Commentary on thromboprophylaxis in hip replacement surgery


Declaration of interest

I am not a haematologist, I am an orthopaedic surgeon, who has worked for the past 5 years with epidemiologists. I do not receive funds from the pharmaceutical industry—in fact my bias, if anything, lies in the opposite direction. I am deeply suspicious of research funded by the pharmaceutical industry, because my experience has been that, although the research is impeccably and honestly performed, the financial stakes are so high that bias can seriously contaminate the conclusions drawn from the research. I believe that the work on thromboprophylaxis has been a case in point. I shall confine my comments to research on thromboprophylaxis in total hip replacement, as I do not believe we know anything as yet about thromboprophylaxis in the fractured neck of femur. That is why the Oxford Clinical Trials Unit (of whom I am not a member) is currently running an international multi-centre study of aspirin versus placebo (the PEP Trial) on the fractured neck of femur. Their analysis of the literature suggests no evidence one way or the other for thromboprophylaxis and so it is ethical to perform a randomised controlled trial.

Comments

In total hip replacement, the incidence of deep vein thrombosis (DVT) appears to vary from 10% to over 80%, depending on how it is measured. Most of these are asymptomatic, and we do not know how many go on to produce a post-phlebitic limb.

Occasionally patients die suddenly after total hip replacement. This is a disaster. The idea of an elective operation ending in death is always a tragedy. We also know that much of the antagonism of orthopaedic surgeons to thromboprophylaxis is due to anxiety that it might cause excessive bleeding at surgery. A haematoma is a potential site for infection, the enemy of the joint replacement surgeon, and oozing at the time of cementing makes good cement technique difficult to obtain, so it may increase aseptic loosening and cause septic loosening.

When we first reviewed the policy for thromboprophylaxis in our own units some 6 years ago, it was clear that the literature was confused. What stuck in my mind, however, was the frequently quoted figure that if total hip replacements were not protected with thromboprophylaxis, between 2% and 5% of the patients would die of pulmonary embolus. The source of this "conventional wisdom", which is quoted at the beginning of almost every paper on the subject, is a paper by Coventry et al. (1974) on 62 total hip replacements, of whom 2 died. At the start of our research, we tried to discover whether we could assemble a bigger series, which would give us a better idea about this figure. Using the Oxford Record Linkage, we traced almost 10,000 primary total hip replacements performed in the late 1970s and early 1980s, when thromboprophylaxis was not being used (Seagroatt et al. 1991). During that time, the death rate up to 90 days was 9 per 1,000. If you compare that against an aged matched population, 3 of the 1,000 would have died anyway. Therefore the additional death rate was 6 per 1,000 from all causes. When we traced the post-mortem results, we found that the cause of death was given as pulmonary embolus in only 10% of such cases. We know that some of these patients did not receive a post-mortem and that, even if they did, post-mortem is not always reliable in giving the cause of death, but what was immediately clear was that the death rate from pulmonary embolus after total hip replacement in unprotected patients was much lower than was currently being quoted by pharmaceutical companies in papers extolling the virtues and need for their thromboprophylactic treatment. We have subsequently performed an opportunist meta-analysis to trace every paper in the world that has been published on the results of total hip replacement which states how many patients in the trial died post-operatively and the number of patients in the trial (Murray et al. 1995). We eventually found reports on over 100,000 patients. The death rate came out again at 3–4 per 1,000, and death from pulmonary embolus at less than 2 per thousand.

I have no problems with Dr Dahl's contention that deep vein thrombosis is common after total hip replacement. Nor do I have a problem with his contention that thromboprophylaxis reduces that rate of DVT. My problem is with the next question, which is "So what?" The pharmaceutical industry has performed a myriad of small, cheap trials of thromboprophylactic agents, using deep vein thrombosis as the
‘surrogate’ outcome measure, because they know they can demonstrate a significant reduction in DVT rate in a small number of patients, and use this to sell their products. Despite an extensive search of the literature, I find no evidence that reducing the rate of DVT after total hip replacement affects the overall death rate. This seems very puzzling as we have all been taught since we were medical students that deep vein thrombosis causes pulmonary embolus and big pulmonary emboli kill. I suspect this simplistic interpretation of the facts is fine for medical students and pharmaceutical companies but may not be actually true in clinical practice. What these myriads of trials have consistently failed to measure is the overall death rate and the complications of excessive bleeding, such as infection or aseptic loosening. The preoccupation of haematologists working in this field with DVT as an outcome measure may be because DVT is important to them or it may be the only outcome that they can use to provide their masters, the pharmaceutical industry, with statistically significant but clinically irrelevant results. If the number of lives which could be saved really is so small, we must also look very carefully at the complications, because any trial is now a cost/benefit analysis, not a simple ‘does it work or doesn’t it’? Until now, these complications have not been studied, because it was felt that the high death rate was overwhelmingly important. Now that we find that it is so low, any clinically relevant trial will not only have to be very large, but it must measure infection and a septic loosening rate, to give the whole picture of benefit versus disadvantage. It is quite clear that the cost of a trial, using proper outcome measures, rather than a selective set of surrogate outcome measures, would not be attractive to the pharmaceutical industry, because of the size and cost. The question then arises, if the research cannot or will not be done, should the pharmaceutical industry be allowed to market these products which have no proven benefit and which may be harmful (Prentice 1997). Certainly, at the moment, if you look at the percentage of orthopaedic surgeons who use thromboprophylaxis in each country, you are probably seeing a direct reflection of the gullibility of that community, and the extent to which they are captives of the pharmaceutical industry. It is certainly not ‘Evidence-based Medicine’.

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