Special Communication

Thromboprophylaxis and Orthopaedic Surgery: Options and Current Guidelines

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Abstract

Antithrombotic therapy remains crucial in the peri- and post-operative management of patients who undergo orthopaedic surgical procedures, particularly total joint arthroplasty (TJA) and hip fracture surgery (HFS). Optimal thromboprophylaxis is currently mandatory in most orthopaedic practices to avoid the dreaded complications of venous thromboembolism (VTE). The pathogenesis of VTE is multifactorial and includes the well-known Virchow's triad of hypercoagulability, venous stasis, and endothelial damage. With current advances in orthopaedic surgery, a multimodal approach to thromboprophylaxis, anaesthetic management, and post-operative convalescence have altered the risks of venous thromboembolism after TJA and HFS in the lower extremity. This article reviews the various VTE prophylactic options and current best practice guidelines for orthopaedic TJA and HFS.

Keywords: *thrombolytic therapy, hip fracture, arthroplasty, venous thromboembolism*

Introduction

The rates of venous thromboembolism (VTE) complications such as deep vein thrombosis (DVT) and pulmonary embolism (PE) have been shown to be around 40–60% within 7 to 14 days following orthopaedic lower limb surgery without thromboprophylaxis (1,2). Most of these thrombi resolve spontaneously; however, a small percentage (1–4%) will develop into symptomatic VTE (3–5). The incidence of fatal pulmonary embolisms in patients not receiving thromboprophylaxis ranges from 0.3–1% following total joint arthroplasty (TJA) and around 3.6% after hip fracture surgery (HFS) (1,6,7). A proactive approach to reduce the incidence of VTE is therefore of paramount importance.

Thromboprophylaxis Options

Mechanical

Many centres use mechanical thromboprophylaxis as an adjunct in the prevention of VTE. These include the use of graduated compression stockings, venous foot pumps, and active external compression devices (continuous and intermittent). The benefits of these include the non-invasive nature of its application, the fact that it requires no monitoring and the fact that it poses no increased risk of bleeding (8,9). The virtue of external pressure applied to the limb promotes blood flow velocity, reduces venous stasis, and increases levels of systemic fibrinolysins (10). Intermittent pneumatic compression devices (IPCD) have been shown to reduce significantly the incidence of VTE when combined with chemoprophylaxis compared to either therapy in isolation (11–14). The literature also supports the use of IPCD over graduated compression stockings in combination with chemoprophylaxis (15). The drawbacks of IPCDs include cost and compliance issues; however, with increased awareness of its benefits combined with recent technological advancements, including size reduction, monitoring and portability, these challenges may be overcome.

Pharmacological

Warfarin

Warfarin is a vitamin K antagonist which expresses its anticoagulant properties via the inhibition of clotting factors (namely II, VII, IX and X) and continuous use in orthopaedic circles to this day. The level of anticoagulation achieved can be determined by close monitoring of the patient's INR (International Normalised Ratio). When compared to low molecular weight heparin (LMWH) for thromboprophylaxis following

hip and knee TJA, warfarin showed statistically significant higher rates of asymptomatic clot formation. It must be noted, however, that in cases of symptomatic VTE, there was no significant difference between the two chemoprophylactic agents (16–22). Though studies have shown that LMWH is associated with increased bleeding complications in the short term, when given for an extended period (six weeks), more symptomatic bleeds were observed in the warfarin group (23–25).

Heparin (unfractionated heparin and low molecular weight heparin)

Unfractionated heparin (UH) and LMWH have been prescribed for orthopaedic thromboprophylaxis for decades. LMWH has largely replaced UH due to the fact that no monitoring is required and to its simple mode of administration via subcutaneous injection. Many studies have shown fewer VTEs and less bleeding complications with LMWH compared with UH in orthopaedic surgery (26,27). As described earlier, LMWH is more effective than warfarin in preventing overall VTE. One must be aware, however, of the potential for delayed fracture healing, thrombocytopenia, and osteoporosis with the extended use of UH and, to a lesser extent, LMWH, though the benefit of overall VTE risk reduction does appear to justify these risks (28–30). The current guidelines from the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (AACP) continue to promote LMWH as the pharmacological thromboprophylactic agent of choice following TJA (31,32).

Aspirin

Aspirin is also used for VTE prevention at present. It inhibits thromboxane, which is necessary for the binding of platelets during the process of clot formation. Apart from orthopaedic surgery, it is widely used in the management of stroke and myocardial infarctions and in hypercoagulopathy. It requires no monitoring and is generally well tolerated (33). A large pulmonary embolism prevention (PEP) study that investigated aspirin versus placebo showed an overall significant risk reduction in the incidence of symptomatic DVT and PE in patients undergoing HFS (n = 13 356) and total hip arthroplasty (n = 4 088). The study did note that nearly 40% of patients also received LMWH, and when observed in isolation, the cohort of hip arthroplasty patients did not have a significant reduction in pulmonary embolisms specifically (34). There is evidence to support the notion that aspirin is not inferior to LMWH in VTE prevention; however, the current AAOS and ACCP guidelines do not advise its use in isolation without combined mechanical prophylaxis (35–37).

Fondaparinux

Fondaparinux is a synthetic pentasaccharide and an indirect factor Xa inhibitor in the coagulation cascade. It is administered via a subcutaneous injection and requires no monitoring. Large multi-centred randomised control trials have indicated that Fondaparinux is superior to LMWH in preventing asymptomatic DVT in both patients undergoing TJA and those undergoing HFS; however, no significant difference in symptomatic VTE was identified (38–41). Its widespread use has been limited due to concerns regarding post-operative bleeding, especially in North America (38,42).

Apixaban

An oral factor Xa inhibitor, apixaban, has been approved for VTE prophylaxis following orthopaedic surgery in Europe since May 2011 and is under review by the United States Food and Drug Administration (FDA) at the present time. Compared to LMWH in patients undergoing TJA, apixaban showed significantly superior results in the prevention of VTE and its related mortality (43–46). As with rivaroxaban and dabigatran, there is debate regarding the safety of apixaban in the situation of a major bleed, as there is no consensus on the best way of reversing its action (47). There are concerns regarding systemic accumulation of the drug in patients with renal impairment, as it is only partially cleared through the kidneys (48).

Rivaroxaban

Rivaroxaban, the first orally available factor Xa antagonist received FDA approval for VTE prophylaxis in July 2011. Four phase III randomised control trials showed rivaroxaban to be superior to LMWH in preventing total VTE and symptomatic events in patients undergoing hip and knee TJA (49–52). Recent studies showing an increased risk of re-operation secondary to infection and wound complications in patients receiving rivaroxaban coupled with

a trend showing an increased risk of bleeding lends appeal to continued LMWH use (53–55). In similar fashion to LMWH and UH, there is a potential inhibition of bony metabolism and osteoblastic function with rivaroxaban (56).

Dabigatran

An orally available direct thrombin (factor IIa) inhibitor, dabigatran has been approved by the European Commission since March 2008 for use in orthopaedic surgery, while FDA approval is reserved for certain indications in patients with atrial fibrillation. Studies on dabigatran, while emphasising non-inferiority, have shown similar but not superior results in VTE prophylaxis compared with LMWH and comparable side effects in terms of bleeding risks (57–60).

Current Guidelines

Various published recommendations, prophylaxis strategies and local protocols shape the way orthopaedic surgeons manage their VTE outcomes following TJA and HFS. The recent guidelines published by the AAOS and ACCP provide the most widely accepted advice regarding the use of thromboprophylaxis in elective orthopaedic hip and knee arthroplasty (31,32). These represent a comprehensive and systematic scrutiny of the literature, an update of previously published guidelines and expert consensus in VTE prevention and management. Different consensuses between physicians and surgeons were noted especially in regard to bleeding risks, so risk stratification of patients is advised and further research into this area is currently on-going.

Overall, both guidelines stress the importance of VTE prophylaxis using various different regimens compared to no prophylaxis. The AAOS guidelines from 2011 include a strong recommendation against the use of routine duplex ultrasonography screening post-operatively. Under the moderate recommendations, the group suggests discontinuing anti-platelet agents (aspirin, clopidogrel, etc.) pre-operatively and pharmacological thromboprophylaxis with/or mechanical compressive devices in patients not at risk following TJA. It also moderately recommends neuroaxial (intrathecal, epidural, and spinal) anaesthesia for TJA to reduce peri- and post-operative blood loss while accepting that this may not affect the incidence of VTE. Recommendations based on consensus were developed in several areas where evidence was not sufficiently reliable. These included (1) the duration of thromboprophylaxis treatment, individually tailored according to patient specifics using a multi-disciplinary approach involving physicians, (2) the combination of mechanical and pharmacological thromboprophylactic agents, (3) mechanical devices in patients with a higher risk of bleeding, and (4) early mobilisation following elective TJA.

The latest ACCP guidelines from 2012 suggest starting anticoagulant prophylaxis 12 or more hours pre-operatively or post-operatively rather than four hours or less pre-operatively or post-operatively. In the absence of a bleeding disorder and not including HFS, any form of thromboprophylaxis is recommended above no prophylaxis for a minimum of 10 to 14 days. LMWH is preferred above all other pharmacological agents, and the addition of an IPCD is recommended. An extended duration of thromboprophylaxis of up to 35 days is suggested following surgery. When subcutaneous injections are rejected or unacceptable for the patient, the oral thromboprophylactic agent apixaban or dabigatran is advisable. Individuals with bleeding disorders are recommended to receive either mechanical prophylaxis in the form of ICPD in isolation or no thromboprophylaxis. No VTE prophylaxis is considered when dealing with lower limb immobilisation following isolated injuries and low-risk patients undergoing elective knee arthroscopy.

In patients undergoing surgery for hip fractures, the United Kingdom National Institute for Health and Clinical Excellence (NICE) have published guidelines covering the overall management of the individual and places significant emphasis on thromboprophylaxis (61). It recommends mechanical agents (compression stockings, foot pumps and IPCD) at the time of admission and pharmacological agents (i.e. LMWH or UH) provided that there are no contraindications. Pharmacological agents are stopped prior to HFS (12 hours for Fondaparinux and six hours for LMWH) and recommenced six to 12 hours post-operatively. Thromboprophylaxis is continued for up to 28–35 days following surgery.

Pharmacoeconomic Implications

Cost-effectiveness may play an important role in choosing the appropriate thromboprophylactic protocol for use in the local setting. Aspirin, given its low cost and ease of administration, has been shown to be non-inferior and a reasonable alternative to LMWH for extended thromboprophylaxis following TJA (37). When

comparing warfarin to LMWH, there are multiple reports in the literature with mixed cost-benefit outcomes, and some authors consider these results inconclusive (62–64). There remains a need for routine blood monitoring that may offset the cost savings based on the purchase price of warfarin alone. There is evidence to support the cost-effectiveness of Fondaparinux over LMWH in the setting of TJA; however, as stated earlier in this article, the sub-cutaneous administration of the drug may prove inconvenient for patients (63). The newer oral anticoagulants, namely apixaban, rivaroxaban, and dabigatran, have all shown improved cost benefits over LMWH for extended prophylaxis following TJA (65–69). The savings were mostly based on direct (lower VTE rates and related long-term complications) and indirect (reduced administration, management, monitoring, and improved quality-adjusted life-years) costs. These findings were based primarily on data from European and North American trials with industry assistance.

Conclusion

Understanding the various mechanical and pharmacological thromboprophylactic agents and their use will significantly alter the incidence of venous thromboembolism following orthopaedic elective and trauma surgery. The guidelines continue to be updated, as more studies in this area will help hone optimal prophylactic strategies and bring about new options in treatment modalities. More independent studies may improve our pharmacoeconomic perception of thromboprophylactic protocols post-TJA and HFS for implementation in the local setting. Appropriate risk stratification measures need continuous development to ensure the right thromboprophylactic protocol for the right patient.

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