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Combined pharmacological and mechanical prophylaxis for DVT following hip and knee arthroplasty

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Abstract Intermittent pneumatic compression (IPC) is an attractive method for prophylaxis of deep venous thromboembolism (DVT) because there is no risk of haemorrhagic complications. However, IPC has not been studied as thoroughly as other methods in orthopaedic and traumatologic surgery. We monitored 328 patients undergoing total hip or knee arthroplasty (THA, TKA) treated with combined pharmacological and mechanical prophylaxis or with pharmacological prophylaxis alone, with pre- and postoperative colour Doppler ultrasound. Prevalences of DVT after THA (4.0%) and TKA (3.2%) were similar, even if the absolute prevalence was lower in the groups given combined prophylaxis. IPC has an important role in preventing postoperative DVT in these patients and reduces the progression from post-thrombotic syndrome (PTS) to DVT.

Key words Mechanical prophylaxis • Deep venous thromboembolism • Hip and knee arthroplasty • Post-thrombotic syndrome

Introduction

Deep venous thromboembolism (DVT) is a potential complication of any kind of surgery (Table 1) [1]. In orthopaedic surgery, DVT is such a frequent occurrence that the recent International Consensus Conference [2] classified patients undergoing hip or knee arthroplasty as being at very high risk.

Aetiological factors in the development of DVT may be related to the patient [3, 4], disease [5, 6] or surgery [3, 7–11]. Each of these factors can be modified to a greater or lesser extent, and the incidence of DVT therefore varies according to each patient's specific situation. There is considerable variation in the figures given in the literature concerning the proportion of patients developing DVT after hip or knee arthroplasty, with or without prophylaxis, e.g. 5% and 85% respectively [7, 12]. This wide variation in incidence is probably related to the absence of any common language, as the various studies often use differing patient inclusion and exclusion criteria (age, morphotype, pre-existing disease) and differ greatly from each other in terms of type of surgery (e.g. hip prosthesis, knee prosthesis, cemented or uncemented), surgical approach, diagnostic studies used, prophylaxis given, if any, and rehabilitation regimen. Above all, the type of prophylaxis reported in the literature differs between studies, with different types of drugs and different forms of mechanical prophylaxis being used.

With regard to the problems of prophylaxis after orthopaedic surgery, in 1993 Khaw [13] used graduated compression elastic stockings, in 1994 Santori et al. [14] used

Table 1 DVT prevalence without prophylaxis in various surgical procedures and medical conditions. (From [1] with permission)

General surgery	25%
Removal of benign gynaecological tumours	14%
Removal of malignant gynaecological tumours	24%
Prostatectomy by urethral approach	8%
Prostatectomy by retroperitoneal approach	31%
Total knee arthroplasty	47%
Total hip arthroplasty	51%
Hip fracture	45%
Multiple trauma	50%
Neurosurgery	22%
Spinal column injury	35%
Advanced age (65 years)	9%
Myocardial infarction	17%
General medicine	22%
Stroke	56%

low-dose and adjusted-dose unfractionated heparin, in 1995 Spiro et al. [15] used warfarin, in 1996 Westrich and Sculco [16] used aspirin, while in 1998 Scarchilli and Pasquali Lasagni [17] reported results with defibrotide. In 1999, Blanchard et al. [18] and Tamir et al. [19] reported clinical trials with mechanial prophylaxis, which had already being used earlier by Santori et al. [14] and by Warwick and Whitehouse [20]. In the same year, Gross et al. [21] studied the efficacy of combined pharmacological and mechanical prophylaxes using warfarin or low molecular weight heparin and intermittent pneumatic compression (IPC), while Westrich et al. [22] studied a combination of aspirin and IPC. Various prophylactic regimes have been used in past studies: low and adjusted-dose heparins, compression stockings, IPC or combinations of these [23]. To further compare the efficacy of pharmacological and mechanical prophylaxes for DVT in patients undergoing hip and knee arthroplasty, we carried out a prospective randomised study. We measured the occurrence of post-thrombotic syndrome (PTS), before and after surgery, as well as that of DVT.

Materials and methods

The study enrolled 328 patients between September 1997 and October 2001. Of these, 176 (54%) underwent total hip arthroplasty (THA), while 152 (46%) had total knee arthroplasty (TKA). The approaches used were a straight lateral incision for THA and a midline longitudinal incision for TKA. Hip prostheses were cementless, while both components of knee prostheses were cemented. Subjects were asymptomatic for venous disease at the time of surgery, and had normal clinical examinations and laboratory studies (complete blood count, platelet count, prothrombin time, partial thromboplastin time, antithrombin III and fibrinogen) and negative family histories for coagulation disorders; preoperative colour Doppler ultrasound examinations of the veins were negative for DVT.

The ultrasound system used (Hewlett-Packard Sonos 1000, 7.5 MHz linear probe for mechanical scanning and 5 MHz pencil probe) also detected any venous insufficiency, which is a common risk factor before surgery. PTS involves vascular disorders in the form of venous insufficiency and dilatation with valvular insufficiency, which simulate post-thrombotic disease in the absence of any previous confirmed thrombotic event. Both legs were examined during the preoperative period and during the first 7–10 days after surgery, with the patient supine, scanning all vascular regions of the lower extremities in both the short (transverse) and long (longitudinal) axes, from the external iliac vein as far as the junction of the posterior and anterior tibial veins. Venous insufficiency was diagnosed if there was clear reflux of blood at baseline or during compression; however a positive standard reflex test suggested venous hypertension. A diagnosis of DVT was made if there was no blood flow and if there was a collateral circulation with direct visualisation of a thrombus and dilatation of the vein, which could therefore not be compressed.

Of the 176 patients undergoing THA, 116 (66%) were woman. Overall, the mean age of this group was 61.8 years. Of the 152 patients undergoing TKA, 129 (85%) were women. The mean age of this group was 67.5 years. Patients undergoing both procedures were randomized to one of two prophylaxis procedures:

– *Group A*. Patients were treated with low-molecular-weight heparin (nadroparin, 60 IU/kg day in one daily dose, from twelve hours before surgery to 30 days postoperative), and wore graduated compression stockings.
– *Group B*. Patients were treated with nadroparin (60 IU/kg day in one daily dose, from twelve hours before surgery to 30 days postoperative), wore graduated compression stockings and received IPC (23 h/day) immediately after surgery until the fourth day, when the patient could stand upright for longer.

All patients received active exercise therapy and walked with the help of two crutches or canes 3–4 days after surgery.

The IPC system used was a Novamedix A-V impulse system (Andover, Hants, England), fitted with a plantar pump delivering an exercise pressure of 130 mmHg, with one-second compressions and a cycle of three compressions per minute.

Pearson's chi-squared test was used for the statistical evaluation. A value of $p<0.005$ was considered significant.

Results

The 328 patients were divided into 4 groups based on surgical procedure and type of prophylaxis for DVT (Table 2).

In subjects who had THA and received pharmacological prophylaxis alone, preoperative colour Doppler ultrasonography revealed 12 cases of PTS (16.9%) (Table 2). Postoperatively, 11 cases of PTS were diagnosed (15.5%), including 8 who had already been diagnosed before surgery. Furthermore, there were 6 cases (8.4%) of DVT, four of which were progressions from PTS diagnosed preoperatively.

In subjects who had THA and received mechanical prophylaxis, 15 cases (14.3%) of PTS were diagnosed before surgery (Table 2). After arthroplasty, there were 17 cases (16.2%) of PTS, 15 of which had been diagnosed preoperatively and two of which occurred in patients who were originally negative. Only one case of DVT was diagnosed (0.9%), in a subject whose results had been completely normal before surgery. The frequencies of preoperative and postoperative PTS and DVT in two groups were significant different according to Pearson's chi-squared test (χ^2=38.6 (group A) vs. χ^2=51.4 (group B); $p<0.001$).

In patients who underwent TKA and received pharmacological prophylaxis alone, PTS was diagnosed preoperatively in 15 (19.7%) cases (Table 2). After surgery we recorded 21 cases (27.6%) of PTS, 10 of which had been diagnosed preoperatively and 11 of which occurred in patients with originally negative results. There were 3 cases (3.9%) of DVT, all resulting from the progression of preoperative PTS. In TKA patients who received mechanical prophylaxis, 18 cases (23.6%) of PTS were diagnosed preoperatively; after surgery, 23 cases of PTS (30.2%) were recorded, 16 of which had been diagnosed preoperatively, while 7 were in patients with negative results before surgery (Table 2). There were also 2 cases (2.6%) of DVT, both in patients with negative preoperative results. Differences in the frequencies of preoperative and postoperative PTS and DVT in two groups were again statistically significant according to the Pearson's chi-squared test (χ^2=21.2 (group A) vs. χ^2=34.0 (group B); $p<0.001$).

The prevalence of DVT in the entire study group was 3.7% (12 of 328 patients). The prevalence of DVT was significantly higher in subjects who underwent THA and received pharmacological prophylaxis alone, compared with subjects who received combined prophylaxis (8.4% vs. 0.9%; χ^2=6.35; $p<0.05$). In the TKA population, there was a higher prevalence of DVT in the group who received pharmacological prophylaxis alone than in those who received combined prophylaxis, without a significant difference (3.9% vs. 2.6%; χ^2=0.30). The difference between overall DVT prevalences in the two surgical groups was not significant (3.9% in THA vs. 3.3% in TKA). However, the prevalence of pre- and postoperative PTS was significantly higher in TKA patients (χ^2=8.75; $p<0.05$).

There was an increase in PTS prevalence during the postoperative period in all patients who underwent surgery, except for those in Group A of the THA population in which PTS was reduced with a simultaneous significant increase in DVT.

Table 2 Prevalence of venous insufficiency in 328 patients, before and after hip or knee replacement, by surgical procedure and type of prophylaxis: pharmacological prophylaxis alone (group A) or combined pharmacological and mechanical prophylaxes (group B)

	Preoperative	Postoperative	
	PTS	PTS	DVT
THA			
Group A (n=71)	12 (16.9)	11 (15.5)	6 (8.4)
Group B (n=105)	15 (14.3)	17 (16.2)	1 (0.9)
Total (n=176)	27 (15.3)	25 (15.9)	7 (4.0)
TKA			
Group A (n=76)	15 (19.7)	21 (27.6)	3 (3.9)
Group B (n=76)	18 (23.6)	23 (30.2)	2 (2.6)
Total (n=154)	33 (21.4)	44 (28.6)	5 (3.2)

PTS, post-thrombotic syndrome; *DVT*, deep vein thrombosis; *THA*, total hip arthroplasty; *TKA*, total knee arthroplasty

These data confirm that if patients who are to undergo surgery and who have significant chronic venous disease preoperatively are given only pharmacological prophylaxis, they will develop significantly higher levels of DVT than patients receiving combined prophylaxes.

Discussion

Hip and knee arthroplasties are associated with a high risk of developing DVT and pulmonary embolism (PE) [24–26]. Venous stasis, injury to the endothelium and release of tissular thromboplastin are common events during surgery; they are non-modifiable risk factors closely related to the surgery itself, which contribute to constitutional factors such as predisposition to thrombosis. If adequate prophylaxis is not given, the incidence of DVT after knee arthroplasty ranges from 40% to 84%, with a higher proportion of proximal DVT, which then contributes to PE (9%–20%) [24, 27]. Late sequelae of DVT are clinical problems in the form of chronic venous insufficiency in 50%–60% of patients with proximal DVT and in 30% of patients with distal DVT [28]. This venous insufficiency is usually secondary to a post-thrombotic event, but it is frequently a result of valvular insufficiency due to breakdown of the vein wall, leading to venous stasis. It is important to screen patients preoperatively for this disorder using colour Doppler ultrasonography, to establish whether there is a further risk factor for subjects who are candidates for joint replacement surgery. The possibility of reducing venous stasis postoperatively by using a mechanical pump was first tested by Gardner and Fox [29] in 1992, on the basis of experimental and clinical reports of a substantial increase in venous velocity and flow in the common femoral vein. A number of authors subsequently studied IPC as prophylaxis against DVT [13, 30–32]. Recently, Blanchard et al. [18] used phlebographic studies to show that prophylaxis with low-molecular-weight heparin (LMWH, nadroparin calcium) was superior to intermittent pneumatic compression alone in preventing DVT in subjects undergoing total knee arthroplasty. Beuhler et al. [33] used duplex ultrasonography screening of patients before discharge after hybrid hip arthroplasty and confirmed the high sensitivity, specificity and diagnostic accuracy of this method, especially in proximal DVT.

Our study in patients receiving pharmacological (nadroparin) or combined (nadroparin and IPC) prophylaxis for DVT after hip or knee arthroplasty shows first of all that the overall prevalence of postoperative DVT in the total population examined was 3.7%. There was a markedly lower incidence of DVT in patients who had received combined prophylaxis (0.9% in the THA population and 2.6% in the TKA population), compared to those who received pharmacological prophylaxis alone (8.4% in the THA group and 3.9% in the TKA group). In the TKA population, progression from PTS to DVT between the pre- and postoperative periods was more common, probably related to the use of a tourniquet on the proximal part of the thigh and to the fact that knee arthroplasty is more likely to damage local and regional vessels.

Clearly the strategy of using colour Doppler ultrasonography to monitor patients between the seventh and tenth postoperative days and administering LMWH until the thirtieth postoperative day means that patients can be discharged in complete peace of mind. We did not record any cases of pulmonary embolism. Beuhler et al. [33] described three general strategies for preventing thromboembolic disease after hip arthroplasty:

- No pharmacological prophylaxis after discharge from hospital and no inhospital screening;
- Extended pharmacological prophylaxis after discharge, with no screening before discharge;
- No pharmacological prophylaxis on discharge after negative screening.

It is clear that it is the last of these options which has produced the least number of complications. With regard to the first strategy, in the multicentre study by Colwell et al. [34] in 3000 subjects undergoing hip arthroplasty, treated with pharmacological prophylaxis (warfarin or LMWH) during their hospital stay and monitored for up to three months after surgery, symptomatic DVT was found in 2.6% of patients who had received warfarin and in 3.4% of patients who had received LMWH. With regard to the second strategy, in a study carried out by Paiement et al. [35] in 268 patients receiving prophylaxis with low-dose warfarin for 12 weeks after hip arthroplasty, there were no cases of pulmonary embolism. Lieberman et al. [36] studied 677 patients undergoing total hip arthroplasty and reported seven cases (1%) of pulmonary embolism despite using warfarin for a mean of 15 days after discharge. Colwell et al. [37], in a randomised study of 610 subjects undergoing hip arthroplasty and examined by phlebography, reported a 5% incidence of DVT in patients taking LMWH twice a day and 12% in those treated with calcium heparin at doses of 5000 IU three times a day. In addition, in 1998, Scarchilli and Pasquali Lasagni [17] studied 423 patients undergoing total knee arthroplasty and receiving extended pharmacological prophylaxis after discharge (defibrotide until the eighth postoperative day and then LMWH until the thirtieth postoperative day); there were 12 cases of DVT (2.8%).

An example of the third strategy is the retrospective study carried out by Pellegrini et al. [38] in 269 patients undergoing total hip arthroplasty who were discharged without any prophylaxis after negative venography done during their hospital stay; only 1.1% of the population had late

venous thromboembolic disease. Grady et al. [39] studied a population of 110 patients undergoing total knee arthroplasty who were given mechanical prophylaxis in hospital, and reported an incidence of 3.3% of late venous thromboembolism. Fauno et al. [40] carried out a prospective, randomised trial in 185 patients undergoing total knee arthroplasty, who were given pharmacological prophylaxis during hospitalisation (unfractionated heparin in 93 patients and LMWH in 92) and examined using ascending venography on postoperative days 7, 8 and 9; the prevalence of DVT in subjects who had received prophylaxis with unfractionated heparin was 27%, while in those treated with LMWH the prevalence was 23%. Beuhler et al.'s study [33] reported 1.5% thromboembolic disease during the first postoperative year in subjects undergoing hybrid total hip arthroplasty and receiving a prophylactic regimen consisting of intermittent pneumatic compression, aspirin and examination by colour Doppler ultrasonography before discharge, with no post-hospital prophylaxis in patients with negative results; the percentage of symptomatic proximal DVT revealed by post-operative diagnostic studies during hospitalisation was 11.3%. Another example of this strategy was reported by Wilson et al. [41], who studied 60 patients undergoing knee arthroplasty and receiving mechanical prophylaxis by intermittent pneumatic compression while in hospital, with post-operative screening by venography; the incidence of DVT in these patients was 50%.

In 1996, Westrich and Sculco [16] studied 122 patients scheduled to have total knee arthroplasty who received pharmacological prophylaxis (aspirin) or combined prophylaxis (pharmacological and mechanical); all patients were examined after surgery by venography and/or colour Doppler ultrasonography. When screening during hospitalisation was negative for DVT, the mechanical prophylaxis was stopped while the pharmacological prophylaxis was continued after discharge. The incidence of DVT in subjects receiving pharmacological prophylaxis was 59%, while the incidence in patients receiving combined prophylaxis was 27%.

In 1999, Blanchard et al. [18] studied 130 patients undergoing knee arthroplasty, 67 of whom received pharmacological prophylaxis with LMWH while 63 received mechanical prophylaxis. Only 108 patients were examined by phlebography 8–12 days postoperatively; there were 47 cases of DVT, 16 in patients treated with LMWH and 31 in patients receiving mechanical prophylaxis. Pharmacological prophylaxis was continued in all patients for 6–8 weeks after discharge.

The protocol which we used represents a "fourth way". It consisted of pharmacological prophylaxis (LMWH) and mechanical prophylaxis (IPC) during hospitalisation, with sonographic screening before discharge and extension of pharmacological prophylaxis after discharge until the thirtieth postoperative day. Immediate results were clearly positive, as cases of DVT were detected before discharge and treated with therapeutic doses of calcium heparin, leading to resolution of the thromboembolic disease.

The main conclusions of this clinical study carried out in patients undergoing hip or knee arthroplasty and treated with pharmacological prophylaxis alone (low molecular weight heparin) or combined prophylaxis (pharmacological and mechanical) are:

- After hip and knee arthroplasty, the prevalence of DVT diagnosed by colour Doppler ultrasonography was similar in both treated populations (3.9% and 3.3%, respectively); the prevalence of PST was significantly higher in TKA population.
- The absolute prevalence of DVT was lower in the groups given combined prophylaxis, with significative difference only for THA patients.
- The frequency of preoperative and postoperative PTS and DVT were significantly different between groups receiving different prophylactic regimes.
- The prevalence of PTS was significantly higher in patients undergoing knee arthroplasty; this agrees with the results of our previous studies [42, 43] on the prevalence of venous insufficiency in subjects suffering from joint disorders of the lower extremities and particularly of the knee;
- The progression from PTS to DVT was lower in patients receiving combined prophylaxis, even though there was a higher percentage of at-risk subjects in these groups.

This study shows that intermittent pneumatic compression has an important role in preventing DVT and lower extremity oedema in patients undergoing THA and TKA. Subjects who are found preoperatively to be at risk of developing DVT because of venous disease (e.g. PTS) derive more benefit from the described strategy, as it is a protective regimen which improves the results obtained using pharmacological prophylaxis and reduces postoperative complications.

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