى لديهم معرفة جيدة بالعقار مقارنة ب16% في
الدراسة السابقة، 60% من المرضى لم يتلقوا أي برنامج تعليمي 4 عن الوارفرين، 71.4% منهم
تلقوا معلومات بعد البدء في الوارفرين. 60% من المرضى يستخدمون عقارات أخرى لها تأثيرات
مختلفة على الوارفرين. 88% لديهم دراية بناية نوعية الغذاء على العقار. 70% يسكنون بعيدا عن
المستشفى خارج ولاية الخرطوم. مريضين فقط لديهم كتيبه الوارفرين وقد تحقحوا عليه من مستشفى
آخر في الدراسة السابقة 12% لديهم الكتيب وقد تحقوا عليه من الخارج. 36% عانوا من النزيف
الأكثرية في صورة رفع. 36.2% عانوا من النزيف لعدة مرات مقارنة ب12% في الدراسة
السابقة وذلك لأن 33% من المرضى لديه في ضوء سبولة أكثر من المستوى المطلوب مقارنة
بمريض واحد في الدراسة السابقة. مرضى ضعف الناتج فقط تعرضوا لتجلط الدم مما أدى إلى حدوث جلطات
دماغية. نسبة المرضى الذين لديهم في ضوء سبولة في المستوى المطلوب عند الأمين والمتعلمين
متقاربة مما يدل على أن التعليم المدرسي ليس لديه أثر الجرعة المثالية للعقار تتراوح بين 5-3 ملجم.

الخلاصة
من هذه الدراسة نستخلص أنه بعد عشرين سنوات لا يزال أكثر من نصف المرضى لديه
فحص سبولة خارج المستوى المطلوب والأسباب هي عدم وجود توعية وارشاد للمرضى
وسكنهم بعيدا عن أماكن الفحص والعلاج بالإضافة إلى غلاء الفحص. لا يزال النزف يهدد حياة
العديد من المرضى أما التجلط فلا يزال من المضاعفات النادرة.
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Chapter (1)

Introduction & Literature review
Chapter (2)

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Appendix(1)

بسم الله الرحمن الرحيم

Graduate college

Medical and health studies board

Serial No (   )

Name:…………………………………………………………………………………

1. Sex : a. male b. female

2. Age: a. 10-19 b. 20-29 c. 30-39 d. 40-49 e. 50-60 f. >60

3. Residence: a. near to the center b. far from the center

4. Education: a. illiterate b. primary c. intermediate d. secondary e. graduate f. postgraduate

5. Occupation: …………………………………………………………………

Patient warfarin therapy

6. Indication for warfarin therapy

7. Duration for warfarin therapy……………………………………….
8. Time of warfarin intake:
   a. in the morning
   b. midnight
   c. evening
   d. at any time during the day

9. Dose of warfarin now.

10.1 No. of visit for warfarin control:
   a. according to the doctor's request
   b. not regular

10.2 If b. explain why?

11.1 Dose the patient take any drug(s) other than warfarin?
   a. yes
   b. no

11.2 If a. mention it( them).

12.1 Have you received education program about warfarin?
   a. yes
   b. no

12.2 If yes when?
   a. before initiation of warfarin
   b. after initiation of warfarin

12.3 If yes where?
   a. private clinic
   b. hospital
   c. abroad

13.1 Have you warfarin booklet?
   a. yes
   b. no

13.2 If yes, from where did you obtain it?
   a. Sudan
   b. abroad
13.3 if yes are you taking it with you all the time?

14. is there any difficulty in taking warfarin?
   a. not available in the nearby pharmacy
   b. expensive
   c. difficult to obtain the exact dose
   d. residence far away from the laboratories and hospitals
   e. other factors

if ( e) mention these factors……………………………………

**Patient knowledge about warfarin**

15. what is warfarin?   a. knows   b. does not know

16. why are you on warfarin? a. knows   b. does not knows

17. what is the type of warfarin tablets and its colour?
   a. knows all types by its dose and colour
   b. knows all types its colour only
   c. knows 2 types by its dose and colour
d. knows 2 types by its colour only

e. knows 1 types by its dose and colour

f. knows 1 types colour only

g. does not know

18.1 does the patient knows diet containing vit k ? a. yes b.no.

18.2 if yes mention few.................................

19.1 does the patient knows that there is interactions between warfarin and

19.1 antibiotics a. yes b. no

19.2 asprin a. yes b. no

20. What the patient will do if he/she is ill and needs antibiotics?

a. goes to a doctor and tell him he/she on warfarin

b. goes to a doctor and tell him he/she on warfarin if asked

c. gets antibiotics from the nearby pharmacy

21. What the patient will do if he/she is ill and needs any surgical or dental operation?

a. To inform the doctor and tell him he/she on warfarin
b. To inform the doctor and tell him he/she on warfarin if asked

22. question to married women

If you get pregnant what to do?

a. to inform the doctor that I am on warfarin.

b. to continue the same dose

**Warfarin complications**

23.1 Have you ever have bleeding while you are on warfarin?

a. yes  b. no

23.2 If a When?...........................................................................................................

23.3 where is are the site(s) of that bleeding? .........................

23.4 How many time? A. once b. twice c.> twice

24.1 Have you any thrombotic attack while you are on warfarin?

a. yes  b. no

24.2 If yes when?........................................................................................................

24.3 Where is/ are the site(s) that thrombosis?.........................
24.4 Number of thrombotic attacks? a. once b. twice c. > twice

24.5 If © specify……………………………………………………………………

**Investigations**

25. last INR investigations………………………………………………………
Appendix(3)

Agents that increase INR or bleeding risk

1. Acetaminophen (Tylenol)
2. Alcohol
3. Amiodarone (Cordarone)

Adjustment per Amiodarone maintenance dose (7):

1. Amiodarone 400 mg/day: Reduce Warfarin dose 40%
2. Amiodarone 300 mg/day: Reduce Warfarin dose 35%
3. Amiodarone 200 mg/day: Reduce Warfarin dose 30%
4. Amiodarone 100 mg/day: Reduce Warfarin dose 25%

4. Anabolic Steroids
5. Antifungal Medications
   1. Fluconazole (Diflucan)
   2. Ketoconazole (Nizoral)
3. Itraconazole (Sporanox)
4. Miconazole (Monistat)
6. Aspirin and Salicylates
7. Cephalosporins
   1. Cefoperazone (Cefobid)
   2. Cefamandole (Mandol)
   3. Cefotetan (Cefotan)
   4. Cefmetazole (Zefazone)
8. Chloral Hydrate
9. Cimetidine (Tagamet)
10. Clofibrate
11. Cranberry Juice (CYP2C9 inhibitor) appears safe in at least one clinical trial (8).
12. Danazol (Danocrine)
13. Diflunisal (Dolobid)
14. Disulfiram (Antabuse)
15. Fluvoxamine (Luvox)
16. Ginkgo Biloba (independent effect due to antiplatelet activity)
17. Heparin
18. HMG CoA Reductase inhibitors
19. **Isoniazid (INH)**

20. **Macrolides**
   1. **Erythromycin**
   2. **Clarithromycin**

21. **Metronidazole (Flagyl)**

22. **Nalidixic Acid**

23. **NSAIDs**

24. **Omeprazole (Prilosec)**

25. **Paroxetine (Paxil)**

26. **Penicillin**

27. **Propafenone (Rythmol)**

28. **Quinidine**

29. **Quinolones**

30. **Sulfinpyrazone (Anturane)**

31. **Tamoxifen**

32. **Tetracycline**

33. **Thyroid Hormone (Thyroxine or Synthroid)**

34. **Ticlopidine (Ticlid)**

35. **Trimethoprim-Sulfamethoxazole (Bactrim, Septra)**

36. **Vitamin E**
Theoretical bleeding risk, but appears to be safe in clinical trials

(9).

**Drugs that decrease INR or increase clotting risk**

37. American Ginseng (no effect on Warfarin with Asian Ginseng)
38. Barbiturates
39. Binding Resins
40. Carbamazepine (Tegretol)
41. Oral Contraceptives
42. Penicillin
43. Rifampin
44. St. John's Wort
45. Vitamin K

**Drugs that have variable effect on INR or bleeding risk**

46. Allopurinol
47. Corticosteroids
48. Phenytoin (Dilantin)
اردشادات لمرضى عيادة سبولة الدم عن عقار الوارفارين

• يستعمل عقار الوارفارين لزيادة سبولة الدم لمنع حدوث الجلطات الدموية في في الجسم.

• أمثلة لبعض الحالات التي تستدعي العلاج بعقار الوارفارين قلة العادات في أوردة القدمين الصمامات المعدنية

• عدم انتظام ضربات القلب مما يؤدي إلى السكتة الدماغية، النزعة الصدرية

• جدل في الرئتين.

• متابعة العلاج تتم عن طريق فحص دورى خاص للدم لمعرفة نسبة السبولة، ويتم تحديد الجرعة على ضوء نتيجة هذا الفحص.

• النزف هو أهم الاعراض الجانبية للعقار.

• يزداد احتمال النزف كلما زادت نسبة السبولة.

• النزف يمكن أن يكون من:

- الألفى صورة راعف
- من اللثة عند تنظيف الأسنان.
- النزيف الجنى في صورة بقع صغيرة أو كبيرة
- وجود الدم في البول أو البراز أو الاستفراغ الدموي
- زيادة كمية الدم المفقود في الدورة الشهرية.

- لتفادي النزف أخبر طبيبك أنك تستخدم الوارفارين إذا كنت مقدمًا على عملية جراحية.

- لتفادي النزف أخبر طبيب الأسنان أنك تستخدم البارفارين.
• لتفادي النزف أخبر طبيبك أنك تستخدم البارفارين في حالة حدوث الحوادث أو تعرضك لأي نوع من الجروح.
• لتفادي النزف أحرص على حمل كتب البارفارين معك في كل الأوقات.
• لضمان سلامتك أثناء تناولك البارفارين أحرص على الأتي:
  • خذ الجرعة المخصصة لك من الطبيب فقط.
  • خذ الجرعة مرة واحدة في اليوم، أفضل في المساء.
  • للنساء إذا كنت تخططين للحمل أو في حالة حدوث حمل عليك اخبار الطبيب المختص فوراً.
• تتأثر فعالية البارفارين بالعديد من العوامل مثل ذلك:
  • بعض أنواع العلاجات مثل الفيتامينات، بعض أنواع المضادات الحيوية و الأسبرين، لذلك
  يجب استشارة طبيبك عند تناولك أي علاج جديد.
• يتأثر أيضًا بتناول الغذاء
  • يأتي غفار البارفارين في ثلاثة ألوان: البنى 1 ملجم، الأزرق 3 ملجم، الزهري 5 ملجم
  • في حالة نسيان أخذ الجرعة في الوقت المحدد أخذها في أي وقت خلال اليوم.
  • في حالة نسيان جرعة اليوم السابق تم أخذ الجرعة المقررة فقط لذا اليوم، من المخاطرة

<table>
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<tr>
<th>Date</th>
<th>INR</th>
<th>Dose until next blood test</th>
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Introduction

The name warfarin stems from the acronym for the organization which funded the key research, \textit{WARF}, for Wisconsin Alumni Research Foundation, the ending \textit{-arin} indicating its link with coumarin (1). Warfarin is a synthetic derivative of the naturally occurring anti-coagulant dicumarol. The anti-coagulant properties of dicumarol were first observed in cattle that suffered a hemorrhagic disorder after being fed spoiled sweet clover hay during the 1920s. Karl Link identified the causative agent by 1939 and later developed warfarin as a rat poison before it was used in humans in the 1950s. However the anticoagulant mechanism of warfarin was not elucidated until twenty years later (2).

Warfarin is a commonly used medication with a narrow therapeutic index. The initiation of warfarin requires consideration of a variety of factors, which include reviewing the indications and contraindications for this agent, performing a thorough clinical assessment along with a risk-benefit analysis for anticoagulation, consideration of warfarin pharmacology, developing strategies to monitor the intensity of anticoagulation and for the detection of adverse events, and education of the patient (3).
Mechanism of Action of Coumarin

Warfarin, a coumarin derivative, produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the carboxylation of glutamate residues to γ-carboxyglutamates (Gla) on the N-terminal regions of vitamin K–dependent proteins (3). These proteins, which include the coagulation factors II, VII, IX, and X, require γ-carboxylation by vitamin K for biological activity. By inhibiting the vitamin K conversion cycle, warfarin induces hepatic production of partially decarboxylated proteins with reduced coagulant activity (4). They are collectively referred to as PIVKAs (proteins induced by vitamin K absence/antagonism), and individual coagulation factors as PIVKA-number (e.g. PIVKA-II) (5)(6).

Carboxylation promotes binding of the vitamin K–dependent coagulation factors to phospholipid surfaces, thereby accelerating blood coagulation. γ-Carboxylation requires the reduced form of vitamin K (vitamin KH₂). Coumarins block the formation of vitamin KH₂ by inhibiting the enzyme vitamin K epoxide reductase, thereby limiting the γ-carboxylation of the vitamin K–dependent coagulant proteins. In addition, the vitamin K antagonists inhibit carboxylation of the regulatory anticoagulant proteins C and S. The
anticoagulant effect of coumarins can be overcome by low doses of vitamin K1 (phytonadione) because vitamin K1 bypasses vitamin K epoxide reductase. Patients treated with large doses of vitamin K1 (usually >5 mg) can become resistant to warfarin for up to a week because vitamin K1 accumulating in the liver is available to bypass vitamin K epoxide reductase (4).

Warfarin also interferes with the carboxylation of Gla proteins synthesized in bone. Although these effects contribute to fetal bone abnormalities when mothers are treated with warfarin during pregnancy, there is no evidence that warfarin directly affects bone metabolism when administered to children or adults (4).

**Pharmacokinetics and Pharmacodynamics of Warfarin**

Warfarin is a racemic mixture of 2 optically active isomers, the R and S forms, in roughly equal proportion. It is rapidly absorbed from the gastrointestinal tract, has high bioavailability, and reaches maximal blood concentrations in healthy volunteers 90 minutes after oral administration. Racemic warfarin has a half-life of 36 to 42 hours, circulates bound to plasma proteins (mainly albumin), and accumulates in the liver, where the 2 isomers are metabolically transformed by different pathways. The relationship between the dose of warfarin and the response is influenced by genetic and environmental
factors, including common mutations in the gene coding for cytochrome P450, the hepatic enzyme responsible for oxidative metabolism of the warfarin S-isomer. Several genetic polymorphisms in this enzyme have been described that are associated with lower dose requirements and higher bleeding complication rates compared with the wild-type enzyme CYP2C9.

In addition to known and unknown genetic factors, drugs, diet, and various disease states can interfere with the response to warfarin (4).

**Drug interaction** (appendix3)

Drugs may influence the pharmacokinetics of warfarin by reducing gastrointestinal absorption or disrupting metabolic clearance. For example, the anticoagulant effect of warfarin is reduced by cholestyramine, which impairs its absorption, and is potentiated by drugs that inhibit warfarin clearance through stereoselective or nonselective pathways. Stereoselective interactions may affect oxidative metabolism of either the S- or R-isomer of warfarin. Inhibition of S-warfarin metabolism is more important clinically because this isomer is 5 times more potent than the R-isomer as a vitamin K antagonist. Phenylbutazone, sulfinpyrazone, metrnidazole, and trimethoprim-sulfamethoxazole inhibit clearance of S-warfarin, and each potentiates the effect of warfarin on the prothrombin time (PT). In contrast, drugs such as cimetidine and omeprazole, which inhibit clearance of the R-isomer, potentiate the PT only
modestly in patients treated with warfarin. Amiodarone inhibits the metabolic clearance of both the S- and R- isomers and potentiates warfarin anticoagulation. The anticoagulant effect is inhibited by drugs like barbiturates, rifampicin, and carbamazepine, which increase hepatic clearance. Chronic alcohol consumption has a similar potential to increase the clearance of warfarin, but ingestion of even relatively large amounts of wine has little influence on PT in subjects treated with warfarin (4).

Drugs may influence the pharmacodynamics of warfarin by inhibiting synthesis or increasing clearance of vitamin K-dependent coagulation factors or by interfering with other pathways of hemostasis. The anticoagulant effect of warfarin is augmented by the second-and third-generation cephalosporins, which inhibit the cyclic interconversion of vitamin K; by thyroxine, which increases the metabolism of coagulation factors; and by clofibrate, through an unknown mechanism. Doses of salicylates >1.5 g per day and acetaminophen also augment the anticoagulant effect of warfarin, possibly because these drugs have warfarin-like activity. Heparin potentiates the anticoagulant effect of warfarin but in therapeutic doses produces only slight prolongation of the PT (4).

Drugs such as aspirin, non steroidal anti inflammatory drugs, penicillins (in high doses), and moxolactam increase the risk of warfarin-associated bleeding by inhibiting platelet function. Of these, aspirin is the most important
because of its widespread use and prolonged effect. Aspirin and non steroidal anti inflammatory drugs also can produce gastric erosions that increase the risk of upper gastrointestinal bleeding. The risk of clinically important bleeding is heightened when high doses of aspirin are taken during high-intensity warfarin therapy (international normalized ratio [INR] 3.0 to 4.5). In 2 studies, one involving patients with prosthetic heart valves and the other involving asymptomatic individuals at high risk of coronary artery disease, low doses of aspirin (100 mg and 75 mg daily, combined with moderate-and low-intensity warfarin anticoagulation, respectively also were associated with increased rates of minor bleeding (4).

The mechanisms by which erythromycin and some anabolic steroids potentiate the anticoagulant effect of warfarin are unknown. Sulfonamides and several broad- spectrum antibiotic compounds may augment the anticoagulant effect of warfarin in patients consuming diets deficient in vitamin K by eliminating bacterial flora and aggravating vitamin K deficiency (4).

**Warfarin - Food interactions**

Green leafy vegetables are among the best food source of vitamin K. The average intake of vitamin K for adults in UK is 70-80 micrograms (mcg) per day. The Daily Value for vitamin K ,an estimate of daily need ,is 80
micrograms. It is important to limit intake of food that provides more than 60% of the Daily Value for vitamin K to help to keep PT/INR in the desired range (10).

Subjects receiving long-term warfarin therapy are sensitive to fluctuating levels of dietary vitamin K, which is derived predominantly from phylloquinones in plant material. The phylloquinone content of a wide range of foodstuffs has been listed by Sadowski and associates. Phylloquinones counteract the anticoagulant effect of warfarin because they are reduced to vitamin KH$_2$ through the warfarin-insensitive pathway. Important fluctuations in vitamin K intake occur in both healthy and sick subjects. Increased intake of dietary vitamin K sufficient to reduce the anticoagulant response to warfarin occurs in patients consuming green vegetables or vitamin K– containing supplements while following weight-reduction diets and in patients treated with intravenous vitamin K supplements. Reduced dietary vitamin K$_1$ intake potentiates the effect of warfarin in sick patients treated with antibiotics and intravenous fluids without vitamin K supplementation and in states of fat malabsorption. Hepatic dysfunction potentiates the response to warfarin through impaired synthesis of coagulation factors. Hypermetabolic states produced by fever or hyperthyroidism increase warfarin responsiveness, probably by increasing the catabolism of vitamin K – dependent coagulation factors (4).
Food high in vitamin K (more than or equal 200% DV)(10)

Eat no more than 1 servings /day.

A cup equals 8 ounces or ½ pound.

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<thead>
<tr>
<th>Food</th>
<th>Serving size</th>
<th>%Daily value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kale , fresh , boiled</td>
<td>1/2 cup</td>
<td>660</td>
</tr>
<tr>
<td>Spinach, fresh, boiled</td>
<td>1/2 cup</td>
<td>560</td>
</tr>
<tr>
<td>Turnip, green, boiled</td>
<td>1/2 cup</td>
<td>530</td>
</tr>
<tr>
<td>Collards, fresh, boiled</td>
<td>1/2 cup</td>
<td>520</td>
</tr>
<tr>
<td>Swiss chard, fresh ,boiled</td>
<td>1/2 cup</td>
<td>360</td>
</tr>
<tr>
<td>Parsley, raw</td>
<td>1/4 cup</td>
<td>300</td>
</tr>
<tr>
<td>Mustard green, fresh ,boiled</td>
<td>1/2 cup</td>
<td>260</td>
</tr>
</tbody>
</table>
**Food moderately high in vitamin K (60-199% DV)** (10)

Eat no more than 3 servings /day

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Vitamin K (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brussels sprouts, frozen or boiled</td>
<td>½ cup</td>
<td>190</td>
</tr>
<tr>
<td>Spinach, raw</td>
<td>1 cup</td>
<td>180</td>
</tr>
<tr>
<td>Turnip, greens, raw, chopped</td>
<td>1 cup</td>
<td>170</td>
</tr>
<tr>
<td>Gree leaf lettuce, shredded</td>
<td>1 cup</td>
<td>125</td>
</tr>
<tr>
<td>broccoli, raw, chopped</td>
<td>1 cup</td>
<td>110</td>
</tr>
<tr>
<td>Endive lettuce, raw</td>
<td>1 cup</td>
<td>70</td>
</tr>
<tr>
<td>Romaine lettuce, raw</td>
<td>1 cup</td>
<td>70</td>
</tr>
</tbody>
</table>
Indications for warfarin therapy:

The Indications for warfarin according to the Fourth American College of Chest Physicians (ACCP) Consensus Conference and product labeling for Coumadin are as follows:

(1) Prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism;

(2) Prophylaxis and/or treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement;

(3) Reducing the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction (3).
Goals of Anticoagulation:

The goal of anticoagulant therapy is to administer the lowest possible dose of anticoagulant to prevent clot formation or expansion. The required degree of anticoagulation continues to evolve as studies provide more information about the efficacy and safety of lower doses. Current therapeutic goals for various disease states are summarized in Table 1 (11-16).

Recommended Therapeutic Goal for Oral Anticoagulation:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Range of INR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis for high-risk surgery</td>
<td>2-3</td>
<td>clinical judgment</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First episode</td>
<td>2-3</td>
<td>3-6 months</td>
</tr>
<tr>
<td>High risk of recurrent thrombosis</td>
<td>2-3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Thrombosis associated</td>
<td>3-4</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Condition</td>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>with antiphospholipid antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First episode</td>
<td>2-3 months</td>
<td></td>
</tr>
<tr>
<td>High risk of recurrent embolism</td>
<td>2-3 months</td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td>2-3 months</td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction (to prevent systemic embolism)†</td>
<td>2-3 months</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease (after thrombotic event or if the left atrium is</td>
<td>2-3 months</td>
<td></td>
</tr>
<tr>
<td>greater than 5.5 cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2-3 months</td>
<td></td>
</tr>
</tbody>
</table>
Chronic or intermittent Cardioversion  |  2-3  |  3 weeks before and 4 weeks after atrial fibrillation if normal sinus rhythm is maintained  

Prosthetic heart valves  |  2.5 -3.5‡  |  Lifelong  
Aortic position  
Mechanical  

Bioprosthetic  |  2-3  |  Clinical judgment (3 months optional)  

Mitral position  |  2.5 -3.5‡  |  Lifelong  
Mechanical  

Bioprosthetic  |  2-3  |  3months  

*--One study suggested that 4 weeks may be an adequate duration of oral anticoagulant therapy in patients without continuing risk factors.
†--If oral anticoagulant therapy is elected to prevent recurrent myocardial infarction, an INR of 2.5 to 3.5 is recommended.

‡--Depending on the type of mechanical valve (i.e., caged ball or caged disk) and the valve position (mitral), some patients may benefit from INRs in the upper end of the range.

Laboratory monitoring of warfarin therapy

Measuring the prothrombin time (PT) remains the primary mechanism by which warfarin anticoagulation is monitored. Prolongation of the PT, however, depends on the responsiveness of the thromboplastin used to initiate coagulation. Hence, the WHO has currently established and international standard by which manufacturers or individual labs can determine an international sensitivity index (ISI) for each lot of thromboplastin. A therapeutic range of PT is then defined by the international normalized ratio (INR), which is the ratio between the patients PT to the mean normal PT for the lab raised to the power of the ISI:

\[ \text{INR} = \left( \frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{\text{ISI}} \]
where the “mean normal PT” is the arithmetic mean prothrombin time for the laboratory. The ISI is a correction factor, specific for each lot of laboratory prothrombin reagent, that correlates the activity of the reagent to a standard maintained by the World Health Organization. A smaller ISI reflects a more sensitive thromboplastin reagent such that a more prolonged PT will be observed for the same therapeutic effect. In most medical institutions, the INR is automatically calculated by the laboratory information system. The INR can also be calculated from the above formula or derived from an INR nomogram (2).

The dosing of warfarin is driven by monitoring the prothrombin time to achieve a PT in the appropriate therapeutic range. Typically 5 to 10 mg of warfarin is administered daily with daily monitoring of the INR. The dose is changed gradually until therapeutic range is reached and then the INR is followed on a regular but less frequent basis. Adjustments in dosage should be based on the weekly dose since warfarin has a long half-life. For most indications the INR should be maintained between 2.0 to 3.0. Exceptions include anticoagulation in patients with mechanical prosthetic heart valves and patients with the antiphospholipid antibody syndrome, in which the INR is usually kept between 2.5 and 3.5. However, it must be remembered that the INR was developed for deep venous thrombosis prophylaxis and may not be the most appropriate monitoring mechanism for other situations. Furthermore,
inhibitors such as lupus anticoagulants can prolong the PT obscuring the appropriate therapeutic range such that it may be necessary to use alternative assays such as the direct quantitation of the plasma warfarin concentration (2).

**Complication of warfarin therapy**

**Hemorrhagic Complications**

The most common complication of warfarin therapy is bleeding, which occurs in 6 to 39 percent of recipients annually. The incidence of bleeding is directly related to the intensity of anticoagulation. With the reductions in anticoagulation intensity that have evolved over the past 20 years, the incidence of hemorrhagic complications has decreased dramatically. In patients receiving warfarin therapy, the median annual rate of major bleeding ranges from 0.9 to 2.7 percent, and the median annual rate of fatal bleeding ranges from 0.07 to 0.7 percent (17). The incidence of complications varies within the ranges, depending on the clinical indication and the intensity of anticoagulation. Intracranial hemorrhage accounts for approximately 2 percent of the reported hemorrhagic complications of warfarin therapy and is associated with a mortality rate of 10 to 68 percent. Patient characteristics associated with a major risk of hemorrhage have been identified in a number of randomized studies.
Bleeding that occurs with an INR of less than 3 is often associated with an underlying occult gastrointestinal or renal lesion. Risk of bleeding is augmented if the INR is out of range (due to accidental or deliberate overdose or due to interactions), and may cause hemoptysis (coughing up blood), excessive bruising, bleeding from nose or gums, or blood in urine or stool.

The risks of bleeding is increased when warfarin is combined with antiplatelet drugs such as clopidogrel, aspirin, or other nonsteroidal anti-inflammatory drugs (18). The risk may also be increased in elderly patients (19) and in patients on hemodialysis (20).

**WARFARIN NECROSIS**

A rare but serious complication resulting from treatment with warfarin is warfarin necrosis, which occurs more frequently shortly after commencing treatment in patients with a deficiency of protein C. Protein C is an innate anticoagulant that, like the procoagulant factors that warfarin inhibits requires vitamin K-dependent carboxylation for its activity. Since warfarin initially decreases protein C levels faster than the coagulation factors, it can paradoxically increase the blood's tendency to coagulate when treatment is first begun (many patients when starting on warfarin are given heparin in parallel to combat this), leading to massive thrombosis with skin necrosis and gangrene of
limbs. Its natural counterpart, purpura fulminans, occurs in children who are homozygous for certain protein C mutations (21)

OSTEOPOROSIS

After initial reports that warfarin could reduce bone mineral density, several studies have demonstrated a link between warfarin use and osteoporosis-related fracture. A 1999 study in 572 women taking warfarin for deep venous thrombosis, risk of vertebral fracture and rib fracture was increased; other fracture types did not occur more commonly (22). A 2002 study looking at a randomly selected selection of 1523 patients with osteoporotic fracture found no increased exposure to anticoagulants compared to controls, and neither did stratification of the duration of anticoagulation reveal a trend towards fracture (23).

A 2006 retrospective study of 14,564 Medicare recipients showed that warfarin use for more than one year was linked with a 60% increased risk of osteoporosis-related fracture in men; there was no association in women. The mechanism was thought to be a combination of reduced intake of vitamin K, which is necessary for bone health, and inhibition by warfarin of vitamin K-mediated carboxylation of certain bone proteins, rendering them nonfunctional (24).
Another rare complication that may occur early during warfarin treatment (usually within 3 to 8 weeks) is purple toe syndrome. This condition is thought to result from small deposits of cholesterol breaking loose and flowing into the blood vessels in the skin of the feet, which causes a bluish purple color and may be painful. It is typically thought to affect the big toe, but it affects other parts of the feet as well, including the bottom of the foot (plantar surface). The occurrence of purple toe syndrome may require discontinuation of warfarin (25).

Contraindications:

PREGNANCY

Warfarin is contraindicated in pregnancy, as it passes through the placental barrier and may cause bleeding in the fetus; warfarin use during pregnancy is commonly associated with spontaneous abortion, stillbirth, neonatal death, and preterm birth (26). Coumarins (such as warfarin) are also teratogens, that is, they cause birth defects; the incidence of birth defects in infants exposed to warfarin in utero appears to be around 5%, although higher figures (up to 30%) have been reported in some studies (27). Depending on
when exposure occurs during pregnancy, two distinct combinations of congenital abnormalities can arise (26).

When warfarin (or another coumarin derivative) is given during the first trimester—particularly between the sixth and ninth weeks of pregnancy—a constellation of birth defects known variously as fetal warfarin syndrome (FWS), warfarin embryopathy, or coumarin embryopathy can occur. FWS is characterized mainly by skeletal abnormalities, which include nasal hypoplasia, a depressed or narrowed nasal bridge, scoliosis, and calcifications in the vertebral column, femur, and heel bone which show a peculiar stippled appearance on X-rays. Limb abnormalities, such as brachydactyly (unusually short fingers and toes) or underdeveloped extremities, can also occur (26) (27). Common non-skeletal features of FWS include low birth weight and developmental disabilities (26) (27).

Warfarin administration in the second and third trimesters is much less commonly associated with birth defects, and when they do occur, are considerably different from fetal warfarin syndrome. The most common congenital abnormalities associated with warfarin use in late pregnancy are central nervous system disorders, including spasticity and seizures, and eye defects (26) (27).
Anticoagulation therefore poses a problem in pregnant women requiring warfarin for vital indications, such as stroke prevention in those with artificial heart valves. Usually, warfarin is avoided in the first trimester, and a low molecular weight heparin such as enoxaparin is substituted; the risk of maternal hemorrhage with heparin is high and preterm birth and stillbirth may still occur but heparins does not cross the placental barrier and therefore does not cause birth defects. Various solutions exist for the time around delivery.

Management of Patients with High INR Values

There is a close relation between the INR and risk of bleeding. The risk of bleeding increases when the INR exceeds 4, and the risk rises sharply with values >5. Three approaches can be taken to lower an elevated INR. The first step is to stop warfarin; the second is to administer vitamin K1; and the third and most rapidly effective measure is to infuse fresh plasma or prothrombin concentrate. The choice of approach is based largely on clinical judgment because no randomized trials have compared these strategies with clinical end points. After warfarin is interrupted, the INR falls over several days (an INR between 2.0 and 3.0 falls to the normal range 4 to 5 days after warfarin
is stopped). In contrast, the INR declines substantially within 24 hours after treatment with vitamin K₁ (3).

Even when the INR is exceedingly high, the absolute daily risk of bleeding is low, leading many physicians to manage patients with INR levels as high as 5 to 10 by stopping warfarin expectantly, unless the patient is at intrinsically high risk of bleeding or bleeding has already developed. Ideally, vitamin K₁ should be administered in a dose that will quickly lower the INR into a safe but not subtherapeutic range without causing resistance once warfarin is reinstated or exposing the patient to the risk of anaphylaxis. Though effective, high doses of vitamin K₁ (e.g., 10 mg) may lower the INR more than necessary and lead to warfarin resistance for up to a week. Vitamin K₁ can be administered intravenously, subcutaneously, or orally. Intravenous injection produces a rapid response but may be associated with anaphylactic reactions, and there is no proof that this rare but serious complication can be avoided by using low doses. The response to subcutaneous vitamin K₁ is unpredictable and sometimes delayed. In contrast, oral administration is predictably effective and has the advantages of convenience and safety over parenteral routes. In patients with excessively prolonged INR values, vitamin K₁, 1 mg to 2.5 mg orally, more rapidly lowers the INR to <5 within 24 hours than simply withholding warfarin. In a prospective study of 62 warfarin-treated patients with INR values between 4 and 10, warfarin was omitted, and vitamin K₁, 1 mg, was administered orally
After 24 hours, the INR was lower in 95%, <4 in 85%, and <1.9 in 35%. None displayed resistance when warfarin was resumed. These observations indicate that oral vitamin K₁ in low doses effectively reduces the INR in patients treated with warfarin. Oral vitamin K₁, 1.0 to 2.5 mg, is sufficient when the INR is between 4 and 10, but larger doses (5 mg) are required when the INR is >10 (3).

Oral vitamin K₁ is the treatment of choice unless very rapid reversal of anticoagulation is critical, when vitamin K₁ can be administered by slow intravenous infusion (5 to 10 mg over 30 minutes). In 2001, the American College of Chest Physicians published the following recommendations for managing patients on coumarin anticoagulants who need their INRs lowered because of either actual or potential bleeding (3):

1. When the INR is above the therapeutic range but <5, the patient has not developed clinically significant bleeding, and rapid reversal is not required for surgical intervention, the dose of warfarin can be reduced or the next dose omitted and resumed (at a lower dose) when the INR approaches the desired range.

2. If the INR is between 5 and 9 and the patient is not bleeding and has no risk factors that predispose to bleeding, the next 1 or 2 doses of warfarin can be omitted and warfarin reinstated at a lower dose when the INR falls into the therapeutic range. Alternatively, the next dose of warfarin may be
omitted and vitamin K₁ (1 to 2.5 mg) given orally. This approach should be used if the patient is at increased risk of bleeding.

3. When more rapid reversal is required to allow urgent surgery or dental extraction, vitamin K₁ can be given orally in a dose of 2 to 5 mg, anticipating reduction of the INR within 24 hours. An additional dose of 1 or 2 mg vitamin K can be given if the INR remains high after 24 hours.

4. If the INR is >9 but clinically significant bleeding has not occurred, vitamin K₁, 3 to 5 mg, should be given orally, anticipating that the INR will fall within 24 to 48 hours. The INR should be monitored closely and vitamin K repeated as necessary.

5. When rapid reversal of anticoagulation is required because of serious bleeding or major warfarin over-dose (eg, INR >20), vitamin K₁ should be given by slow intravenous infusion in a dose of 10 mg, supplemented with transfusion of fresh plasma or prothrombin complex concentrate, according to the urgency of the situation. It may be necessary to give additional doses of vitamin K₁ every 12 hours.

6. In cases of life-threatening bleeding or serious warfarin overdose, prothrombin complex concentrate re-placement therapy is indicated, supplemented with 10 mg of vitamin K₁ by slow intravenous infusion; this can be repeated, according to the INR. If warfarin is to be resumed
after administration of high doses of vitamin K, then heparin can be given until the effects of vitamin K have been reversed and the patient again becomes responsive to warfarin.

7.

**Warfarin booklet**

Warfarin is a useful medicine that helps many patients. It can be dangerous when not used correctly or without proper medical attention. Warfarin booklet will help patients to take their warfarin correctly and safely. It answers common questions patients ask about warfarin {(suggested booklet (appendix4)}.

Every patient read the warfarin booklet should be able to know:

- Why he takes warfarin.
- How to take warfarin.
- What dose he needs.
- When he needs to see the doctor.
- How warfarin can affect his lifestyle.

After the patient read the book, he should talk with the pharmacist or warfarin educator at the hospital. Once the patient leaves the hospital, the doctor or the local pharmacist can help to answer patients questions about warfarin.
**General objective:**

To assess the control of warfarin therapy in patients attending anticoagulation clinic in the cardiac surgery and renal transplant center in Ahmed Ghasim Hospital.

**Specific objectives:**

1. To identify different factors that affect control of warfarin therapy in these patients.

2. To determine level of knowledge of these patient regarding warfarin therapy.

3. To generate guidelines of warfarin therapy in Sudanese patients.
Study design

This is a descriptive retrospective cross sectional study.

Study area:

The study area is the cardiac surgery and renal transplant center at Ahmed Ghasim Hospital that lies in Khartoum North, this center was opened in 1998. It contains hundred beds. 1812 open heart surgery were done in the period from 1998-2009.

Anticoagulation clinic was opened in 2008, about 250-320 patients are seen in the clinic per months. It is run by medical officers who are covered by physicians, it is follow up clinic for warfarin therapy.

The center divisions:

1. Catheter lab.
2. Theatre.
3. Two intensive care units.
4. Two wards.
5. Haemodialysis unit.
6. Pharmacy.

7. Clinical pharmacy unit.

8. Therapeutic drug monitoring unit.

9. X-ray unit

10. Echo lab

11. Referral clinics

12. A laboratory, which covers investigation in hematology, clinical chemistry, histopathology, there is 17 technicians and a histopathologist.

13. Anticoagulation clinic

Subjects:

Subjects were one hundred cardiac patients on warfarin therapy attending the warfarin clinic in the cardiac surgical center.

Controls:

Control blood samples were obtained from working staff, all apparently healthy.

Procedure:

A questionnaire was designed to include all the needed information (Appendix 1). All individuals in the study were subjected to an oral
interview after oral consent, they were asked direct questions concerning their illness, their knowledge about warfarin, any difficulties facing their warfarin therapy, the occurrence of complications, and the last INR.

**Blood sampling:**

Blood samples were collected in the morning at 9:00-10:00am. After cleaning the site with a cotton pad soaked in dilute alcohol, using a 5 ml disposable syringe blood was collected in trisodium citrate dihydrate containers (9 volumes of blood to 1 volume of trisodium citrate dihydrate).

**Laboratory analysis:**

Analysis of the samples was done at the cardiac surgical center using coagulometer (Diamed CD4).

**Methods of analysis:**

**Prothrombin time (PT) analysis:**

Semi automated method using coagulometer (Diamed CD4).

**Principles of measurement:**

Diamed CD4 is a highly sensitive 4 channel photometer. A fifth channel controls the transmitter, which ensures accurate and precise results. For clot and chromogenic based tests. A standard filter of 405nm is provided. The Diamed
CD4 can detect light absorbance up to 2.5 OD (optical density) with a resolution of 0.001 OD (= E (Extinction) = unit of light absorbance)

**Turbidity method (clotting method)**

The thrombin catalyzed conversion of fibrinogen to fibrin is the final reaction in the coagulation cascade. Fibrin formation results in an increase in sample turbidity which is detected by the photometer. Photometric detection is started manually by pressing the optic key with simultaneous addition of the test reagent. Alternatively, the reaction is started by the addition of the sample using the Autopipette. The time between the start of the photometric detection, and the turning point of the reaction curve is the result. The result is displayed in seconds on the liquid crystal display and printed automatically to the thermal printer (appendix 2).
Table (4.1):  

**Indications for warfarin therapy in the patients studied:**

<table>
<thead>
<tr>
<th>Indication for warfarin</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valves</td>
<td>77</td>
<td>77</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.2):

Time of warfarin administration in the patients studied:

<table>
<thead>
<tr>
<th>Time of warfarin administration</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the morning</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Midday</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Evening</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>At any time during the day</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.3):

**Last INR investigation in the patients studied:**

<table>
<thead>
<tr>
<th>Last INR</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the therapeutic range</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Below the therapeutic range</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Above the therapeutic range</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.4):

**Difficulties in taking warfarin in the patients studied:**

<table>
<thead>
<tr>
<th>Difficulties</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not available in the nearby pharmacy</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Expensive</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Difficult to obtain the exact dose</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Residence far away from the laboratories and hospitals</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Expensive and far residence</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No difficulty</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.5):

Number of patients having warfarin booklets in the population studied:

<table>
<thead>
<tr>
<th>Warfarin Booklets</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients having warfarin booklets</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Patients not having warfarin booklets</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.6):

**Patient knowledge about warfarin in the population studied:**

<table>
<thead>
<tr>
<th></th>
<th>Knows</th>
<th>Doesn’t know</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is warfarin</td>
<td>90</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Indication of warfarin</td>
<td>44</td>
<td>56</td>
<td>100</td>
</tr>
<tr>
<td>Diet containing Vitamin K</td>
<td>88</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>interaction between warfarin and antibiotics</td>
<td>42</td>
<td>58</td>
<td>100</td>
</tr>
<tr>
<td>interaction between warfarin and aspirin</td>
<td>47</td>
<td>53</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.7):

**Patient knowledge about warfarin tablets in the population studied:**

<table>
<thead>
<tr>
<th>Knowledge Description</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knows all types by its strength and colour</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Knows all types by its colour only</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Knows 2 types by its strength and colour</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Knows 2 types by its colour only</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Knows 1 type by its strength and colour</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Knows 1 type by its colour only</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Does not know</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.8):

Knowledge among ladies in the patients studied about the effect of warfarin on pregnancy:

<table>
<thead>
<tr>
<th>Action</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>To inform the doctor that I am on warfarin</td>
<td>22</td>
<td>31.8</td>
</tr>
<tr>
<td>To continue the same dose</td>
<td>47</td>
<td>68.2</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.9):

Effect of school education on control of INR in the patients studied:

<table>
<thead>
<tr>
<th>Last INR investigation</th>
<th>illiterate No. (%)</th>
<th>primary No. (%)</th>
<th>intermediate No. (%)</th>
<th>Secondary No. (%)</th>
<th>postgraduate No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled</td>
<td>18 (37.5)</td>
<td>9 (42.9)</td>
<td>1 (50%)</td>
<td>10 (52.6)</td>
<td>5 (55.6)</td>
</tr>
<tr>
<td>Low</td>
<td>18 (37.5)</td>
<td>9 (42.9)</td>
<td>0 (0%)</td>
<td>6 (31.6)</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>High</td>
<td>12 (60.0)</td>
<td>3 (14.3)</td>
<td>1 (50%)</td>
<td>3 (15.8)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (100)</td>
<td>21 (100)</td>
<td>2 (50%)</td>
<td>19 (100)</td>
<td>9 (100)</td>
</tr>
</tbody>
</table>

P value 0.102 (not significant)
Table (4.10)

Occurrence of bleeding or thrombosis complications in the population studied:

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No complication</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.11):

**Frequency of bleeding in the population studied:**

<table>
<thead>
<tr>
<th>Frequency of bleeding</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once</td>
<td>15</td>
<td>41.6</td>
</tr>
<tr>
<td>Twice</td>
<td>8</td>
<td>22.2</td>
</tr>
<tr>
<td>Several times</td>
<td>13</td>
<td>36.2</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100</td>
</tr>
</tbody>
</table>
Table (4.12)

The sites of bleeding due to warfarin overdose in the population studied:

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>15</td>
<td>41.7</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>9</td>
<td>25.0</td>
</tr>
<tr>
<td>genitourinary bleeding</td>
<td>6</td>
<td>16.7</td>
</tr>
<tr>
<td>Black stool</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>Multiple sites</td>
<td>3</td>
<td>8.3</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure (4.1)
Sex distribution of the population studied

male  female
66%  34%
Figure (4.2)
Age distribution of the population studied
Figure (4.3)
Resedience of the population studied
Figure (4.4)
Level of education of the population studied

Series1
figure 4.5
level of control of the INR in the patient studied

- Prolonged INR: 33%
- Controlled INR: 38%
- Low INR: 29%
figure (4.6)
level of patient knowledge about warfarin
The different factors which affect proper warfarin control in one hundred patient taking warfarin for different indications were assessed at this study. The study population composed of 66 female and 34 male of different age groups. The results were compared to the results of a similar Sudanese study which was conducted at 2000 in the same hospital on a same number of patients (28).

It was noted that in our group of patients the most frequent indication for lifelong warfarin was prosthetic heart valves, in contrast to the previous Sudanese study which was rheumatic heart disease, this reflects the increase in the number of operations, and the opening of the warfarin clinic.

In our study 38% of the patients were properly controlled having an INR within the therapeutic range, in contrast to the previous study when the number is 34%, this is again a small number and as warfarin is a dangerous drug and therefore if it is prescribed it must be properly controlled.

20% of our patients had good level of education regarding warfarin, compared to 16% in the previous study which means no significant change occurred after these 10 years, and this again a small number as warfarin is a
serious drug and all patients must be fully educated before initiation of the therapy.

When we considered the elements of education we found that, 60% of our patients did not receive education programme about warfarin, 71.4% of them were educated after starting the therapy, 20% only knew the color and strength of the warfarin tablets compared to a similar Chinese study when the figure was 40-45% (29).

60% of the patients were taking different medication with different interaction with warfarin. 88% of the patients knew the different interaction of warfarin with different types of diet; this a good effort done by the nutrition unit which is a part of the warfarin clinic.

Other factors that affect warfarin control include financial and geographical factors. 70% of the population studied live far from the center outside Khartoum state.

Booklets providing information about the drug and registering INR results are very important for the proper management of these patients but unfortunately only 2 of our patients were provided with the booklets, and they obtained it from another hospital. In the previous study 12 of the patients had the booklet and they obtain it from abroad; so in the previous 10 years, no booklets was provided from the hospital to the patients to improve their INR. In
a similar Chinese study all the patients had booklets and 49.2% had read the information booklet on warfarin and had better knowledge than those who had not. Illiteracy was the main reason for not reading the booklets. There was a positive correlation between patients' warfarin knowledge and the number of INR values that were within the target range in the 4 most recent clinic visits (29).

36% of our patients suffer from bleeding, the commonest site being the nose in the form of epistaxis; 36.2% from them have bleeding for several times, this is a large number as only 12% of the patients had bleeding in the previous study. This reflects the bad control as 33% of our patients have prolonged INR, compared to one patient in the previous study. These figures are higher than those reported in the literature in patients receiving warfarin therapy. The median annual rate of major bleeding ranged from 0.9 to 2.7 percent, and the median annual rate of fatal bleeding ranged from 0.07 to 0.7 percent (17).

Regarding thrombosis only 2 of our patients suffered from one attack of cerebral thrombosis in the form of cerebrovascular accident, in contrast to one patient in the previous study.

School education did not seem to affect warfarin control since in both educated and illiterate patients, the percentage of those who have controlled INR are similar.
In our study the optimum maintainance dose was found to be 3-5mg. Reports in the literature have given figures of 4-6 mg (30).
Conclusion

From this study it was concluded after 10 years that more than half of the patients were not well controlled having an INR outside the therapeutic range.

It seems still after 10 years that the most significant causes of poor control are lack of full education about the drug and the far residence from hospital and laboratories and the high cost of the INR investigation.

Unfortunately after 10 years more complications occur to the patients, bleeding endangers a large number of our patients life. Thrombosis still seems to be a rare complication.
Recommendations

1. All patients should have full education about warfarin before initiating the therapy.

2. Methods of education like personalized patient education, group discussion, warfarin booklets, videotapes should be available to patients at the center.

3. To provide more centers for follow up of INR investigation especially outside Khartoum state.

4. To solve the financial problems facing warfarin therapy, the cost of the therapy and the investigation.


10. Important drug and food information from the warren grant magnuson clinical center, from the national institute of health drug nutrient interaction task force.


Serial No ( )

Name: ...........................................................................................

1. Sex: a. male b. female

2. Age: a. 10-19 b. 20-29 c. 30-39 d. 40-49 e. 50-60 f. >60

3. Residence: a. near to the center b. far from the center

4. Education: a. illiterate b. primary c. intermediate d. secondary e. graduate f. postgraduate

5. Occupation: .....................................................................................

**Patient warfarin therapy**

6. Indication for warfarin therapy

7. Duration for warfarin therapy......................................................

8. Time of warfarin intake a. in the morning b. midday c. evening d. at any time during the day

9. Dose of warfarin now.............................

10.1 No. of visit for warfarin control:

   a. according to the doctor request b. not regular

10.2 If b. explain why?

11.1 Dose the patient take any drug(s) other than warfarin?

   a. yes b. no

11.2 If (a) mention it( them)............................................................

12.1 Have you received education program about warfarin?

   a. yes b. no

12.2 If yes when?

   a. before initiation of warfarin b. after initiation of warfarin

12.3 If yes where? a. private clinic. b. hospital c. abroad

13.1 Have you warfarin booklet? a. yes b. no.

13.2 If yes, from where did you obtain it? a. Sudan b. abroad
13.3 if yes are you taking it with you all the time?

14. is there any difficulty in taking warfarin?
   a. not available in the nearby pharmacy
   b. expensive
   c. difficult to obtain the exact dose
   d. residence far away from the laboratories and hospitals
   e. other factors

   if ( e) mention these factors……………………………………

**The knowledge about warfarin**

15. what is warfarin?   a. knows   b. does not know

16. why are you on warfarin? a. knows   b. does not knows

17. what is the type of warfarin tablets and its colour?
   a. knows all types by its dose and colour
   b. knows all types its colour only
   c. knows 2 types by its dose and colour
   d. knows 2 types by its colour only
   e. . knows 1 types by its dose and colour
   f. knows 1 types colour only
   g. does not know

18.1 does the patient knows diet containing vit k ?   a. yes   b.no.

18.2 if yes mention few……………………………………

19.1 does the patient knows that there is interactions between warfarin and

19.1 antibiotics  a. yes  b. no

19.2 asprin  a. yes  b. no

20. What the patient will do if he/she is ill and needs antibiotics?
a. goes to a doctor and tell him he/she on warfarin
b. goes to a doctor and tell him he/she on warfarin if asked
c. gets antibiotics from the nearby pharmacy

21. What the patient will do if he/she is ill and needs any surgical or dental operation?
   a. To inform the doctor and tell him he/she on warfarin
   b. To inform the doctor and tell him he/she on warfarin if asked

22. Question to married women
If you get pregnant what to do?
   a. to inform the doctor that I am on warfarin.
   b. to continue the same dose

**Warfarin complications**

23.1 Have you ever have bleeding while you are on warfarin?
   a. yes.       b. no

23.2 If a When? ........................................................................................................

23.3 Where is/are the site(s) of that bleeding? ..............................................

23.4 How many time?        A. once        b. twice c.> twice

24.1 Have you any thrombotic attack while you are on warfarin?
   a. yes  b. no

24.2 If yes when? .....................................................................................................

24.3 Where is/are the site(s) that thrombosis? ..............................................

24.4 Number of thrombotic attacks? a. once    b. twice c.> twice

24.5 If © specify ....................................................................................................

**Investigations**

25. last INR investigations.................................................................................