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A review of the evidence for and against thromboprophylaxis in total hip replacement

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Deep vein thrombosis (DVT) after an unprotected total hip replacement (THR) is common and this review explores the balance between risks and benefits of thrombo-prophylaxis in protecting patients undergoing THR.

A literature search for English publications was conducted on Medline & PubMed. Governance bodies and their guidelines were consulted. MESH terms included Deep Vein Thrombosis OR DVT AND Prophylaxis AND Hip AND/OR Surgery AND/OR Total Replacement OR Arthroplasty.

THR results in significant risk of thrombo-embolic complications with studies showing that as many as one half of patients suffer from DVT post-operatively. Prophylactic treatments are used to reduce the incidence of DVT. However, there are also risks associated with the use of prophylaxis, including excessive bleeding and major cardio-vascular events. Further investigation is required to determine which patients should be given what prophylaxis and for how long post THR.

Keywords : DVT ; thromboprophylaxis ; orthopaedics ; total hip replacement.

INTRODUCTION

Total hip replacement (THR) is one of the most common and successful major elective operations, with over 50,000 being performed in Britain each year (*26,35*). Patients undergoing this procedure have a high risk of deep vein thrombosis (DVT) with some studies showing as many as one half of patients suffering from DVT post-operatively (*14, 17,33*). It also remains the most common cause of hospital readmission after hip surgery and can theoretically lead to fatal pulmonary embolism (PE).

The incidence of DVT after THR can be reduced using both pharmacological and non-pharmacological treatments. There are, however, a number of risks associated with chemical prophylaxis including excessive bleeding. This leads to haematoma formation which in turn raises the risk of infection, the most devastating complication of total hip replacement. So, the value of thrombo-prophylaxis

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in preventing a serious thrombo-embolic event must be balanced against the increased risk of complications caused by that treatment in all the patients given prophylaxis.

Deep vein thrombosis (DVT)

1. *Pathophysiology & Risk factors*

DVT is the abnormal clotting of blood in the veins of the lower limbs. It can be precipitated by blood stasis, hypercoagulability and injury to the intimal wall of the vein. This combination is referred to as Virchow's triad. Stasis and pooling of blood in the leg veins occurs during total hip replacement, and in the immediate post-operative period before the patient mobilizes. On top of this, surgery activates local and systemic coagulation processes, which leads to a period of hypercoagulability. Intimal damage also occurs from a combination of endothelial hypoxia and venous manipulation during surgery itself (*40*). Whilst Virchow's triad provides a useful model for understanding DVT formation, it appears that systemic coagulation activation also has a major role to play.

Sharrock *et al* studied markers of thrombus formation (prothrombin and fibrinopeptide A). They found that thrombogenesis rises during the preparation of the femur and is most pronounced during implantation of the femoral component with cement (*36*). In this phase thrombotic mediators are released which can potentially lead to femoral venous occlusion.

The likelihood of a DVT developing during or after hip replacement is increased by pathologies causing or associated with increased coagulation. A prospective cohort of 21,903 consecutive surgical patients identified the following as DVT risk factors : age over 50, history of varicose veins, previous myocardial infarction, cancer, atrial fibrillation, ischaemic stroke and diabetes mellitus (*22*).

2. *Diagnosis*

DVT can be identified primarily by clinical investigation. The 'gold standard' is considered to be intravenous venography (*8*), but this is now rarely performed because of its invasiveness and instead venous ultrasound can be used to confirm the presence of a DVT. Measurement of the patient's D-dimer, a degradation product of fibrin, in combination with the Well's score, is useful for both excluding DVT from a differential diagnosis, and as a pointer to the need for further investigations such as CT pulmonary angiogram to exclude pulmonary embolus.

3. *Complications*

A study by Seagroatt *et al* of 10,000 total hip replacement patients who did not receive thrombo-prophylaxis found DVT to be the most common cause of hospital readmission and death after THR (*35*). The overall excess death rate in the first 30 post-operative days was less than 1%, of which the majority was heart attacks and strokes. However it was also found that 1% of patients with DVT suffered from fatal PE. Post-thrombotic syndrome was another common complication, characterized by chronic pain, swelling and venous ulcers of the affected leg. The severity of these complications and possibility of mortality make DVT prophylaxis an important consideration in THR management.

Prophylaxis

In the absence of thrombo-prophylaxis the risk of developing a DVT after THR has been identified by some studies to be as high as 50% (*14,17,33*). With appropriate prophylaxis however this incidence has been dramatically reduced to nearly one tenth of its previous level (*23*). Consequently the National Institute for Health and Clinical Excellence (NICE) and the National Collaborating Centre for Acute Care have issued guidelines on DVT prevention (*27*), stating that patients undergoing hip replacement surgery should be offered prophylaxis.

Several types of prophylaxis exist, broadly being categorized into pharmacological and mechanical. NICE guidelines state that both should be offered to patients, and pharmacological prophylaxis should be continued for at least 28-35 days after THR (*9,27*). Effects of extended VTE prophylaxis analyzed from nine randomized control trials (consisting of 3999 patients and eight trials that used

low-molecular weight heparin) required 62 patients to be treated to avoid one DVT (with NNT of 250 for PE) but there was a greater risk of sustaining a minor bleed (NNH = 83) as well as no significant reduction in risk of developing PE or increased risk of major haemorrhaging (*9*).

The current guidelines in the USA illustrate the controversy regarding which method of prophylaxis is superior. Three pharmacological agents have been endorsed by the American College of Chest Physicians (ACCP) for prevention of venous thrombotic episodes (VTE) : warfarin, heparin and fondaparinux whilst the sole use of either aspirin or mechanical devices has been discouraged (*13*). Mechanical prophylaxis can give no protection against the effects of systemic hyper-coagulability so it is felt that this form of protection cannot be adequate alone (*40*).

In contrast, The American Academy of Orthopedic Surgeons (AAOS) take the view that if chemical prophylaxis increases bleeding risk while reducing embolic risk, the bleeding risk is more serious and important to the overall clinical outcome (*21*). Thus, AAOS guidelines stipulate that warfarin or aspirin should be reserved for situations where there are major concerns about post-operative bleeding. Furthermore, the bleeding risk associated with LMWH and fondaparinux means that neither are endorsed by the AAOS. It would seem necessary to take into account the views of both orthopaedic surgeons and chest physicians when forming guidelines on thromboprophylaxis as each group is likely to have its own bias as to which complication (VTE or bleeding) is more serious. With respect to numbers needed to treat and numbers needed to harm to prevent fatal PE in THR, it is difficult to provide any figures due to little published literature with dissimilar interventional groups and different therapeutic options.

1. *Pharmacological prophylaxis*

Pharmacological agents offer powerful means of reducing the incidence of DVT in patients undergoing THR. An incidence of 50% DVT post-THR has been shown to be reduced to 41.7% with aspirin, 22.3% with adjusted- dose warfarin, 14.8% using low molecular weight heparin (LMWH) and 4.7% with fondaparinux (*5,19,23,24,29*). Furthermore, a higher dose enoxaparin of 40 mg (versus 10 mg) in a double-blinded concealed randomized trial with intention-to-treat had an 11% reduction in DVTs (*38*). In fact, patients having hip replacement who were given adjusted dose heparin (to maintain aPPT range of $1 < x < 1.1$) had fewer DVTs post-operatively, than those given a fixed dose of 3500 IU every 8 hours (NNT = 4 at 9 days) with an absolute risk reduction of around 26% (*25*). However there is no equivalent data on the much more serious but rarer complication of symptomatic Pulmonary Embolus, nor is there any data on whether patients with the common below knee DVT are at increased risk of Pulmonary Embolus.

There has been some controversy over the use of aspirin in DVT prophylaxis. The Antiplatelet Trialists' Collaboration carried out an important meta-analysis of the use of aspirin in combination with heparin versus use of heparin alone (*4*). The combined therapy reduced the likelihood of PE by 62% and DVT by 12%. Although these results seemed promising, it was found that total mortality and complication rates were higher in the combination treatment group, potentially overturning any benefits of this form of treatment (*34*). The Pulmonary Embolism Prevention trial, conducted in Australia and New Zealand on elective THR patients, also found that there was no difference between aspirin and placebo in terms of efficacy in venous thrombo-embolic (VTE) disease prevention (*31*).

The use of synthetic antithrombotic agents in DVT prevention has been investigated by Turpie *et al* who studied the effects of the pentasaccharide Org31540/SR90197A, a highly selective inhibitor of activated factor X (*39*). In their double-blinded study with 593 patients the agent decreased DVT risk by 82%, with a considerable improvement over outcomes achieved by Low Molecular Weight Heparin (LMWH). Such compounds could provide a means of further reducing the incidence of DVT in the future, but once again there is no information on any reduction in the risk of symptomatic PE or of an increased risk of the other fatal complications which reversed the findings in the PEP trial (*4*).

2. *Mechanical prophylaxis*

NICE guidelines endorse the use of mechanical prophylaxis (*27*). This includes graduated compression stockings, electrical stimulation of the calf muscles, intermittent external pneumatic calf compression (IPC), and rotating tables. IPC is commonly used and aims to reduce stasis and improve venous return from lower extremities (*12,18*). This it is believed reduces the risk of DVT and its complications with seven patients needed to be treated to prevent one DVT (*15*). However, an investigation by White *et al* demonstrated that above a body-mass index (BMI) of 25, the efficacy of IPC was significantly limited (*41*). Consistent with this they found that the majority of patients who were readmitted for symptomatic VTE had a BMI above 25. This suggested that the IPC treatment that they received may have been insufficient to protect against the increase in blood coagulability following hip surgery. Given that a large proportion of patients undergoing THR are overweight or obese, this study suggests that further research and optimization of mechanical prophylaxis is required to effectively decrease DVT incidence and hospital readmission in these patients. Furthermore, Best *et al* found that 98% of the below-knee graduated stockings failed to produce an optimal pressure gradient in their study of 89 patients who underwent elective hip (or knee) replacements (*1*). Interestingly, in the majority of cases a reverse gradient was produced which, in fact, significantly increased the risk of DVT by nearly 20% (compared with those with normal gradients).

Even with the National Health Service spending over two million pounds on these products (*1*), many mechanical devices have been hampered by the fact that they are uncomfortable and often not very portable. The industry has attempted to combat this issue with newer devices that are lightweight or use internal batteries to increase patient mobility (*42*). Perhaps more importantly, some devices also include built-in compliance monitoring. A study by Colwell *et al* (*7*) found that patients used the device for 83% of each day. This suggests that the device is well tolerated. They also found that patients using the newer devices had similar rates of VTE compared to those on pharmacological prophylaxis but with significantly reduced bleeding events. Data such as this could highlight a greater role for mechanical prophylaxis in the coming years.

Is prophylaxis necessary ?

For over two decades the use of prophylaxis has been questioned (*2*) ; although thrombo-prophylaxis has been shown to reduce DVT risk (especially with LMWH and mechanical intervention (*20*)), it is still unclear whether complications such as pulmonary embolism are similarly reduced. Furthermore, there are several risks associated with the use of anti-coagulation which must be considered in the equation of risk/benefit. These include excess bleeding, haematoma formation, secondary infection, and failure of fixation of the joint replacement due to excessive bleeding during the cementing stage. It also includes systemic adverse events such as gastro-intestinal bleeds, myocardial events and haemorrhagic strokes (*3,32*).

Initially, in the face of literature suggesting a 2-5% fatal PE complication rate for patients not on prophylaxis, many centers in the late 1980's began to adopt prophylactic measures despite the potential drawbacks (*3*). However, subsequent studies of large groups of THR patients have shown that the overall mortality rate in unprotected patients was significantly lower than that previously quoted, so undermining the perceived benefit of DVT prevention (*21,28,35*). Indeed such investigations have demonstrated rates of fatal PE to be as low as 0.19% after total hip replacement with no reduction when prophylaxis is used (*11*). Several shortcomings have also been identified in these studies including the failure to collect data on a routine basis for all patients, limited follow-up and poor internal validity (i.e. randomization methods, blinding, analysis and study losses (*10*)). It is clear that further evidence on the incidence of DVT, PE and the complications of anti-coagulation are required to confirm the overall benefit of prophylaxis.

Recent studies have also shown that patient compliance with pharmacological prophylaxis can be very poor (~6% (*10*)). It was also found that most

patients were only placed on LMWH for the duration of their inpatient stay. There is much scope for improving this compliance rate and Faroug *et al* (*10*) suggested that greater district nurse follow-up combined with teaching of administering subcutaneous LMWH injections to patients (or relatives) could most likely improve compliance, always assuming that chemical thrombo-prophylaxis is actually needed after discharge from hospital when the patient should be mobilizing normally. Most importantly, hospital staff highlighted the high number of different thrombo-prophylaxis protocols in each orthopaedic department as a potential source of confusion. This is perhaps unsurprising given the controversy over the subject within the literature.

There has also been disagreement on the duration of post-operative prophylaxis with recent guidelines by the ACCP suggesting that some treatments should be continued for up to 35 days after THR (*6*). A recent publication from NICE recommends post-THR VTE prophylaxis for 4-5 weeks (*27*). As with any clinical situation, it is important to consider the cost-benefit ratio carefully. The risks associated with giving anti-coagulation will remain constant for as long as it is given, whilst the benefit in avoiding an adverse thrombolic event declines sharply within days after THR (with some studies showing that the excess mortality after THR is no longer detectable 5 days post-surgery (*35*)). Thus, there will be a rapid change in the risk/benefit ratio in the days after surgery which must be considered when deciding how long prophylaxis should be considered. With the development of newer anti-coagulant therapies, the pharmaceutical industry will be eager to see greater uptake and prolonged use of their drugs. However, there is currently little high-quality evidence to support the assertion that a longer duration of prophylactic treatment is of clinical benefit.

A further issue lies in whether, given the risks of post-operative bleeding, there are any additional benefits to pharmacological prophylaxis over mechanical intervention alone. Sharrock *et al* found that both non-fatal PE and all-cause mortality were significantly higher in patients on LMWH, direct Factor Xa or thrombin inhibitors compared to those on mechanical prophylaxis and aspirin (*37*). However, others have contested this with findings that mechanical compression alone can result in a four-fold higher incidence of proximal clot formation (*12*). Whether mechanical prophylaxis is safer than pharmacological prophylaxis remains uncertain. It is nevertheless clear that greater emphasis needs to be placed on understanding and improving the safety of these methods rather than simply their efficacy (*30*).

Finally, it should also be remembered that flexibility in thromboprophylaxis is important. Guidelines should not aim for a 'one size fits all' approach, nor should they endorse an 'either or' situation as to whether mechanical or chemical prophylaxis is superior. For example, patients with a greater risk of bleeding could be given a larger ratio of mechanical to pharmacological prophylaxis and assessing the individual risk factors for each patient would be key to this more appropriate prophylactic strategy. In reference to what was mentioned earlier, such risk factors would include age over 50, history of varicose veins, previous myocardial infarction, cancer, atrial fibrillation, ischaemic stroke and diabetes mellitus (*22*).

CONCLUSION

Deep vein thrombosis is a common and preventable complication of total hip replacement, yet the association between DVT and fatal PE is not altogether clear. Hence, the use of DVT as a surrogate end-point for measuring the efficacy of anti-coagulation in preventing death from PE after THR is not reliable. The incidence of symptomatic PE after THR is very low ; so trials to assess the efficacy of any preventative treatment are unlikely to be feasible because the number of patients which would need to be entered even to show a significant reduction in incidence would run into the tens of thousands (*3*).

Several effective methods of prophylaxis exist, both pharmacological and mechanical. These are recommended by numerous international governance bodies including NICE and have been shown in several contexts to decrease the rate of DVT significantly. However, there is currently little evidence to support extending the length of time for which prophylactic anti-coagulation is given after

hip replacement. The question that remains, is whether the benefit of anti-coagulation during and after major surgery already outweighs the risks of prophylaxis; this should be gauged based upon the patients' individual risk factors in addition to the properties of the prophylactic agent.

Moreover, it is still unclear whether these prophylactic measures which are shown to reduce the incidence of DVT effectively protect against severe complications such as fatal PE. Further investigation and evidence is, therefore, required to determine the types of patients and context under which DVT prophylaxis should be used, considering practical and logistical measures, whilst abiding by evidence-based medicine for the provision of optimal patient care.

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