B. Borghi · A. Casati

Thromboembolic complications after total hip replacement

Accepted: 29 September 2001 / Published online: 15 January 2002
© Springer-Verlag 2002

Abstract We conducted a retrospective analysis of 1,640 consecutive patients undergoing total hip replacement between 1990 and 1997 under general anesthesia and receiving three different prophylactic regimens. The thromboembolic prophylaxis consisted of low-dose unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or indobufen (INDO). Postoperatively, occurrence of symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) was recorded during the first 30 days after surgery and at a routine follow-up visit. Symptomatic DVT was diagnosed in 16 patients (0.9%), while PE occurred in eight patients (0.5%). Patients receiving UFH showed a higher incidence of symptomatic DVT (3.6%) than those patients receiving either LMWH (1.3%) or INDO (0.3%), with an odds ratio for developing symptomatic DVT when receiving UFH versus other treatments of 6.05 (95% confidence intervals [CI_{95%}]: 3.63–10.07) ($P=0.001$). On the other hand, the diagnosis of PE was more frequently seen in patients receiving cemented hip arthroplasty (2.4%) than in patients receiving uncemented hip arthroplasty (0.34%), with an odds ratio of 3.185 (CI_{95%}: 2.01–5.02) ($P=0.05$).

Resume Nous avons conduit une analyse rétrospective de 1640 patients consécutifs opérés pour arthroplastie totale de la hanche entre 1990 et 1997, sous anesthésie générale, et recevant trois régimes différents de prophylaxie thromboembolique : soit héparine fractionnée à basse dose, soit héparine de bas poids moléculaire poids moléculaire soit indobufen. Après l'intervention une thrombose profonde symptomatique ou une embolie pulmonaire a été recherchée pendant les premiers 30 jours après la chirurgie, et à une visite habituelle de routine. La thrombose veineuse profonde symptomatique a été diagnostiquée chez 16 patients (0.9%), pendant que l'embolie pulmonaire s'est produite chez 8 patients (0.5%). Les patients qui recevaient de l'héparine fractionnée ont montré une plus haute fréquence de thrombose veineuse profonde symptomatique (3.6%) que ceux patients qui recevaient de l'héparine de bas poids moléculaire (1.3%) ou de l'indobufen (0.3%), avec une majoration du risque de 6.05 (intervalle de la confiance de 95% [CI_{95%}]: 3.63–10.07) ($P=0.001$). Le diagnostic d'embolie pulmonaire a été fait plus fréquemment chez les patients qui ont eu une arthroplastie cimentée (2.4%) que chez ceux patients qui ont eu une arthroplastie non-cimentée (0.34%), avec une majoration du risque de 3.185 (CI_{95%}: 2.01–5.02) ($P=0.05$).

The authors wrote on behalf of the Rizzoli Study Group on Orthopaedic Anaesthesia, Dept. of Anaesthesiology, IRCCS Rizzoli Orthopaedic Institute, Bologna, Italy. Participating physicians were: G.C. Caroli, E. Pignotti, M. Montebugnoli, N. de Simone, K. Elmar, U. Righi, A.M. Laguardia, S. Bugamelli, F. Cataldi, R. Ranocchi, M.A. Feoli, M. Painsi Bonfati, S. Baroncini, L. Lorenzini, and L. Castellazzi

B. Borghi
Department of Anaesthesiology,
IRCCS Rizzoli Orthopaedic Institute, Bologna, Italy

A. Casati (✉)
Vita-Salute University of Milan, Department of Anaesthesiology,
IRCCS H. San Raffaele, Via Olgettina 60, 20132 Milan, Italy
e-mail: casati.andrea@hsr.it
Tel.: +390-22-6432656, Fax: +390-22-6412823

Introduction

Since 1990 a large database was recorded at our institution for quality control of an integrated auto-transfusion regimen, including information from nearly 3,000 patients undergoing major orthopedic surgery [5, 6]. The database includes data on thromboembolic prophylaxis and symptomatic thromboembolic complications up to 30 days after surgery. In the present investigation these data were analyzed to evaluate the incidence of symptomatic thromboembolic complications in a large number of consecutive patients undergoing total hip arthroplasty.

Table 1 Dose regimens for thromboembolic prophylaxis used in patients according to their bodyweight. *UFH* low-dose unfractionated heparin, *LMWH* low-molecular-weight heparin, *INDO* indobufen

UFH		LMWH		INDO	
Weight (kg)	Dose (units)	Weight (kg)	Dose (units)	Weight (kg)	Dose (mg)
≤70	5000×2	≤65	2000	≤55	100×2
>70	5000×3	>65	4000	>55	200×2

Table 2 Anthropometric parameters, duration of surgery, use of bone cementation, and occurrence of thromboembolic complications, including deep vein thrombosis (*DVT*) and pulmonary embolism (*PE*) in patients receiving either low-molecular-weight

heparin (*LMWH*), indobufen (*INDO*), or low-dose unfractionated heparin (*UFH*) as thromboembolic prophylaxis after total hip arthroplasty. (Data are presented as mean ± SD or as number [%])

	LMWH (n=457)	INDO (n=991)	UFH (n=192)
Age (years)	61±12	60±12	62±11
Weight (kg)	69±11	67±12	67±11
Height (cm)	163±9	161±9	160±9
Sex (male/female)	166/291	372/619	59/133
Duration of surgery (min)	113±34	113±37	116±37
Bone cementation	26 (5.6%)	44 (4.4%)	11 (5.7%)
Thromboembolic complications	7 (1.5%)	10 (1.0%)	*7 (3.6%)
DVT	6 (1.3%)	3 (0.3%)	**7 (3.6%)
PE	1 (0.2%)	7 (0.7%)	0 (/)

* $P < 0.05$ and ** $P < 0.001$ as compared with the two other groups

Materials and methods

We analyzed our database for consecutive patients undergoing total hip replacement from January 1990 to December 1997 [5]. Data concerning the anesthetic technique, thromboembolic prophylaxis, duration of hospital stay, and occurrence of symptomatic thromboembolic complications were recorded up to 30 days after surgery. We considered 1,640 patients receiving elective total hip replacement under general anesthesia. All patients came from the same orthopedic department and were treated by the same surgical team.

Thromboembolic prophylaxis consisted of low-dose unfractionated heparin (*UFH*), low-molecular-weight heparin (*LMWH*), or indobufen (*INDO*), and did not start until after surgery. Dose regimens are shown in Table 1. From 1990 through 1993 the prophylaxis consisted of either low-dose *UFH* or *INDO* according to the choice of the anesthesiologist taking care of the patient. From 1994 *LMWH* was introduced in the department instead of *UFH*.

After surgery patients were evaluated on a daily basis to assess the presence of symptoms or clinical signs of thromboembolic complications, including deep venous thrombosis (*DVT*) and pulmonary embolism (*PE*). Patients in whom *DVT* was suspected underwent ascending venography while patients with clinical features suggestive of pulmonary embolism were scheduled to undergo ventilation-perfusion lung scanning. A normal perfusion scan was considered to rule out *PE* whereas a scan indicating one or more segmental perfusion defects with relatively preserved ventilation was considered to confirm *PE*. If the diagnosis of either *DVT* or *PE* was confirmed standard intravenous heparin was given according to routine protocol [17] and patients were followed until resolution. A follow-up visit was performed in all patients 1 month after hospital discharge [5].

Statistical analysis

Statistical analysis was performed using the program Systat 7.0 (SPSS Inc, Chicago, IL). Normal distribution of considered data was first evaluated using the Kolmogorov-Smirnow test. Categorical variables were analyzed using the contingency table analysis with Yates corrected chi-square or Fisher's exact tests as indicated. Continuous variables were assessed using the analysis of vari-

ance with Tukey's test for multiple comparisons. The Student's *t*-test with Bonferroni's correction was used as indicated. Multiple regression analysis was also used as indicated. Duration of hospital stay after surgery was evaluated by a log-rank test using the Kaplan-Meier estimation of survival analysis. Results are presented as mean ± standard deviation or count (percentage). A value of *P* equal to or lower than 0.05 was considered significant.

Results

Mean age of patients was 60±12 years, mean weight 68±11 kg, and mean height 161±9 cm. Bone cementation was performed in 81 patients. The surgical procedure lasted 113±36 min., and mean hospital stay was 11±5 days. Seven patients (0.4%) died during the first month after surgery: one died before hospital discharge due to a massive acute *PE*, two due to surgery-related hemorrhagic complications, three due to acute myocardial infarction, and one due to acute pneumonitis.

Thromboembolic complications were suspected in 42 patients (2.5%): 28 of them (1.7%) received contrast venography for suspected *DVT* while 14 (0.8%) received pulmonary perfusion and ventilation scintigraphy for suspected *PE*. *DVT* was confirmed by ascending venography in 16 patients (0.9%) (in one patient this complication occurred after hospital discharge); *PE* was diagnosed with pulmonary scintigraphy in eight patients (0.5%) (in two the diagnosis was made after hospital discharge).

Thromboembolic prophylaxis was performed with subcutaneous low-dose heparin in 192 patients (12%), with *LMWH* in 457 (28%), and with *INDO* in 991 (60%). No differences were reported among the three prophylactic regimens with respect to demography, duration of surgical procedure, and use of bone cementation during surgery (Table 2). However, patients receiving *UFH* showed a higher

Fig. 1 Trend of hemoglobin concentration during the first 5 days after surgery with respect to the type of thromboembolic prophylaxis in patients receiving either low-molecular-weight heparin (LMWH), indobufen (INDO), or low-dose unfractionated heparin (UFH) as thromboembolic prophylaxis after total hip arthroplasty. (Data are presented as mean $\pm$ SD)

Fig. 2 Kaplan-Meier estimation of survival analysis for patient discharge from the orthopedic ward. Percentage of patients present in the orthopedic ward receiving either low-molecular-weight heparin (LMWH), indobufen (INDO), or low dose unfractionated heparin (UFH) as thromboembolic prophylaxis after total hip arthroplasty. Discharge from the orthopedic ward constituted the response variable for the Kaplan-Meier survival analysis for the patients concerned. The log-rank curves representing the three groups are significantly different ($P=0.0005$).

incidence of DVT than those receiving either LMWH or INDO (Table 2), with an odds ratio for developing DVT of 6.05 (95% confidence intervals [$CI_{95\%}$]: 3.63–10.07) when receiving UFH versus the other treatments ($P=0.001$). On the other hand, diagnosis of PE was more frequently associated with the use of bone cementation during surgery (incidence of PE: 2.4%) than in patients receiving uncemented hip arthroplasty (incidence of PE: 0.34%), with an odds ratio of 3.185 ($CI_{95\%}$: 2.01–5.02) ($P=0.05$).

No differences in hemoglobin concentration were reported according to the prophylactic regimen during the first 5 days after surgery (Fig. 1). Fig. 2 shows the log-rank curves describing the duration of hospital stay after surgery according to the Kaplan-Meier method: mean hospital stay was 11.3 days with low-molecular-weight heparin (25th–75th percentiles: 8–13 days), 11.6 days with INDO (25th–75th percentiles: 8–13 days), and 13.5 days with UFH (25th–75th percentiles: 9–15 days) ($P=0.0005$).

Discussion

Results of this observational study on 1,640 consecutive patients receiving elective total hip arthroplasty showed an overall incidence of thromboembolic complications of nearly 1.4%, with an incidence of DVT of 0.9% and an incidence of PE of 0.5%. Interestingly, thromboembolic prophylaxis with UFH was associated with a nearly six-fold higher risk for DVT as compared with low-molecular-weight heparin or INDO, while intraoperative use of bone cementation was associated with a three-fold higher risk for perioperative PE.

It is now the current opinion that ascending venography should be performed in all patients in order to disclose all cases of thrombi in the veins [11, 15, 17], while in the present investigation ascending venography and pulmonary scintiphotography were performed based on clinical suspicion of thromboembolic complication. This can be considered as a major shortcoming of the study, and probably accounts for an underestimation of the actual incidence of thromboembolic complications in studied patients. Agnelli and colleagues [1], evaluating the efficacy and safety of enoxaparin in conjunction with the use of compression stockings in neurosurgical patients, reported DVT in up to 17% of patients. However, in a large observational study including 1,492 hip arthroplasties other authors reported a 1% incidence of symptomatic DVT [18] similar to that observed in our investigation. White and colleagues [19], evaluating the incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty, reported a cumulative incidence of DVT within 3 months after surgery of about 2.4%; in half of those cases diagnosis was made after hospital discharge. Similar findings were also reported in a multiinstitutional cohort study of the Canadian Collaborative Group [11], which reported symptomatic thromboembolic events ranging from 3.3% to 5% of cases, with an incidence of symptomatic PE of 0.15%. These values are markedly lower than those reported in patients undergoing elective hip arthroplasty without prophylaxis, in whom the reported frequency of fatal PE is as high as 3% [8].

Interestingly, the use of LMWH or INDO prophylaxis was associated with a reduced risk for developing symptomatic thromboembolic events. Similar results have been reported in a meta-analysis of various randomized clinical trials by Palmer and colleagues [16], who demonstrated that LMWH is significantly superior both to UFH and warfarin in the prevention of DVT in orthopedic patients. In this meta-analysis the use of low molecular weight heparin rather than low-dose UFH was associated with a relative risk for DVT of 0.76 (95% CI 0.6–0.91).

INDO is an inhibitor of platelet aggregation blocking the conversion of arachidonic acid to cyclic endoperoxides [7, 12]. Antiplatelet agents, particularly aspirin, are widely used in patients with cardiac, cerebral, and peripheral vascular disease [3, 9], and also provide some positive effects in the prevention of DVT [4, 10, 18]. However, although meta-analyses indicated that aspirin decreases the frequency of venous thrombosis following

general or orthopedic surgery, this reduction is less effective than that obtained with other agents [14]. For this reason aspirin is not recommended to prevent venous thrombosis in high-risk patients [2]. Nonetheless, results of this observational study demonstrated that, in orthopedic patients undergoing major joint replacement, INDO is as effective as LMWH in preventing thromboembolic events, suggesting that the perioperative production of endoperoxides could be an important mechanism of venous thrombosis after major joint replacement.

Patients receiving UFH also showed a delayed hospital discharge as compared with the two other treatments. Because of the study design we cannot infer a cause-effect relationship; however, since no other differences were reported between the three groups, it seems reasonable that the explanation for longer hospital stay of patients receiving UFH might be related to the increased incidence of complications as compared with the other two treatments.

Even though a small proportion of patients received bone cementation during surgery the use of this surgical technique was associated with a higher risk for PE. Animal studies demonstrated that marked amounts of emboli obstructed the pulmonary vessels during bone cementation, and marrow elements were the primary constituents of the emboli [13]. Accordingly, the advantages of bone cementation to minimize prosthesis dislocation should be always balanced with the disadvantages of an increased risk for perioperative pulmonary impairment due to the cement implantation syndrome.

In conclusion, results from this large observational study confirmed that routine use of thromboembolic prophylaxis minimizes the incidence of symptomatic thromboembolic complications in orthopedic patients receiving total hip arthroplasty under balanced general anesthesia; however, LMWH or INDO rather than UFH should be advocated, as they are associated with significant reduction in risk for thromboembolic complications.

Acknowledgments This study was supported by a grant from the IRCCS Istituti Ortopedici Rizzoli, Bologna. Authors thank Dr Paola Garancini (Department of Biostatistics, IRCCS San Raffaele Hospital) for her helpful suggestion in doing statistical analysis, as well as the staff of anesthesia and ward nurses (Istituti Ortopedici Rizzoli) without whose help and cooperation this study would not have been possible.

References

1. Agnelli G, Piovella F, Buoncristiani P, et al (1998) Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. *New Engl J Med* 339:80–85
2. Antiplatelet Trialists' Collaboration (1994) Collaborative overview of randomized trials of antiplatelet therapy – III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *Br Med J* 308:235–246
3. Belcaro G, Errichi BM, Laurora G, et al (1989) Chronic treatment of vascular diseases with indobufen. *Minerva Cardioangiolog* 37:241–450
4. Belcaro G, Errichi BM, de Simone P. (1993) Prevention of recurrent deep venous thrombosis with indobufen. A 3-year follow-up study using color duplex scanning. *Angiology* 44: 328–331
5. Borghi B, Casati A. (2000) Incidence and risk factors for homologous blood transfusion during major orthopaedic surgery using an integrated autotrasfusion regimen. *Eur J Anaesthesiol* 17:411–417
6. Borghi B, Pignotti E, Montebugnoli M, et al (1997) Autotrasfusion in major orthopaedic surgery: experience with 1785 patients. *Br J Anaesth* 79:662–664
7. Cattaneo M, Bevilacqua C, Lecchi A, et al (1987) In vitro and ex vivo effects of indobufen on human platelets aggregation, the release reaction and thromboxane B₂ production. *Haemostasis* 17:293–300
8. Coventry MB, Nolan DR, Beckenbaugh RD. (1973) Delayed prophylactic anticoagulation: a study of results and complications in 2012 total hip arthroplasties. *J Bone Joint Surg [Am]* 55:1487–1492
9. Fornaro G, Rossi P, Mantica PG, et al (1993) Indobufen in the prevention of thromboembolic complications in patients with heart disease. A randomized, placebo-controlled, double-blind study. *Circulation* 87:162–164
10. Harris WH, Salzman EW, Athanasoulis CA, et al (1977) Aspirin prophylaxis of venous thromboembolism after total hip replacement. *New Eng J Med* 297:1246–1247
11. Leclerc JR, Gant M, Hirsh J, Geerts WH, Ginsberg JS. (1998) The incidence of symptomatic venous thromboembolism during and after prophylaxis with enoxaparin: a multi-institutional cohort study of patients who underwent hip or knee surgery. Canadian Collaborative Group. *Arch Intern Med* 158:873–878
12. Mannucci LM, Maderna P, Colli S, et al (1987) Indobufen as a potent inhibitor of whole blood aggregation in patients with high atherosclerotic risk. *Thromb Res* 48:417–426
13. Markel DC, Femino JE, Farkas P, Markel SF (1999) Analysis of lower extremity embolic material after total knee arthroplasty in a canine model. *J Arthroplasty* 14: 227–232
14. Morris GK, Mitchell JRA (1977) Preventing venous thromboembolism in elderly patients with hip fractures: studies of low dose heparin, dypiridamole, aspirin, and flubiprofen. *Br Med J* 1:535–536
15. Paiement GD, Wessinger S, Harris WH (1987) Survey of prophylaxis against venous thromboembolism in adults undergoing hip surgery. *Clin Orthop* 223:188–193
16. Palmer AJ, Copenhagen K, Kirchhof B, Weber U, Bergemann R (1997) Efficacy and safety of low molecular weight heparin, unfractionated heparin and warfarin for thromboembolism prophylaxis in orthopaedic surgery: a meta-analysis of randomised clinical trials. *Haemostasis* 27:75–84
17. Pineo GF, Hull RD (1996) Prevention and treatment of venous thromboembolism. *Drugs* 52:71–92
18. Sarmiento A, Goswami D (1999) Thromboembolic prophylaxis with use of aspirin, exercise, and graded elastic stockings or intermittent compression devices in patients managed with total hip arthroplasty. *J Bone Joint Surg [Am]* 81:339–346
19. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W (1998) Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med* 158: 1525–1531