VENOUS THROMBOEMBOLISM PROPHYLAXIS – THE OTHER SIDE OF THE COIN: A REVIEW OF LITERATURE

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ABSTRACT

Background: There are no local guidelines for prophylaxis against Venous Thrombo-Embolism (VTE). In the absence of any guidelines, most of the information available has been provided mainly by the pharmaceutical industry which is an interested party. There have been publications in local journals that lean more on endorsing guidelines developed elsewhere. Unfortunately, such guidelines have not been embraced by everyone even in their countries of origin yet they are sometimes presented as the universally accepted standard of care.

Objective: We sought to elucidate some of the reasons for the opposition to these guidelines in this article. Our aim is not to convince readers to change their practice but to provide information that may be useful to them as they make decisions on this matter. We also hope to stimulate debate on this issue and hopefully contribute to the development of a national guideline for and by the orthopaedic community.

Data source: Publications from peer reviewed journals.

Results: The assumed relationship between deep vein thrombosis and pulmonary embolism is erroneous. The "post-phlebitic limb" is not always post-phlebitic. Large studies comparing the morbidity and mortality prior to and after introduction of various VTE prophylaxis guidelines find that the measures proposed by various guidelines are not efficacious. Most early deaths occurring after orthopaedic procedures are not a result of pulmonary embolism. There exists a serious conflict of interest in many of the studies that support chemo-prophylaxis for VTE prevention. The risks from chemoprophylaxis for VTE are greater than the anticipated benefit.

Conclusions: Evidence adduced in this article casts doubts on the rationale and efficacy of VTE chemoprophylaxis recommendations by various international guidelines and does not support their whole-scale adoption.

Recommendations: Kenya Orthopaedic Association needs to put in place mechanisms to develop local guidelines based on the local data and spearheaded by the orthopaedic fraternity.

INTRODUCTION

The classic teaching is that stasis, hypercoagulability and endothelial injury - the Virchow's triad (1) predispose a large number of orthopaedic patients to deep vein thrombosis that may be complicated by pulmonary thromboembolism (which may be fatal) or the post-phlebitic limb. To prevent these undesired events, prevention of deep vein thrombosis by use of both mechanical and pharmacological agents has been recommended (2-5). Various guidelines have been developed, the most well-known being the American College of Chest Physicians (ACCP) guidelines, the American Academy of Orthopaedic Surgeons (AAOS) guidelines and the National Institute for Health and Care Excellence (NICE) guidelines (for England and Wales).

There are no local guidelines for prophylaxis against Venous Thrombo-Embolism (VTE). In the absence of any guidelines, most of the information available has been provided mainly by the pharmaceutical industry which is an interested party. As expected, this information is skewed in favour of their products. There are very few publications on prophylaxis against venous thrombo-embolism in local journals and most of these publications lean more on endorsing guidelines developed elsewhere. Unfortunately, such guidelines have not been universally accepted even in their countries of origin yet they are sometimes presented to us as the standard of care.

We seek to elucidate some of the reasons for the opposition to these guidelines in this article by examining six main areas namely:

- The relationship between Deep Vein Thrombosis (DVT) and pulmonary embolism
- The post-phlebitic limb
- The effectiveness of VTE chemo-prophylaxis
- Early deaths after orthopaedic procedures
- Conflict of interest
- Risks associated with VTE chemoprophylaxis

Our aim is not to convince readers to change their practice but to provide information that may be useful to them as they make decisions on this matter. We also hope to stimulate debate on this issue as we seek to build broad consensus and hopefully contribute to the development of a national guideline for and by the orthopaedic community.

DISCUSSION

Deep vein thrombosis and pulmonary embolism: Many of the published studies that support use of various methods for thrombo-prophylaxis measure Deep Vein Thrombosis (DVT) as a surrogate for Pulmonary Embolism (PE). This is especially so for studies conducted before 2000 which most of the guidelines are based on. Most of these studies measured asymptomatic DVT by use of screening tests as an end-point (6). Based on the assumption that DVT is a surrogate for PE, DVT prophylaxis as a way of reducing the incidence of PE is proposed. However, the use of DVT as a surrogate for PE has been challenged. Parvizi *et al* (7) examined the association between DVT and pulmonary embolism in a review of records of 11,000 patients who had had different orthopaedic procedures. Of these, 1,495 patients had been evaluated for either or both of DVT and PE within 90 days of an orthopaedic procedure. The incidence of DVT amongst the 1,016 patients evaluated for the same was 15.9%. The incidence of pulmonary embolism in the 876 patients evaluated for the same was 20.6%. Of the patients evaluated for both DVT and PE, only 8.1% were positive for both. This translated to only 1.5% of all the patients screened. Tests of association even within subsets of patients did not demonstrate that patients were more likely to have both DVT and PE than either alone. They were thus unable to demonstrate a statistically significant association between lower extremity DVT and pulmonary embolism. A similar study to assess the association between DVT and PE amongst patients undergoing total hip arthroplasty arrived at similar results and conclusions (8).

The post-phlebitic limb: The post-phlebitic limb is the other complication that VTE chemoprophylaxis aims at preventing. However, the relationship between DVT and the post-phlebitic limb has been questioned. Muller *et al* (9) followed up 244 patients after TKR for five years. Fifty three per cent were found to have venographically proven DVT. Of these, only 8.6% developed ulceration. This is similar to the incidence of leg ulceration in the age matched general population (9.6% to 12.6%). This led to their conclusion that there was no clear association between venographically-confirmed postoperative DVT and the incidence and prevalence of ulcers at five years. For that reason, perioperative chemical thromboprophylaxis may not be justified on the grounds of preventing the post-phlebitic limb.

Browse *et al* (10) similarly found no correlation between the phlebography severity of the thrombus and the late symptoms and signs of ulceration.

The effectiveness of VTE chemo-prophylaxis: The other common reason for the rejection of the VTE prophylaxis guidelines is that studies have shown them not to be effective. Warwick *et al* (11) followed up 1,000 patients who had had TKR with the aim of determining the incidence of DVT and comparing the rate amongst those who received VTE chemoprophylaxis and those who did not. Thirty three point nine per cent had received VTE chemoprophylaxis. The incidence of VTE amongst the patients who had received VTE chemoprophylaxis was 10.6% compared to 10.1% amongst those who had not received VTE chemoprophylaxis indicating no reduction in VTE events after thromboprophylaxis. Other studies similarly show no difference in VTE events in orthopaedic patients receiving DVT chemoprophylaxis compared to those not receiving chemoprophylaxis (12 – 15).

In 2007, the NICE guidelines were introduced recommending that all orthopaedic in-patients receive LMWH for duration of their stay while high risk patients were to continue with LMWH after discharge. This, it was hoped, would reduce the incidence of DVT and PE. Jameson and colleagues (16) compared the incidence of VTE events i.e. Symptomatic DVT and pulmonary embolism amongst 104,640 TKR/THR patients managed prior to the introduction of the NICE guidelines with 114,962 TKR / THR patients managed after the introduction of the NICE guidelines.

A significant increase in the reported use of LMWH (59.5% to 67.6%) following the publication of the guidelines was noted. However, the 90-day venous thromboembolism events actually increased slightly following THR (1.69% to 1.84%) and remained unchanged following TKR (1.99% to 2.04%).

A similar study was conducted by Howie and colleagues (17) in Scotland. Here, guidelines for use of anticoagulation were introduced in 1995. Howie *et al* (17) followed up patients who had had TKR or THR over a ten year period between 1991 and 2002. They documented an increase in the use of VTE prophylaxis from 50% before the introduction of the guidelines to 80% after the introduction of the guidelines. They however did not find any significant reduction in VTE events as a result of the increased use of VTE prophylaxis.

As for the mortality following total hip arthroplasty or total knee arthroplasty, several studies have reported no reduction in mortality rates resulting with the use of VTE thromboprophylaxis. One such study was conducted by Fender *et al* (18). Two Thousand one hundred and eleven consecutive primary THR patients were followed up for forty two days. Of the 2111 patients, 1226 had used chemical prophylaxis. The mortality rate was 0.82% (10 out of 1226) amongst

the patients who had used chemoprophylaxis for VTE. The mortality amongst those patients who did not use VTE prophylaxis was 1.05% (7 out of 667) which was not statistically significant. This, they felt, suggested that contrary to certain opinions, it is not negligent to withhold VTE chemoprophylaxis agents. This view was agreed to by 36% of a sample of members of the British Orthopaedic Association; they considered that low-dose anticoagulants were not a medico-legal necessity in routine THR (19).

Early deaths after orthopaedic procedures: Most of the early deaths after orthopaedic procedures are assumed to be as a result of pulmonary embolism by the proponents of VTE chemoprophylaxis. This has been shown not to be the case. Blom *et al* (20) followed up 1727 patients for 90 days after THR and established the number of deaths and its cause amongst these patients.

The mortality at 90 days was 17 out of 1727 patients (1%). Of the 17 patients who died, 7 patients died of ischaemic heart disease, 4 died following cerebrovascular events while 2 died from pulmonary embolism. Four patients died from non-vascular causes. From the vascular deaths, ischaemic heart disease outnumbered cerebrovascular events which, in turn outnumbered pulmonary embolism (7 vs 4 vs 2).

A study by Fender *et al* (18) arrived at similar results. After following up 2070 patients for 42 days after THR, 19 (0.91%) died. Of these, only 4 (0.19%) died from pulmonary embolism. Other studies have shown that the deaths attributable to pulmonary embolism are very few even when VTE prophylaxis measures are not instituted (21).

Conflict of interest: The other issue that has muddied the waters is the conflict of interest amongst some of the proponents of VTE chemoprophylaxis. Lee *et al* (22) did a systematic review of studies on this topic and found that of 71 eligible articles 52 (73.2%) were funded by industry and only 14 (19.7%) were not. Five did not disclose the source of funding. A significant association was found between the funding source and the qualitative conclusions. Only 2 (3.8%) of the 52 industry funded articles had unfavourable conclusions whereas 3 (21.4%) of the 14 non-industry sponsored articles had unfavourable conclusions. Unfortunately, many of the guidelines are developed based on the findings of such studies.

Even worse, in some instances, guidelines are developed by organisations with close ties to the pharmaceutical industry as was reported in Australia and New Zealand (23). The issue of conflict of interest is not unique to the area of VTE chemoprophylaxis but affects medicine as a whole (24).

Risks: The agents used for chemoprophylaxis for VTE are not without side effects. These include bleeding, infection, poor wound healing, re-operation, re-admission, prolonged hospital stay, increased transfusion needs, injection site complications, thrombocytopenia, an overall increase in mortality as well as other less common side effects.

These occur not infrequently. Burnett *et al* (25) reported an incidence of major complications of 9% in patients in whom chemoprophylaxis was used. Other studies too document a high incidence of bleeding and infection amongst patients in whom VTE chemoprophylaxis is administered (26–28). Many of the studies that advocate for the use VTE chemoprophylaxis under-report these and other complications that lead to poor clinical results (29).

CONCLUSION AND RECOMMENDATION

Evidence adduced in this article casts doubts on the rationale and efficacy of VTE chemoprophylaxis recommendations by various international guidelines and does not support their whole-scale adoption.

We recommend that the Kenya Orthopaedic Association puts in place mechanisms to develop local guidelines based on the local data and spearheaded by the orthopaedic fraternity.

REFERENCES

1. Virchow, R., Neuer fall von todlichen. Embolider lungenarterie. *Arch Pathol Anat*. 1856; **10**:225-228.
2. Paiement, G.D., Wessinger, S.J., Hughes, R. *et al.* Routine use of adjusted low-dose warfarin to prevent venous thromboembolism after total hip replacement. *J Bone Joint Surg [Am]*. 1993; **75-A**: 893-898.
3. THRIFT. Thromboembolic Risk Factors Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *Br Med J.* 1992; **305**: 567-574.
4. Coventry, M.B., Nolan, D.R. and Beckenbaugh, R.D. 'Delayed' prophylactic anticoagulation: A study of results and complications in 2012 total hip arthroplasties. *J Bone Joint Surg [Am]*. 1973; **55-A**: 1487-1492.
5. European Consensus Statement. Prevention of venous thromboembolism. London etc: Med-Orion Publishers, 1992.
6. Falck-Ytter, Y., Francis, C.W., Johanson, N.A. *et al*. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; **141**(2 Suppl): 278S.
7. Parvizi, J., Jacovides, C.L., Bican, O. *et al*. Is deep vein thrombosis a good proxy for pulmonary embolism? *J Arthroplasty*. 2010; **25** (6 Suppl):138-144.

8. Parvizi, J., Parmar, R., Raphael, J., *et al*. Proximal deep venous thrombosis and pulmonary embolus following total joint arthroplasty. *J Arthroplasty.* (2014), http://dx.doi.org/10.1016/j.arth.2014.04.023
9. Muller, S.D., Khaw, F.M., Morris, R. *et al.* Ulceration of the lower leg after total knee replacement. *J Bone Joint Surg [Br]*. 2001**; 83-B**: 1116-1118.
10. Browse, N.L., Clemenson, G. and Thomas, M.L. Is the postphlebitic leg always postphlebitic? Relation between phlebographic appearances of deep-vein thrombosis and late sequelae. *Brit Med J.* 1980; **281** (No. 6249): 1167-1170.
11. Warwick, D.J. and Whitehouse, S. Symptomatic venous thromboembolism after total knee. *J Bone Joint Surg [Br]*. 1997; **79-B**: 780-786.
12. Khaw, F.M., Moran, C. G., Pinder, I.M. *et al.* The incidence of fatal pulmonary embolism after knee replacement with no prophylactic anticoagulation. *J Bone Joint Surg [Br]*. 1993; **75-B**:940-941.
13. Kim, Y-H. and Kim, J-S. The incidence of deep vein thrombosis after cementless and cemented knee replacements. *J Bone Joint Surg [Br]*. 1990**; 72-B**: 779- 783.
14. Mohr, D.N., Silverstein, M.D., Ilstrup, D.M. *et al*. Venous thromboembolism associated with hip and knee arthroplasty: Current prophylactic practices and outcomes. *Mayo Clin Proc*. 1992; **67:** 861-870.
15. Stulberg, B.N., Insall, J.N., Williams, G.W. *et al.* Deep-vein thrombosis following total knee replacement: an analysis of six hundred and thirty-eight arthroplasties. *J Bone Joint Surg [Am]*. 1984; **66-A:** 194-201.
16. Jameson, S.S., Bottle, A., Malviya, A. *et al.* The impact of national guidelines for the prophylaxis of venous thromboembolism on the complications of arthroplasty of the lower limb. *J Bone Joint Surg Br.* 2010; **92**(1): 123-129.
17. Howie, C., Hunges, H. and Watts, A.C. Venous thromboembolism associated with hip and knee replacement over a ten-year period: a population-based study. *J Bone Joint Surg Br*. 2005; **87**(12):1675-1680.
18. Fender, D., Harper, W.M., Thompson, J.R. *et al*. Mortality and fatal pulmonary embolism after primary total hip replacement. Results from a regional hip register. *J Bone Joint Surg Br*. 1997; **79**(6):896-899.
19. Unwin, A.J., Jones, J.R. and Harries, W.J. Current UK opinion on thromboprophylaxis in orthopaedic surgery: its use in routine total hip and knee arthroplasty. *Ann R Coll Surg Engl.* 1995; **77**: 351-354.
20. Blom, A., Pattison, G., Whitehouse, S. *et al.* Early death following primary total hip arthroplasty: 1,727 procedures with mechanical thrombo-prophylaxis. *Acta Orthop*. 2006**; 77**(3): 347-350.
21. Warwick, D., Williams, M.H. and Bannister, G.C. Death and thromboembolic disease after total hip replacement. A series of 1162 cases with no routine chemical prophylaxis. *J Bone Joint Surg Br.* 1995; **77**(1):6-10.
22. Lee, Y.K., Chung, C.Y., Koo, K.H. *et al.* Conflict of interest in the assessment of thromboprophylaxis after total joint arthroplasty: a systematic review. *J Bone Joint Surg Am.* 2012; **94**(1):27-33.
23. Millar, J.A. Genesis of medical thromboprophylaxis guidelines in Australia: a need for transparency and standardisation in guideline development. *Med J Aust*. 2009; **190** (8): 446-450.
24. Norris, S.L., Holmer, H.K., Burda, B.U., *et al*. Conflict of interest policies for organizations producing a large number of clinical practice guidelines. *PloS one.* 2012**; 7**: e37413.
25. Burnett, R.S., Clohisy, J.C., Wright, R.W., *et al*. Failure of the American College of Chest Physicians-1A protocol for lovenox in clinical outcomes for thromboembolic prophylaxis. *J Arthroplasty*. 2007; **22**(3): 317-324.
26. Galat, D.D., McGovern, S.C., Hanssen, A.D., *et al*. Early return to surgery for evacuation of a postoperative hematoma after primary total knee arthroplasty. *J Bone Joint Surg Am*. 2008; **90**:2331-2336.
27. Parvizi, J., Ghanem, E., Joshi, A., *et al*. Does "excessive" anticoagulation predispose to periprosthetic infection? *J Arthroplasty*. 2007; **22**: 24-28.
28. Wang, Z., Anderson, F.A., Ward, M.M., *et al.* Association between surgical site infections and anticoagulant thromboprophylaxis following elective THA or TKA. Paper, Posters & Scientific Exhibits AR HIP 2013.
29. Barrack, R.L. First do no harm: A new approach to VTE prophylaxis. *J Trauma Orthop*. 2014; **2**(1):50-56.