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ORIGINAL ARTICLE

RETROSPECTIVE ANALYSIS OF PATIENTS ON WARFARIN THERAPY UNDERGOING SURGICAL PROCEDURES: AN INSTITUTION BASED STUDY

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ABSTRACT:
Background: warfarin is one of the frequent causes of negative reactions associated with patients undergoing surgical procedures. It is the drug of choice for most of the surgeons despite its adverse effects. Challenges imposed during the management of warfarin reactions include its narrow therapeutic index, frequent drug drug interactions, and patient variability in metabolism of warfarin. Thus, we conducted this retrospective analysis to assess the complications and prognosis of general surgical procedures carried out on patients receiving warfarin therapy. **Materials & Methods**: A total of 122 patients who underwent surgery in the Surgery department from June 2002 to July 2012 were included in the present study. Complete records and data of all the patients along with pathologic and diagnostic reports were thoroughly analyzed. Surgeries that lasted more than 45 minutes or involved cardiothoracic or orthopaedics field were included under the category of major surgeries. All the results were analyzed by SPSS software. Chi-square test was used to evaluate the level of significance. P-value of less than 0.05 was taken as significant. **Results:** Mean age of the patients in the present study was 56 years. Comorbidities were present in 64 % of the cases. Various warfarin indications mainly included mitral valve replacement, aortic valve replacement and atrial fibrillation. Pre-operative INR, aPTT and PT values were 1.4, 39 and 17 respectively. Elective surgeries included Hepatobiliary pancreatic surgery, hernia, thyroid and parathyroid surgeries, proctological surgery and colorectal surgery while Emergency surgery included Upper gastrointestinal system, colorectal surgery, hernia and Hepatobiliary pancreatic surgery. While comparing all the parameters between patients undergoing elective and emergency surgeries, only duration of the procedure and length of stay in hospital showed non-significant difference while all other variables showed significant difference. **Conclusion:** Patients on oral anticoagulant therapy are always at risk levels while undergoing invasive surgical procedures.
Key words: Surgery, Warfarin

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INTRODUCTION

One of the common causes of adverse drug reaction in patients hospitalized for surgical procedure is warfarin.[1] Drug of choice for the physicians despite of emergence of newer anti-coagulants is the Warfarin.[2] Due to ease of availability and cost effectiveness, use of warfarin is more in developing countries in comparison to

other anti-coagulants.[3] Challenges imposed during the management of warfarin reactions include its narrow therapeutic index, frequent drug drug interactions, and patient variability in metabolism of warfarin.[4] Thus in hospitalized patients, warfarin remains a significant cause of adverse reactions occurring in approximately 8% of exposed patients, depending on metabolic factors.[2, 5] Thus, we conducted this retrospective analysis to assess the complications and prognosis of general surgical procedures carried out on patients receiving warfarin therapy.

MATERIAL ANS METHODS

The present study was carried out in the department of general surgery of the institute. Ethical clearance was obtained from the institute in written after explaining the complete study protocol. A total of 120 patients who underwent surgery in the department over a period of 10 years: from June 2002 to July 2012 were included in the present study. Record of patient's demographic data, mode of presentation, American Society of Anesthesiologists (ASA) score, indication and duration of OAC therapy, comorbidities, international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT) values, surgical technique, and duration of procedures were recorded and analyzed. Recordings were done including length of stay in hospital, treatment outcomes, mortality rates and thromboembolic or bleeding events. The patients who were to have warfarin discontinued postoperatively were excluded along with the ones receiving no warfarin prior to their procedure in addition the patients receiving anticoalgulant agents excluding warfarin were excluded also. Assuring the condition stated, exclusion was taken including patients having deep venous thrombosis and pulmonary embolism. Discontinuation of the warfarin was done prior to the surgery in patients who were undergoing elective surgical procedures. 3 days prior to the surgery, patients were admitted to an inpatient clinic 3 days before surgery. When INR levels dropped below 2.0, Bridging therapy with unfractionated heparin (UFH) was started. For surgery, a level of INR of 1.5 or below was considered suitable. A final PT and INR level was obtained for every patient on the morning of surgery. If the patient still had an increased INR after 3 days, administration of vitamin K was done. 6 hours before surgery, unfractionated heparin was stopped. Administer 15 mL of fresh-frozen plasma (FFP) per kilogram of patient body weight was the next step. UFH was started again 6 hours after surgery in cases where no bleeding was observed. Post-operative analysis of complete blood count and INR levels were obtained. After the target level of INR was reached, follow-up INR levels were obtained. In cases of no additional problems, levels of INR were obtained monthly. Criteria's available in the previous literature were used to classify bleeding events into major and minor bleedings.[6] Surgeries that lasted more than 45 minutes or involved cardiothoracic or orthopaedics field were included under the category of major surgeries.[7] Those occurring within 30 days postoperatively or for a longer period when the patient was still in hospital follow-up were considered under the category of postoperative morbidity and mortality.[8-10] All the results were analyzed by SPSS software. Chi-square test was used to evaluate the level of significance. P-value of less than 0.05 was taken as significant.

RESULTS

Table 1 highlights the various demographic and clinical details of the patients included in the present study. Mean age of the patients in the present study was 56 years while mean BMI was 26. Comorbidities were present in 64 % of the cases. Various warfarin indications mainly included mitral valve replacement, aortic valve replacement and atrial fibrillation. Pre-operative INR, aPTT and PT values were 1.4, 39 and 17 respectively. **Graph 1** highlights the **v**arious surgical procedures received by patients in warfarin therapy. Elective surgeries included Hepatobiliary pancreatic surgery, hernia, thyroid and parathyroid surgeries, proctological surgery and colorectal surgery while Emergency surgery included Upper gastrointestinal system, colorectal surgery, hernia and Hepatobiliary pancreatic surgery. **Graph 2** shows the **f**ollow-up and comparison of various parameters in patients undergoing emergency and elective surgery. P-value for comparison of various parameters in patients undergoing emergency and elective surgery is shown in **Table 2**. While comparing all the parameters between patients undergoing elective and emergency surgeries, only duration of the procedure and length of stay in hospital showed non-significant difference while all other variables showed significant difference (**p-value <0.05**).

Table 1: Demographic and clinical details of the patients included in the present study

Parameter		Total % or Mean ± SD
Age (years)		56 ± 12
Mean BMI		26 ± 6
Warfarin's indications	Mitral valve replacement	65
	Aortic valve replacement	22
	Coronary bypass grafting	1
	Atrial fibrillation	12
Comorbidities	Present	64
	Absent	36
ASA classification	II	34
	III	66
Preoperative INR value		1.4 ± 0.5
Preoperative aPTT value		39 ± 14
Preoperative PT		17± 6
Mean duration of procedure, min		98± 62
Length of stay, days	Pre-operative	5 ± 4
	Postoperative	7 ± 4

Graph 1: Various surgical procedures received by patients in warfarin therapy

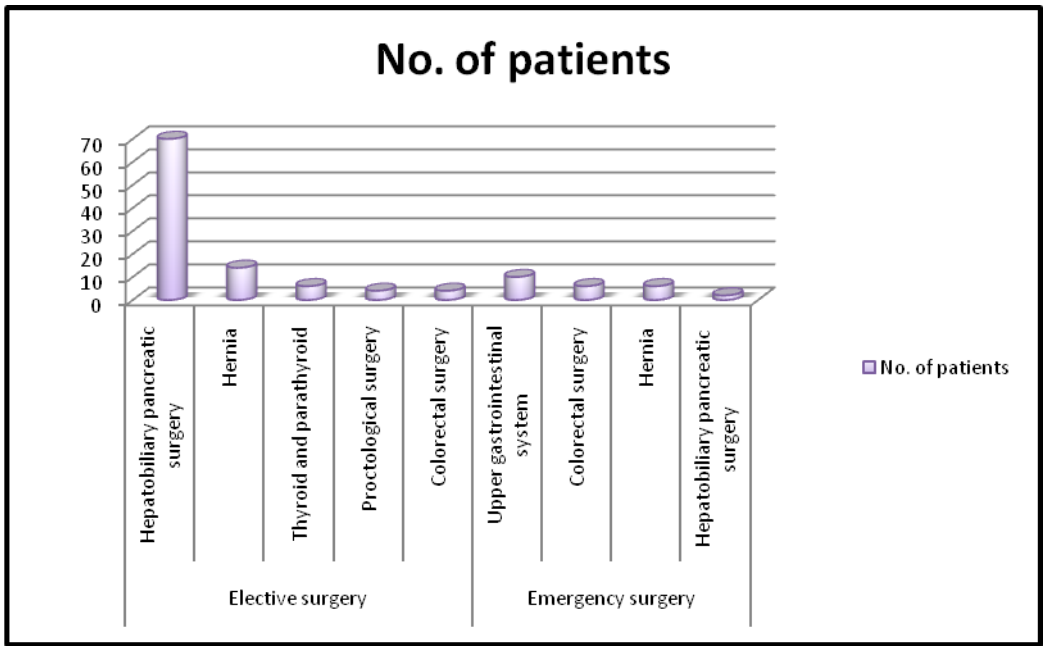
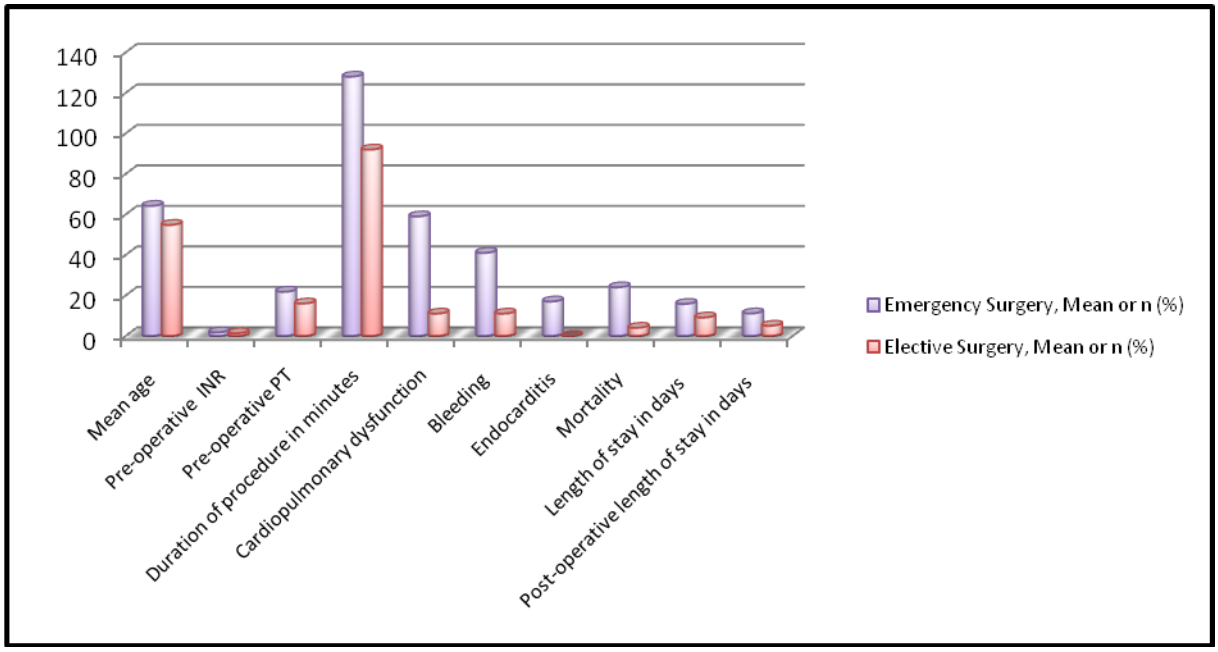


Table 2: P-value for comparison of various parameters in patients undergoing emergency and elective surgery

Postoperative complications and variable	p-value
Mean age	0.030 (s)
Pre-operative INR	0.004 (s)
Pre-operative PT	0.005 (s)
Duration of procedure in minutes	0.220 (n.s)
Cardiopulmonary dysfunction	0.001 (s)
Bleeding	0.007 (s)
Endocarditis	0.003 (s)
Mortality	0.020 (s)
Length of stay in days	0.070 (n.s)
Post-operative length of stay in days	0.004 (s)

s: Significant, n.s: Non-Significant



Graph 2: Follow-up and comparison of various parameters in patients undergoing emergency and elective surgery

DISCUSSION

To minimize the risk of haemorrhage, approximately over two lakh persons receive long-term oral anticoagulant therapy for surgical procedures on a yearly basis for an assessment of treatment interruption.[11] For the past several decades, warfarin has been the mainstay of long-term outpatient anticoagulation ever since it has got approval by the US Food and Drug Administration in 1954. Prevention and treatment of venous thromboembolism (VTE), and the prevention of stroke and systemic embolism in patients with chronic atrial fibrillation (AF) is included in this. AF associated thromboembolic events demonstrated to be prevented by utilization of warfarin.[12-14] Need for laboratory monitoring, which is needed to ensure appropriate anticoagulation dose adjustments, multiple drug and food interactions, and a long offset and onset of action are some of the inherent drawbacks of warfarin, which necessitates the need for standardized peri-procedural management protocols. Recently, several new oral anticoagulants have been introduced for the prevention and treatment of VTE and stroke prevention from AF that does not require the intensive laboratory monitoring of warfarin. These include dabigatran etexilate, a direct thrombin inhibitor approved for VTE prevention and chronic AF in 2008, and 2011, respectively; rivaroxaban, a direct factor Xa inhibitor approved for VTE prevention and chronic AF in 2011, and 2012, respectively; and apixaban, a direct factor Xa inhibitor with expected regulatory approval in 2012. The key indication for the new Oral anticoagulants will be chronic AF, given the increasing number of eligible patients and need for indefinite (or life-long) treatment in such patients. Therefore, careful assessment of the needs and health and metabolic status of the patient should be done before being considering them for long-duration anti-coagulant therapy.[15] Thus, we retrospective analysed the complications and prognosis of general surgical procedures carried out on patients receiving warfarin therapy.

In the present study, patients undergoing elective laparoscopic cholecystectomy and which were also on warfarin therapy, quite high likelihood of bleeding was encountered in them. No thromboembolism was reported in these patients. In the literature, few related studies and consensus are there which present the same ratio. At the same time, in these patients, uncertainness about the bridging therapy protocol exists. In various branches of surgical procedures and operations, different rates of major haemorrhage were reported in the literature.[16-19] In patients who underwent emergency surgeries or operations, bleeding, endocarditis, CPD, and mortality was found to be significantly higher number. In group containing patients undergoing emergencies surgeries, PT/ INR levels were found to be significantly higher as compared to the group containing patients undergoing elective surgery. Such conditions are evaluated only on one or two occasions in the past

literature. Recent data show that discontinuation of warfarin 5 days prior to the surgery for achieving INR of 15 is required for the reduction of the risk of bleeding.[20] Before starting of the warfarin therapy, the 2015 Joint Commission anticoagulant-focused National Patient Safety Goal (initially issued in 2008) mandates the assessment of baseline coagulation status along use of "current" INR for deciding the dose of warfarin. Neither the extent to which the mandate for assessing baseline coagulation status is adhered to nor the relationship between this process of care and patient outcomes is known. [21, 22] Association of low frequency of acute gastrointestinal haemorrhage with endoscopic procedures has been reported by Chaudari et al in patients receiving warfarin treatment.[23] A high incidence of cerebral infarction have been reported by Kumada in the past after warfarin discontinuation before undergoing endoscopic procedures.[24] One of the society of Japan formulated guidelines in context with the anticoagulation and anti-platelet therapy indicating the discontinuation of warfarin 3–4 days prior to surgical procedures along with less than 1.5 PT-INR value at that.[25] Belli et al retrospectively analyzed the patients undergoing surgical procedures receiving warfarin therapy. From the results, they concluded that close monitoring of the patients should be done during the postoperative follow-up period as a higher mortality rate is was found to be associated with patients undergoing emergency surgeries.[26]

CONCLUSION

From the results, it can be concluded that patients on oral anticoagulant therapy are always at risk levels while undergoing invasive surgical procedures. Risk of bleeding and mortality is higher in patients in warfarin therapy undergoing emergency surgeries. Hence, careful follow-up should be maintained in such patients in order to avoid further complications.

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