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Research Article

Management of Elective Surgery Patients on Long Term Warfarin Bridged with Enoxaparin

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Abstract

This article reports the management of 675 patients requiring warfarin cessation prior to surgery over a six-year period. The management of warfarin cessation was uniform involving an institutionally developed guideline in which 405 patients at high risk of thromboembolic events were prescribed Low Molecular Weight Heparin (LMWH) bridging prior to surgery. In this retrospective cohort review there were no cases of preoperative thromboembolic events after cessation of warfarin therapy in either low risk or highrisk thromboembolism patients and no cases of bleeding prior to surgery in patients receiving (LMWH) bridging prior to surgery. Haemorrhagic complications occurred more commonly in patients who received LMWH bridging therapy and are common overall than thrombotic complications. Thromboembolic complications only occurred in patients who were not returned to warfarin therapy according to the institutional guidelines developed for these patients.

This study adds a large number of patients with standardised preoperative and postoperative management to the body of knowledge on this topic and will inform future studies in this specialist area.

Introduction

The ideal management of patients scheduled for elective surgery, who are receiving long term warfarin therapy, is still debated despite described protocols for some conditions [1-6]. The role of Low Molecular Weight Heparin (LMWH) or unfractionated heparin 'bridging' therapy for those patients on long term warfarin treatment scheduled for elective surgery has been clarified for some patient groups in the BRIDGE study [1].

The contribution of continued preoperative warfarin treatment or 'bridging' therapy to haemorrhagic complications following major surgery is assumed in case series reported in the literature but the contributory factors have not been confirmed [6-9]. Additionally, the postoperative management of patients returning to their longterm warfarin therapy has been identified as contributing to both thromboembolic and bleeding events [6,10]. Consequently, optimal guidelines for pre-operative and post-operative management have not been clearly defined for all patients. In particular, the optimal management of high risk patients (e.g. presence of mechanical heart valves, Deep Vein Thrombosis (DVT) in the previous 3 months or hypercoagulable state) remains to be clearly defined.

The recent publication of the BRIDGE randomised controlled trial has clarified some aspects of clinical care particularly for low risk patients (e.g. non-valvular atrial fibrillation (AF), DVT more than 3 months previously, biological heart valve in situ more than 3 months) [1]. Prior to this the best guidelines available to inform perioperative practice were derived from observational studies, meta-analyses and reviews based on the published data coupled with expert opinion [6,11-14]. There is one prospective Inception Cohort Management Study of 1,262 patients from the Italian Federation of Centres for the Diagnosis of Thrombosis and Management of Antithrombotic Therapies (FCSA) but this study only recruited 295 patients with high risk of thromboembolism [10]. A retrospective cohort study of 1812 procedures in 1178 patients was published in 2015 [6].

This article reports the experience of one Australian University Hospital in managing 675 patients on long term warfarin therapy, 405 of which were at high risk of thromboembolism and required LMWH (Enoxaparin) bridging who presented for major and intermediate elective surgery over 6 years. Management was by a single perioperative protocol guiding cessation of warfarin therapy in the preoperative phase and also the reintroduction of

warfarin in the postoperative period.

Materials and Methods

1928 patients receiving long-term warfarin therapy were assessed in the perioperative clinic before surgery. 1253 patients were excluded from the analysis because their operation did not require warfarin to be ceased. In the remaining 675 patient's warfarin management was dictated by the perioperative anticoagulation risk stratification flow. Patients were risk stratified to a High Risk or Low Risk hospital protocol according to the reason for long term warfarin treatment and associated patient comorbidities (Table 1).

Low Embolic Risk Patients	High Embolic Risk Patients
Atrial Fibrillation **without** valvular heart disease or previous stroke or embolus	Atrial Fibrillation **with** valvular heart disease or previous stroke or embolus
Cardiomyopathy **without** heart failure, previous stroke or embolus	Cardiomyopathy **with** heart failure, previous stroke or embolus
Biological heart valves EXCEPT during first 3 months	Biological heart valves ONLY during first 3 months
Previous history (**>3 months prior**) uncomplicated DVT	Previous history (<3 months prior) uncomplicated DVT
Cerebrovascular disease (intracranial stenosis)	Multiple pulmonary emboli or DVT
Post myocardial infarction (mural thrombus prophylaxis)	History of DVT/PE with laboratory confirmed hypercoagulable state
Vascular surgical prosthetic grafts.	Past systemic arterial emboli.
Post vascular stent insertion	Mechanical Mitral or Aortic Valve

Table 1: Risk stratification of patients taking long term warfarin.

Patients at Low Risk of thromboembolic complications were managed as described in Table 2 and those at High Risk of thromboembolic complications were managed according to Table 3. (Tables 2 and Table 3).

LOW Embolic Risk management before surgery
Take last warfarin on **Day -6**, (i.e. miss 5 days' pre-op)
Measure INR on **Day -4**. If INR >5 review with treating medical team/anaesthetist/consult with haematologist.
Measure INR on **Day-1**, If INR > 1.5 then repeat INR on **Day of procedure**.
On **Day of procedure**, if INR >1.5 on **Day -1**, repeat INR.
If still >1.5 consider delay procedure/administer Prothrombinex 25units/kg IV stat.

Table 2: Hospital protocol for the management of LOW embolic risk patients before surgery.

Time	Guideline
Day -5	Take last warfarin, not to resume until post-procedure
Day -4	Measure INR • If INR <3 proceed to protocol • If INR >/= 3-5, withheld enoxaparin on Day -3 and repeat INR • If INR >5 review with treating medical team or anesthetist or consult with hematologist
Day -3	Give Vitamin K 2mg orally stat (regardless of INR result) If INR was <3 on Day -4, commence enoxaparin or IV heparin infusion If INR was >/=3, on D-4 repeat INR today. If INR >/=3 again withhold enoxaparin or IV heparin infusion on Day -2 and repeat INR.
Day -2	In INR <3.0 on Day -3 commence enoxaparin or IV heparin infusion If INR >/=3.0 on Day -3 repeat INR today. If INR >/= 3 again withhold enoxaparin/IV heparin infusion on Day -1 AND report to treating team for further instructions
Day -1	If INR was <3 on Day -2 commence enoxaparin dosing or IV heparin infusion Measure INR: If INR >/= 1.5, then repeat INR on day of procedure Last dose of enoxaparin must be given at least 22 hours prior to procedure (before 10am) Cease IV heparin infusion 4-6 hours prior to surgery
Day 0 (Day of procedure)	If INR was >/= 1.5 on D-1, repeat INR. If INR still >/=1.5 consider delaying procedure or administering prothrombin 24units/kg IV stat. No enoxaparin to be given morning of surgery Cease IV heparin infusion 4-6 hours prior to surgery

Table 3: Hospital protocol for the management of high embolic risk patients before surgery.

The protocol for patients at high risk of thromboembolic events involved bridging with LMWH. The protocol was developed

collaboratively with Specialists in Haematology, Cardiology, Neurology and Anaesthesia. The protocol was applied by Specialist Anaesthetists in an existing perioperative service and managed by the Department of Anaesthesia Perioperative Medicine & Pain Management in conjunction with a Specialist-led 'Hospital in the Home' (HITH) programme [15].

The reintroduction of long term warfarin therapy was guided by a separate protocol, which was available to all surgical staff (nursing & medical) through a paper-based and on-line guideline repository (Table 4).

	Low Risk of Bleeding	High risk of Bleeding
Day of procedure	Recommence warfarin at the patient's usual dose Commence therapeutic anticoagulant bridging until INR is in therapeutic range - small dose enoxaparin 40mg stat 6 hours post-op	No anticoagulation therapy for first 24 hours and then review
Day +1	Commence or continue warfarin, PLUS; - therapeutic dose enoxaparin (per dosing guidelines above) • OR - IV heparin infusion	

Table 4: Hospital protocol for re-introduction of warfarin treatment following surgery time.

Monitor INR every 2-3 days. Continue therapeutic dose enoxaparin or IV heparin infusion until INR is in the target range on 2 consecutive days.

For patients transferring to HITH after surgery the enoxaparin dose on the day of the procedure can be given 1-2 hours after surgery post-procedure, before leaving the day procedure unit as these patients commonly have low risk of bleeding.

A retrospective case note review was completed by one author (SB) to identify thrombotic or haemorrhagic complications of either High Risk or Low Risk protocols. The same author reviewed adherence to the 'return to long term warfarin' protocol in those who suffered either haemorrhagic or thrombotic complications. Deviations from either protocol were identified. Patients identified with thrombotic or haemorrhagic complications were further reviewed to assess the severity and likely contributory causes of the complications (SNB).

Results

A total of 675 patients on long term warfarin treatment were identified from the electronic hospital record who were subject to management with LMWH by the peri-operative warfarin protocol. Of the 675 patients identified 270 (40%) were risk stratified to the Low Embolic Risk protocol and the remaining 405 (60%) were risk stratified to the High Embolic Risk protocol.

Thrombotic complications were defined as clinical events, which were confirmed by imaging, and indicated the underlying thrombotic or embolic pathology. No patients suffered from thrombotic complications in the preoperative period following warfarin withdrawal. Furthermore, no patients suffered haemorrhagic complications in the preoperative period as a result of LMWH treatment. All thrombotic complications occurred in patients while warfarin therapy was being reintroduced after surgery.

Overall the number of thrombotic complications was 5/675 (0.74%). There was no statistical difference in the rate of thrombotic complications between the Low Risk Group; 3/267 (1.11%) and the High Risk Group; 2/403 (0.49%). Odds ratio (95% confidence interval) for thrombotic events in High Risk versus Low Risk patients: 0.44 (0.088 - 2.226); p = 0.36 (Table 5).

		Thrombotic Event		
Warfarin protocol		Yes	No	Total
	Low Risk	3	267	270
	High Risk	2	403	405
	Total	5	670	675

Table 5: Thrombotic event rate for High Risk v Low Risk patients.

Thrombotic complications contributed to the most serious outcomes including one postoperative death. Bleeding complications were classified according to the definitions used by Pengo's group (10). In the first 5 postoperative days there were 57 bleeding complications (8.4%), which ranged in severity from minimal impact to re-operation for bleeding and prolonged hospital stay. Of the 405 patients assigned to the High Risk protocol, 44 (10.9%) suffered haemorrhagic complications. This compared with 13/270 (4.8%) experiencing bleeding complications in the Low Risk group. This difference in bleeding complications was statistically significant with an odds ratio (95% confidence interval) for haemorrhagic events in high versus low risk patients of 2.41 (1.28-4.52), p = 0.0056.

		Haemorrhagic event		
Wafarin Protocol		Yes	No	Total
	Low Risk	13	257	270
	High Risk	44	361	405
	Total	57	618	675

Table 6: Major haemorrhage in first five postoperative days.

Of the patients in whom bleeding complications were observed all had documented deviations from the approved protocol for the re-introduction of warfarin following surgery (Table 4).

Discussion

The number of patients assigned to the High-Risk protocol in our study is comparable with the study by Pengo's group where 295 patients were assigned to the high thromboembolic risk protocol [10]. The retrospective cohort study by Clark's group included more patients requiring bridging from warfarin treatment, however the bridging regimen for high risk patients is not described in Clark's paper (e.g. mechanical valve with AF) [6]. The most effective management of high risk patients (e.g. mechanical heart valve, VTE in last 3 months, arterial thromboembolism) on long term warfarin treatment requiring elective surgery is still debated and the place of preoperative bridging therapy with LMWH is also still to be defined [3,4]. This gap in knowledge relating to the management of patients with a high risk of venous or arterial thromboembolism is acknowledged by the authors of the BRIDGE study and also the American College of Chest Physicians in their Expert Consensus Decision Pathway [1,11].

This retrospective cohort study contributes 675 patients in whom warfarin was ceased prior to elective surgery. Of these patients 405 were defined as high thromboembolic risk and commenced on bridging LMWH therapy prior to surgery. The protocol for classification of patients as either High Risk and Low Risk was developed before the publication of the classification based on Congestive heart failure, Hypertension, Age, Diabetes mellitus and prior Stroke/TIA or CHADS 2 score [16].

This paper describes a relatively large cohort of surgical patients managed by warfarin cessation and bridging therapy with LMWH to replace long term warfarin therapy in preparation for elective surgery. The results confirm the safety of both warfarin cessations in low risk patients and enoxaparin bridging in high risk patients in the lead up to surgery. No major preoperative complications were observed in patients managed according to the protocols used in this study (Tables 1 - 4). This finding in a large retrospective cohort study confirms the safety of warfarin cessation in low risk patients prior to elective non-cardiac surgery. The observation also confirms the safety of enoxaparin bridging in preventing thrombotic and haemorrhagic complications prior to non-cardiac surgery in line with the work of the Italian Federation of Centres for the Diagnosis of Thrombosis and Management of Antithrombotic Therapies and the recommendations of the American College of Chest Physicians [10,11].

There is no evidence from other studies to suggest an increased risk of thromboembolic events in patients who have ceased warfarin therapy with or without LMWH or heparin bridging therapy [6,7,9,17-19]. Those studies also observed a limited number of perioperative thrombotic complications although Deep Vein Thrombosis (DVT) was observed as a complication in two studies [9,10]. We observed one patient who suffered a DVT following management with the High-Risk Protocol.

Previous reviews have commented on the increased incidence of bleeding complications observed in patients receiving LMWH 'bridging' therapy at the time of surgery compared to patients not using bridging therapy. Our study also confirms that haemorrhagic complications are more likely to occur in patients who have received bridging therapy [1,6,10].

The balance of clinical risk remains between perioperative haemorrhage, resulting from adequate or excessive anticoagulation, and thrombotic events resulting from inadequate anticoagulation [3,4]. The current evidence suggests that the risk is currently weighted towards excessive perioperative haemorrhage with very few thrombotic events reported in patients managed according to existing protocols [6,7,9,10,17]. While failure to adhere to guidelines as a consequence of haemorrhage may paradoxically lead to an increased risk of thrombosis as observed by Pengo and co-workers this was not confirmed by our study or the BRIDGE study [1,10].

Our study identified 5 patients overall with venous or arterial thrombosis following surgery (0.74%), which is a smaller percentage of patients with this thrombotic complication than other studies [1,6,9,10]. The rate of thrombotic complication was 1.11% in the Low Risk group and 0.49% in the High-Risk group, which is not statistically significantly different. However, the risk of bleeding complications requiring treatment was higher in this retrospective observational cohort study as might be expected [1,9,10].

Current UK Guidelines admit there is not enough published data to categorically demonstrate the safety of LMWH in patients with AF or mechanical heart valves, while acknowledging that an increased incidence of bleeding has been reported for major surgery, which is echoed in later smaller observational reports and the Italian Federation cohort study [9,10,17,20].

One serious complication that emerged in our observational study was the death of a patient from thrombotic complications. This was caused paradoxically by failure to adhere to the postoperative protocol for the reintroduction of warfarin because of continuing haemorrhagic complications. This patient was palliated and died but their management did not adhere to the postoperative warfarin reintroduction protocol.

One patient managed within the constraints of the preoperative (warfarin withdrawal) protocol and the postoperative (warfarin reintroduction) protocol suffered minor thrombotic complications. No patients with haemorrhagic complications died. This finding emphasises the inherent safety of a rigorously applied,

logically derived protocol for the management of patients on long term warfarin therapy at the time of elective surgery. The finding also emphasises the requirement to adhere to such protocols in the perioperative period despite the occurrence of bleeding complications in the postoperative phase. We would recommend that divergence from either the preoperative or the postoperative component of the protocol should only be undertaken in conjunction with a specialist haematologist or perioperative physician.

Patients requiring LMWH 'Bridging Therapy' were managed by the HITH programme under the auspices of the Anaesthetic Specialists in the Department of Perioperative Medicine. This meant that patients were tested and treated at home without the need for hospital admission or attendance. This contributed to lowered bed days in hospital for major procedures [20].

Conclusion

1. Protocols derived with multidisciplinary input can safely guide the perioperative management of patients on long term warfarin therapy.
2. No patient whose warfarin was ceased before surgery suffered thrombotic complications prior to surgery.
3. No patient bridged with enoxaparin before surgery suffered haemorrhagic complications prior to surgery.
4. No thrombotic complications were observed in 405 patients bridged with enoxaparin from long term warfarin therapy.
5. Haemorrhagic complications are more common than thrombotic complications in patients managed with enoxaparin bridging therapy from long term warfarin therapy.
6. Thrombotic complications were only observed in patients who were not returned to long term warfarin therapy in line with approved protocols.

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