EFORT open reviews

Anticoagulation therapy and proximal femoral fracture treatment: an update

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- Hip fractures in the elderly population have become a 'disease' with increasing incidence.

- Most of the geriatric patients are affected by a number of comorbidities.

- Coagulopathies continue to be a special point of interest for the orthopaedic trauma surgeon, with the management of this high-risk group of patients a hot topic of debate among the orthopaedic community.

- While a universal consensus on how to manage thromboprophylaxis for this special cohort of patients has not been reached, multiple attempts to define a widely accepted protocol have been published.

Introduction

Approximately 77 000 proximal hip fractures occur in the United Kingdom annually, accounting for 1.5 million bed-days, at an inpatient cost of £2 billion.[1,2] The majority of them (65 000) occur in England, with a median post-operative length of stay (LOS) of 23 days and a 30-day mortality of between approximately 8% and 10% which has remained constant for the last two decades.[2]

The majority (95%) of hip fractures occur in patients over the age of 60 years, 75% of which occur in females.[1,2] More than 98% of fractures are treated surgically in order to reduce the risk of development of complications (pneumonia, pressure sores, deep vein thrombosis, respiratory insufficiency, etc) and to facilitate early mobilisation and prompt hospital discharge. It is of note that 25% of patients with hip fractures have at least moderate cognitive impairment (abbreviated mental test score less than 7), 20% are institutionalised and 50% require walking aids or are immobile.[1,2]

One of the major post-surgical complications following hip fracture surgery is the development of deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] The incidence of DVT has been reported to be between 1% and 3% approximately, whereas PE is in the region of 0.5% and 3%.[3] Nonetheless, DVT occurs in approximately 37% of patients with hip fracture and pulmonary embolism in 6%; these figures are derived from research studies employing venograms or VQ scans in a large cohort of patients, therefore representing the true incidence of asymptomatic events.[3]

It is of interest that clinicians managing this cohort of patients usually have to deal with two possible case scenarios: patients presenting with no current intake of anticoagulation therapy; and patients who are already taking anticoagulation drugs for pre-existing medical conditions.

The aim of this study is to report on the available protocols for prevention of thromboembolic events in patients admitted with proximal femoral fractures who are not receiving any anticoagulation therapy, and to investigate current trends of patients who are already on treatment for pre-existing medical conditions.

Materials and Methods

This study was divided into two parts.

Part A focussed on the currently acceptable protocols of thromboprophylaxis in patients presenting with a hip fracture without taking any anticoagulant therapy for other medical conditions. Large-scale studies providing evidence of the need for treatment were assessed, as well as existing guidelines.[3,4]

Part B focussed on patients presenting with a hip fracture who were already on anticoagulation therapy for different medical reasons. A literature search was conducted using PubMed, the Cochrane Library and Embase databases using the keywords 'anticoagulation therapy', 'proximal femur fracture' and 'hip fracture'. Manuscripts

were eligible for inclusion if they described comparative studies of patients who sustained hip fracture and were under any anticoagulation therapy (warfarin, aspirin, dipyridamole, clopidogrel) with a control group and only in the English language. Exclusion criteria included manuscripts that did not compare any patient group and did not describe any inversion protocol.

Details were extracted from each study, such as number of patients, type of anticoagulation treatment that the patient was receiving at the time of admission, time to surgery and outcomes and recommendations made. Results were shown in tables.

Results

For part A, the following guidelines were reviewed (see Table 1).[1,3-6] NICE guidelines (CG92) recommend combined VTE prophylaxis with mechanical and pharmacological methods for patients undergoing hip fracture surgery.[7] Initiation of mechanical venous thromboembolism (VTE) prophylaxis at admission is advocated by selection of one of the following methods based on individual patient factors: anti-embolism stockings (thigh or knee length); foot impulse devices or intermittent pneumatic compression devices (thigh- or knee-length). Mechanical VTE prophylaxis should continue until the patient's mobility is no longer significantly reduced.

Providing there is no contra-indication, chemical VTE prophylaxis can be started before surgery by selecting one of the following medications. Low molecular weight heparin (LMWH) is started on admission, stopped 12 h before surgery and restarted 6 to 12 h post-operatively. Unfractioned heparin (UFH) for patients with severe renal impairment or established renal failure is started on admission, stopped 12 h before surgery and restarted between 6 and 12 h after surgery. Fondaparinux sodium is started 6 h post-operatively. The pharmacological VTE prophylaxis continues for 28 to 35 days post-operatively according to the summary of product characteristics.[7]

The Scottish Intercollegiate Guidelines Network (SIGN)[4] guidelines recommend combined mechanical and chemical prophylaxis for patients that do not receive any anticoagulation treatment before sustaining hip fracture.[4] Prior to surgery, the use of cyclic sequential compression and arterial-venous (A-V) foot impulse systems is strongly advised and if surgery is delayed, patients should receive heparin (UFH or LWMH), which should be stopped 12 h before surgery and restarted 6 to 12 h post-operatively. Fondaparinux is not recommended before surgery due to increased potential complications with neuraxial anaesthesia. However, providing there is no contra-indication, fondaparinux is recommended post-operatively for 28 days starting 6 h after surgery. Aspirin is not recommended post-operatively as monotherapy for hip fracture

surgery.[4] The British Orthopaedic Association, in the Blue Book of Guidelines on the care of patients with fragility fractures states: "Almost ten years ago, a non-consensus between units existed regarding the anticoagulation chemical VTE prophylaxis pre-operatively. But they advocated the start of Heparin (UFH or LWMH) 6-12 hours after surgery for 4 weeks, the early mobilization of the frail patient and the simultaneous use of mechanical VTE prophylaxis".[6]

For part B, out of 108 publications (screened) only five met the inclusion criteria (Table 2).[8-12]

Vitale et al[8] conducted a study among 1634 patients presenting to the Columbia Presbyterian Medical Centre (CPMC) between 1997 and 2010, who underwent operative intervention of a hip fracture. Of these, 93 patients (5.7%) were identified as having a pre-operative international normalised ratio (INR) >1.50 and were taking warfarin on admission. Two study groups comprised the study population. The control (watch-and-wait) group consisted of patients whose warfarin was held upon admission without any further pre-operative intervention (23 pt). The treatment (pharmacological intervention) group consisted of patients who underwent pharmacological reversal of elevated INR (with vitamin K and/or fresh-frozen plasma (FFP)) in addition to their warfarin being held (70 pt). The INR at admission was dichotomised such that the values of INR at admission above the median value (INR = 2.17) were classified as 'high INR' and those less than or equal to the median value were classified as 'low INR'. Among those with a high INR, patients in the watch-and-wait group had a mean time to surgery of 6.8 days and those in the treatment group had a mean time to surgery of 2.8 days. Significant differences were not found among the post-operative complication and mortality rates. The authors concluded that reversal of warfarin-associated coagulopathy with vitamin K and/or FFP is not associated with a greater rate of post-operative complications in the high-risk geriatric population of patients with hip fractures and was found to be a safe alternative to warfarin cessation alone, which may result in increased delay to surgery.[8]

Reversal of high INR is important to avoid a significant delay in surgery as suggested by the International Scholarly Research Network (ISRN) after a retrospective study conducted in four different hospitals in the UK. Ashuri et al[9] retrospectively reviewed 1797 hip fractures. Of these, 1740 were the control group and the remainder, 57 of whom were on warfarin, were divided into two groups. The first group consisted of 16 patients who did not receive any treatment (watch-and-wait), and the second group of 41 patients was reversed pharmacologically. The mean time to surgery from admission in patients not given pharmacological treatment was 4.4 days (between 1 and 8 days). The average time to surgery from admission in patients given pharmacological treatment was 2.4 days (between 1 and 5 days). The study

Table 1. Protocols of thromboprophylaxis in patients presenting with a hip fracture without taking any pharmacological agents for anticoagulation

Author	Year	VTE chemoprophylaxis pre-op	Mechanical VTE prophylaxis pre-op	VTE chemoprophylaxis post-op	Mechanical VTE prophylaxis post-op
The National Hip Fracture Database National Report, 2010.[1]	2010	1. LMWH starting on admission. Stop 12 h before surgery, restart 6 to 12 h after surgery 2. UFH (starting on admission for patients with renal failure). Stop 12 h before surgery and restart 6 to 12 h after surgery 3. Fondaparinux is not recommended before surgery. If used should stop 24 h before surgery	1. Anti-embolism stockings 2. Foot impulse device 3. Intermittent pneumatic compression devices	Heparin (UFH or LMWH), fondaparinux × 28 to 35 days	Continue mechanical VTE prophylaxis until patient no longer has significantly reduced mobility
NICE[3]	2011	1. LMWH starting on admission. Stop 12 h before surgery, restart 6 to 12 h after surgery 2. UFH (starting on admission for patients with renal failure). Stop 12 h before surgery and restart 6 to 12 h after surgery 3. Fondaparinux is not recommended before surgery. If used should stop 24 h before surgery	1. Anti-embolism stockings 2. Foot impulse device 3. Intermittent pneumatic compression devices	Heparin (UFH or LMWH), fondaparinux × 28 to 35 days	Continue mechanical VTE prophylaxis until patient no longer has significantly reduced mobility
Scottish Intercollegiate Guidelines Network (SIGN)[4]	2009	"If surgery is delayed patients should receive thromboprophylaxis with heparin (UFH or LMWH. Fondaparinux is not recommended before surgery"	Cyclic sequential compression and arterial venous (A-V) foot impulse systems	Fondaparinux × 28 days or heparin (UFH or LMWH). Aspirin as a monotherapy is not recommended	Continue mechanical VTE prophylaxis until patient no longer has significantly reduced mobility
National Institute for Health and Care Excellence (NICE)[5]	2015	1. Low molecular weight heparin (LMWH) starting on admission. Stop 12 h before surgery, restart 6 to 12 h after surgery 2. Unfractioned heparin (UFH) (starting on admission for patients with renal failure). Stop 12 h before surgery and restart 6 to 12 h after surgery 3. Fondaparinux is not recommended before surgery. If used should stop 24 h before surgery	1. Anti-embolism stockings 2. Foot impulse device 3. Intermittent pneumatic compression devices	Heparin (UFH or LMWH), fondaparinux × 28 to 35 days	Continue mechanical VTE prophylaxis until patient no longer has significantly reduced mobility
Blue Book on Fragility Fracture Care, British Orthopaedic Association (BOA)[6]	2007	Controversy over thromboprophylaxis if it remains as effective its initiation is delayed until after surgery	1. Anti-embolism stockings 2. Foot impulse device 3. Intermittent pneumatic compression devices	Chemoprophylaxis (fondaparinux or LMWH) continued for 4 weeks after surgery	Advocates mechanical prophylaxis and early mobilisation

VTE: venous thromboembolism

concluded that reversal of warfarin anticoagulation facilitates earlier surgery and that a national policy should be developed for reversing warfarin anticoagulation in patients with hip fractures requiring surgery.[9]

In another study, Leonidou et al[10] compared the effects of different warfarin reversal protocols on surgical delay and complication rates in patients with hip fractures. The medical records 24 patients who were on warfarin and sustained a hip fracture, and were reviewed retrospectively. The time to surgery, complication rate and mortality were recorded as well as the INR on admission and the day of operation, the dose, route and time of administration of vitamin K for reversing the anticoagulation effect of warfarin. Patients were divided into four groups based on the warfarin reversal treatment. Group 1 (n = 4) included patients who did not receive reversal treatment, as their admission INR was ≤1.5. Group 2 (n = 6) included patients who did not receive reversal treatment even though their INR was >1.6. Group 3 (n = 5) included patients who

received inappropriate reversal treatment (late or low-dose oral administration). Group 4 (n = 9) included patients who received appropriate reversal treatment in terms of dose, route and time of administration. Patients on warfarin who did not receive reversal pharmacotherapy (between 5 and 10 mg of intravenous vitamin K) waited longer for surgery compared to those who received it (4.4 *versus* 2.4 days). Six of the patients developed complications, including gastro-intestinal bleeding, ileus, chest infection, respiratory failure and peri-operative cardiac arrest; one patient died. Group A was excluded from further analysis. In Groups B, C and D, the mean times to surgery were 2.3, 2.6 and 1.2 days and the complication rates were 67%, 20% and 11% respectively.[10] The figures in this review make interpretation difficult.

Eardley et al[11] studied the time to surgery of the warfarinised patients affected with hip fractures and the economic impact on the best tariff practice (BTP) over the study period of 32 months.

Table 2. Studies on patients presenting with a hip fracture and who are on anticoagulation therapy for different medical reasons

Author	Year	N =	Anticoagulation type and patient	Time to theatre
Vitale, USA[8]	2011	1634	Group A: 70 patients on warfarin	2.8 days
			Group B: 23 control patients (watch-and-wait)	6.8 days
Ashouri, UK[9]	2011	1797	57 patients on warfarin divided	
			Group A: 16 patient sin watch-and-wait	4.4 days
			Group B: 41 patients reversed pharmacologically	2.4 days
Leonidou, UK[10]	2013	24	Group A: not receive reversal 4 patients	Excluded
			Group B: appropriately reversed 9 patients	1.2 days
			Group C: not reversed 6 patients	2.3 days
			Group D: inappropriately reversed 5 patients	2.6 days
			Group E: not reversed (6 patients) and inappropriately reversed (5 patients)	2.4 days
Eardley, UK[11]	2014	1024	Group A: 908 control patients	32.09 h
			Group B: 83 patients on warfarin	53.71 h
Crawford, Australia[12]	2015	330	Group A: 167 control patients	1.6 days
			Group B: 30 patients on warfarin	3.3 days
			Group C: 105 patients on aspirin	1.8 days
			Group D: 28 patients on clopidogrel	1.6 days

A total of 1054 patients were admitted with hip fractures, 86 of them were taking warfarin on admission and were retrospectively assessed. Non-operative management accounted for three patients in the warfarin group and 30 patients in the non-warfarin control group. Following exclusion, there were 83 patients in the warfarin group and 908 patients in the control group. The parameters measured were: time to theatre; LOS; Nottingham Hip Fracture Score (NHFS); and predicted 30-day mortality. Large differences were not found between groups on the LOS, the NHFS and the predicted percentage of 30-day mortality. However, a statistically significant difference was seen in the time to theatre between the warfarin group and the control group. The average time to theatre for the non-warfarinised group was 32.09 h compared with 53.71 h in the warfarinised group. In terms of BTP, 28% (257 of 908) of non-warfarinised patients breached the 36 h window on time to theatre, in contrast with 79% (66 of 83) in the warfarin group. The loss of BTP in the warfarin group over the study period equated to a

loss of £80 000 in revenue within the unit. The authors went on to suggest that bedside INR testing should be considered as a means of investigation in these patients, an approach that could further reduce delays in blood sample processing and resultant IV vitamin K prescription where required, reinforcing near-patient care and instigating the culture of corporate responsibility for the early management of patients with hip fracture on warfarin.[11]

Crawford et al[12] reviewed records of 330 patients with hip fractures. A total of 167 patients were controls; 30 patients were on warfarin, 105 patients were on aspirin and 28 patients were on clopidogrel. Hospital mortality, time from admission to surgery, LOS, return to theatre and post-operative complications (wound infection, DVT and PE) were assessed. The non-warfarinised patients (aspirin, clopidogrel, control) were the group that had a mean time to theatre of 1.7 days compared with warfarinised patients who had 3.3 days to theatre. All the other parameters included in the study were found to have no significant deviations from other studies. The authors concluded that it is safe to continue aspirin and clopidogrel prior to surgical treatment for femoral neck fracture. The risk of delaying surgery outweighs the peri-operative bleeding risk.[12]

Discussion

Femoral neck fractures constitute increasingly common injuries in the elderly population. Such fractures are orthopaedic emergencies that require a multi-disciplinary approach and simultaneous involvement of different specialties for a safe and prompt access to the operating theatre for stabilisation of the fractures and rapid rehabilitation.

Fracture fixation is mandatory for pain relief, early mobilisation and rehabilitation. DVT and PE represent recognised post-operative complications. It is currently accepted that the incidence of asymptomatic thrombo-embolic events is greater when compared to symptomatic ones.[3] Consequently, an effort has been made to establish national guidelines in order to minimise the risk of morbidity and mortality.

The NICE and SIGN guidelines include a combined VTE prophylaxis approach with both mechanical and pharmacological methods. Mechanical means of prophylaxis include anti-embolism stockings, foot impulse devices and intermittent pneumatic compression devices. Chemical prophylaxis includes the administration of LMWH and UFH for patients with severe renal impairment or established renal failure. Fondaparinux sodium can also be used, starting 6 h after surgery. Overall, chemical prophylaxis is recommended for a period of 28 to 35 days post-operatively.[3,4]

Special emphasis is given to the patient with hip fracture and taking different anticoagulant therapies. Those on

aspirin and antiplatelet agents represent a group that is not substantially different from patients that do not receive any treatment. However, those on warfarin demonstrate significant differences, whether they have pharmacological reversal of the anticoagulant effect of warfarin or not.

Patients at risk of cerebrovascular events, PE, atrial fibrillation, acute thromboembolism and those with prosthetic heart valves are treated with oral anticoagulants such as warfarin.[13] Warfarin is a long-term anticoagulant antagonising the reversing effect of vitamin K, which decreases the production of modified clotting factors II, VII, IX and X. After the administration of warfarin is ceased, it may take up to five days for the INR to return to normal values because of the long half-life of warfarin. By contrast, vitamin K disperses the liver reserves, triggering the opposite effect of warfarin.[14]

A lot of time has been spent debating 'watch-and-wait or reverse'. However, it is well known that surgery can be planned earlier by reversing the effect of warfarin with vitamin K.[15] Ashouri et al[16] reported a delay of two days in a cohort of patients who did not receive reversal treatment.[9]

The SIGN has recommended reversing the pharmacological effect of warfarin either with oral or intravenous vitamin K in order to accelerate hip fracture surgery in the elderly. Of note, the highest INR decrease was observed 4 h after the first administration dose. A dose of between 1 and 2.5 mg administered either orally or intravenously has been established as a safe protocol.[7]

NICE guidelines underline the importance of the prompt surgical management of elderly patients with fragility hip fractures within the first 36 h, and it has been highlighted that delays related to anticoagulation are unjustified.[3,5] Where it is deemed appropriate, FFP should be used in accordance with national guidelines from the British Committee for Standards in Haematology. To reduce the risk of surgical bleeding, the American College of Chest Physicians recommends stopping the antiplatelet therapy and not delaying the transfusion with platelets, except in cases with excessive surgical bleeding.[7]

Up to 4% of patients take clopidogrel, an irreversible inhibitor of platelet aggregation. Clopidogrel is generally not stopped on admission, especially in patients with drug-eluting coronary stents. Operation should not be delayed, nor should platelets be administered prophylactically, but marginally greater blood loss should be expected. Although this is associated with an increased risk of intra-operative bleeding and also an increased risk of spinal haematoma where regional anaesthesia is employed, the recent SIGN guidelines recommend that surgery should not be delayed.[4]

Aspirin is taken regularly by 30% of patients presenting with hip fracture.[8] There is a risk of significant bleeding if aspirin is taken in combination with other thromboprophylactic medication. Aspirin may be withheld during inpatient stay unless indicated for unstable angina or recent/frequent transient ischaemic attacks.

Overall, one can argue that a non-consensus exists about which protocol to follow. However, it is commonly agreed and demonstrated from the above studies that patients who received vitamin K orally, subcutaneously or intravenously have seen a benefit. The time to surgery was reduced with continuous positive consequences, including a reduction in LOS and development of post-operative complications.[8-10,16]

The current evidence favours the use of oral vitamin K for anticoagulation reversal in hip fracture patients. The need for further prospective studies to establish a protocol to apply for patients already receiving anticoagulant therapy is mandatory in order to acquire strong evidence for the establishment of a robust pathway at a national level.

The so-called new oral anticoagulants (NOAs) such as dabigatran, rivaroxaban and apaxiban have recently been proposed for the prevention and treatment of thrombosis. Their mechanism of action modifies the activity of thrombin and factor Xa.[17]

The approved dose of rivaroxaban is 10 mg daily beginning 6 to 10 h after surgery, and continued for five weeks following total hip arthroplasty (THA) and two weeks after total knee arthroplasty (TKA). It is excreted predominantly by the kidneys (70%) with a small component excreted by the liver (30%).[18] Dabigatran is administered once daily. It has rapid onset of activity and predictable anticoagulation activity. Its excretion is renal (80%) and is contra-indicated for patients with severe renal failure (creatinine clearance under 30 mL/min), but it can be used at reduced dose in patients with moderate renal impairment with creatinine clearance of 30 to 50 mL/min.[19] Apixaban is administered twice a day and is only 30% excreted by the kidneys. For this reason it is considered as the anticoagulant of choice for patients with renal impairment.[20] Regulatory agencies have approved them with specific indications based upon results from clinical trials where their efficiency and safety have compared with the traditional and well established drugs, such as warfarin.

The NOAs are well studied, having in general such advantages as low drug interaction and quick on set and offset. They do not require laboratory monitoring in a fixed dose, but their disadvantage is that they do not have an antagonist to reverse their pharmacologic effect. Usually, NOAs are prescribed in patients undergoing THA and TKA. Attempts to extend their indications for lower limb fracture surgery have been made, but there still does not exist strong evidence with regard to their use in patients with fragility fractures around the hip. Further studies are desirable in order to establish their routine use in hip fracture surgery.

Conclusion

Patients presenting with hip fractures are at high risk of developing DVT and PE. Those that do not receive any anti-coagulation therapy on admission for medical reasons are easy to manage with the implementation of existing national protocols. Patients who are already on anticoagulation treatment for pre-existing medical conditions are more complex to manage. A national agreement needs to be developed by surgeons, haematologists and cardiologists in order to avoid delays in patient management and reduce further complications related to hip fracture surgery.

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