A Comparative Analysis of Warfarin and Low-dose Heparin as Thromboembolism Prophylaxis in Total Hip Replacement Patients

MERRILL A. RITTER, M.D., COLIN W. HAMILTON, M.D.

Warfarin, low-dose heparin, or a combination of low-dose heparin and hydrocortisone was administered to 300 patients undergoing total hip replacement. The lowest incidence of thromboembolic (5 per cent) was attained with Warfarin. Further investigation into the method of administration of low-dose heparin is necessary before it can be used effectively as thromboembolism prophylaxis in total hip replacement patients. The addition of hydrocortisone was not found useful.

Department of Orthopaedic Surgery, Indiana University Medical Center, 1100 West Michigan Street, Indianapolis, Indiana

PULMONARY embolism has been long recognized as a tragic complication of hospitalized patients. Most often this complication presents without clinical evidence of antecedent thrombophlebitis, and the episode is unheralded by clinical signs and symptoms.

The introduction of modern reliable techniques which detect the presence of almost all thromboses in the lower extremities, including the "silent" ones, has complemented the earlier necropsy work[41,43,46] Using the ^{125}I-labeled fibrinogen test, authors have determined the incidence of deep vein thrombosis to be 24 per cent,[34] in their patients over 40 years old not prophylactically treated, 31 per cent,[38] 41 per cent,[50] 42 per cent,[18] 44 per cent[16] and 56 per cent[29] following major abdominal surgery. A higher incidence of thrombosis is generally reported in elderly patients, in patients with a history of thromboembolism, and in those patients undergoing extensive surgery.[16,26]

^{125}I-labeled fibrinogen and venography techniques have been used to establish the incidence of deep venous thrombosis as greater than 45 per cent in patients who have undergone fixation of fractures of the proximal femur.[7,14,19] However, clinically manifest thromboembolic complications in hip fracture surgery patients have been reported to be considerably less frequent, ranging in incidence from a low of 15 per cent[48] to a high of 39.3 per cent.[42] Evarts and Feil[13] performed venograms on 56 postoperative elective hip surgery patients and found 54 per cent to be positive for thrombosis.

Some papers have presented large groups of hip arthroplasty patients who received no thromboembolism prophylactic treatment, other than the usual conservative measures (Table 1 and 2). Many authors have expressed their dissatisfaction with the strictly clinical appraisal of deep vein thrombosis, noting that the frequency of thrombophlebitis found in a group of hospitalized patients is somewhat related to how vigorously this complication is sought. If we compare Table 1, hip arthroplasty series in which no patients received thromboembolism prophylaxis, with Table 2, controls in hip arthroplasty series where thromboembolism prophylactic medications were used, it is apparent that the series in Table 1 have a much lower incidence of reported thromboembolic complications than the series in Table 2. A possible explanation for this fact may be that the authors in Table 2 followed their control patients for evidence of thromboembolic complications much more carefully than those of Table 1, because they were interested in comparing their control patients with patients undergoing thromboembolic prophylaxis. Therefore, we consider the incidence of thrombophlebitis, as detected by clinical examination in untreated hip arthroplasty patients, is between 4

Submitted for publication January 27, 1975.

Reprint requests: Merrill A. Ritter, M.D., 1815 N. Capitol Avenue, Suite 214, Indianapolis, Indiana 46202.

TABLE 1. *Hip Arthroplasty Series in Which There Was No Thromboembolism Prophylaxis Employed.*

	Ring[37] 1968	Johnston & Larson[25] 1969	Patterson & Brown[35] 1972	Evanski et al.[10] 1973	Langenskiold & Paavilainen[30] 1973	Maczynski et al.[32] 1973
Procedure	THR	THR	THR	THR	THR	THR
Total	128	543	368	102	116	216
% Phlebitis	2.3%	5.8%	6.0%	2.9%	0.9%	3.7%
% PE	0.8%	3.6%	1.4%	1.4%	0.0%	4.6%

and 34 per cent and the incidence of pulmonary embolism between 4 and 10 per cent.

Because deep venous thrombosis has been shown to be such a common and often serious postoperative complication of hip arthroplasty patients, the total hip replacement patients at the Indiana University Medical Center were subjected to several methods of aggressive thromboembolism prophylaxis. The relative incidence of thromboembolic disease with each form of prophylaxis was then studied.

Materials and Methods

Three hundred eighty consecutive total hip replacement arthroplasties of the McKee-Farrar, Müller and Charnley design were carried out on 300 patients at the Indiana University Medical Center. The 80 patients who underwent bilateral replacements (26.7%) had both procedures performed concurrently. All operative procedures were either performed by, or strictly supervised by, a single physician (M.A.R.), who also directed their postoperative care. A nearly identical pre-and postoperative regimen was followed in each patient. The operative procedure varied little, with transposition of the greater trochanter and the use of two hemovac drains 24 to 48 hours postoperative in each case. The usual postoperative measures to prevent venous stasis in the lower extremities were employed. At the conclusion of each operation, both lower extremities were wrapped with compressive bandages from the toes to the hips, which were replaced by thigh length antiembolic stockings within a few days. During the first two postoperative days, the patients were placed at bed rest in a mild Trendelenberg position and function of their calf and thigh musculature encouraged. On the third postoperative day, the vast majority of patients were in acceptable medical condition to be sent to the Physical Therapy Department for tilt-table standing, progressing to ambulation with a walker or crutches as quickly as possible. As may be expected, the patients who underwent bilateral replacement required more time for gait training in order to become functionally ambulatory. Their average duration of hospital stay was 21 days compared to 14 days for the unilateral replacement patients.

Four schemes of thromboembolism prophylaxis were used consecutively in this series. The Group I patient (108 cases) received 15 mg sodium Warfarin on the night of surgery. No Warfarin was given on the first postoperative day, but commencing on the second day, daily doses were given, based on the results of the daily prothrombin time test, with an effort to maintain the prothrombin time at twice the control value in seconds. The anticoagulant was continued throughout the duration of the hospitalization and tapered off over a two to three day period prior to discharge.

Group II patients (31 cases) received low-dose ("minidose") heparin as recommended by Kakkar et al.[27] and others.[11,34] The Group II patients received 5,000 international units (IU) of sodium (lung) heparin subcutaneously two hours before surgery and then every 12 hours postoperatively, commencing 7 to 9 hours after surgery. The differences in this regimen from that of Kakkar was that these patients received their second dose of minidose heparin 7 to 9 hours postoperatively, instead of the 24 hours postoperatively, and they were maintained on it until discharge, instead of only 5 days. Because of excessive intraoperative and postoperative hemorrhage in this group of patients, it was not considered reasonable to continue the series after 31 patients.

Group III patients (71 cases) were treated identically to Group II patients with the exception that the minidose heparin was administered 8 hours, instead of 2 hours, preoperatively.

TABLE 2. *The Control Series in Which Thromboembolism Prophylaxis Was Studied in Hip Arthroplasty Patients.*

	Harris et al.[20] 1967	Wilson et al.[51] 1972	Ruthermel et al.[39] 1973	Coventry et al.[5] 1973	Lazanski[31]
Procedure	CUP	THR	THR	THR	THR
Total	67	49	60	58	81
% Phlebitis	34.3%	14.3%	10.0%	3.4%	3.7%
% PE	10.4%	4.1%	6.7%	5.2%	6.2%

TABLE 3. *The fractions represent the number of patients with that complication/number of patients in the group. The columns marked "P.E. and/or Phlebitis" represent the total number of patients in the group with thromboembolic complications and this number does not necessarily equal the arithmetic sum of patients in the "P.E." column and the "Phlebitis" column because some patients had both pulmonary embolism and phlebitis. Groups II, III and IV used low-dose heparin (LDH) alone or with hydrocortisone (HC).*

	UNILATERAL			BILATERAL			ALL PATIENTS		
	P.E.	Phlebitis	P.E. &/or Phlebitis	P.E.	Phlebitis	P.E. &/or Phlebitis	P.E.	Phlebitis	P.E. &/or Phlebitis
GROUP I (Warfarin-108 pts)	0/78 (0%)	1/78 (1.3%)	1/78 (1.3%)	1/30 (3.3%)	3/30 (10.0%)	4/30 (13.3%)	1/108 (0.9%)	4/108 (3.7%)	5/108 (4.6%)
GROUP II (LDH 2 h preop-31 pts)	1/23 (4.3%)	3/23 (13.0%)	3/23 (13.0%)	1/8 (12.5%)	0/8 (0%)	1/8 (12.5%)	2/31 (6.5%)	3/31 (9.7%)	4/31 (12.9%)
GROUP III (LDH 8 h preop-71 pts)	2/53 (3.8%)	4/53 (7.5%)	4/53 (7.5%)	2/18 (11.1%)	2/18 (11.1%)	3/18 (16.7%)	4/71 (5.6%)	6/71 (8.4%)	7/71 (9.9%)
GROUP IV (LDH 8 h preop-90 pts) + H.C.	0/66 (0%)	6/66 (9.1%)	6/66 (9.1%)	2/24 (8.3%)	2/24 (8.3%)	3/24 (12.5%)	2/90 (2.2%)	8/90 (8.9%)	9/90 (10.0%)

Group IV (90 cases) was identical to Group III except that in addition to minidose heparin, hydrocortisone phosphate 100 mg was administered intramuscularly three times daily one day preoperatively, on the day of operation, and on the first postoperative day.

These four groups were considered quite similar, and, therefore, comparable, as there was a nearly equal percentage of bilateral total hip replacement in each group, with the smallest percentage of bilateral cases in Group III (25%) and the largest in Group I (28%). Because of the known high incidence of thromboembolic complications in hip arthroplasty patients, it was not considered justifiable to include a control group of patients in this study who received no thromboembolic prophylaxis.

In evaluating these patients, thrombophlebitis was detected only by clinical means, and the classical signs of calf tenderness, warmth, edema, Homan's sign, and fever were sought. If a diagnosis of probable mild thrombophlebitis could be made with only one or two of the above signs present for several days, the case was considered a thromboembolic complication. Therefore, many of the cases of phlebitis reported here were quite mild. Also included in the study were cases of thrombophlebitis discovered in outpatients 3 to 6 weeks postoperatively. Pulmonary embolism was detected only after clinical symptoms and signs such as tachycardia, tachypnea, pleuritic chest pain, hemoptysis, and pleural friction rub became evident. All patients suspected to have sustained an embolism were subjected to routine laboratory investigation including electrocardiogram, chest roentgenogram, blood chemistry and enzyme determinations, arterial blood gas determinations, and lung scan to verify the diagnosis. In confirmed cases, appropriate treatment, usually consisting of anticoagulation with intravenous heparin, was promptly initiated.

An attempt was made to compare the amount of blood lost in the four groups of patients. The extensive laboratory work necessary to quantitate exactly the blood lost by each patient was not performed. Instead the total amount of blood transfused to each patient was tabulated. Although this method of estimating blood loss was rather imprecise, most patients were transfused to a hematocrit of approximately 30 per cent, and the blood given to those patients who had extensive postoperative bleeding was included in the tabulation.

Results

A compilation of the thromboembolic complications in each group appears in Table 3. The lowest incidence of thromboembolic complications occurred in Group I with an incidence of 4.6 per cent, considering unilaterally and bilaterally operated patients together. The incidence of both thrombophlebitis and pulmonary embolism was lower in Group I than any other group. Although the overall incidence of thromboembolic complications was higher in Groups II, III and IV with rates of 12.0 per cent, 9.9 per cent, and 10 per cent respectively, only the patients in Group II had a higher than Group I incidence of thromboembolic phenomena that was statistically significant ($P<0.05$) higher frequency of thrombophlebitis than the Group I patients.

In comparing bilaterally operated patients alone (only 80 patients), no significant difference was found in the incidence of phlebitis or embolism in the four groups.

The frequency of thromboembolic complications in the bilaterally operated patients was compared to the unilaterally operated patients in each group. The total incidence of thromboembolism was greater in the bilaterally operated patients in all groups except Group II. The incidence of phlebitis and total thromboembolic complications was significantly greater ($P<0.05$) in the bilaterally operated patients of Group I only. The incidence of

TABLE 4. *The Average Blood Replacement in Units (500 cc) Per Different Thromboembolic Prophylaxis.*

	Unilateral	Bilateral
Group I (Warfarin)	2.5	5.7
Group II (LDH 2 h preop)	5.1	9.5
Group III (LDH 8 h preop)	3.0	6.7
Group IV (LDH 8 h preop) + H.C.	2.8	6.0

TABLE 5. *The Study Groups of Hip Arthroplasty Patients in Which Thromboembolism Prophylaxis was Employed.*

	Harris et al.[20] 1967	Harris et al.[21] 1972	Harris et al.[21] 1972	Wilson et al.[51] 1973	Coventry et al.[5] 1973	Evarts et al.[12] 1973	Johnston[25] 1973	Lazanski[31] 1973	Rothermel[39] 1973
Agent	Warfarin	Warfarin	Dextran	Warfarin	"Delayed"	Dextran	Dextran	Dextran	Dextran
No. Cases	70	114	113	51	1,950	200	256	104	60
Phlebitis	7%	2.6%	6.2%	0%	2.4%	7.5%	—	0%	6.7%
PE	0%	5.3%	6.2%	0%	1.1%	1.5%	2.3%	0%	5%

pulmonary emboli in the bilaterally operated patients was greater than twice that of the unilaterally operated patients in all groups. This was statistically significant in Group IV only ($P<0.05$). Although statistical analysis does not confirm a higher incidence of thromboembolism in all groups, these data support the belief that bilateral surgery exposes the patient to an increased risk of thromboembolism.

The only fatal case of pulmonary embolism occurred in Group I. Two of the 4 cases of phlebitis in Group I were first noted at the routine 6-week postoperative visit. One of the 3 phlebitis cases in Group II was first noted 3 weeks postoperative, while 5 of the 8 phlebitis cases in Group IV were observed 3 to 6 weeks postoperatively. In Group III, all of the phlebitis cases were first diagnosed while the patients were hospitalized. Eight other patients in this study suffered severe arterial thromboembolic complications. In Group III, two patients suffered cerebrovascular accidents while two others developed arterial emboli in their lower extremities. In Group IV, there was one case of myocardial infarction, one cerebrovascular accident, and two lower extremity arterial emboli.

The average blood replacement in the four groups is shown in Table 4. The average quantity of blood given varied little between Groups I, III and IV. However, the average blood replaced in Group II patients was significantly greater than the patients of the other three groups. Excessive hematoma formation and wound bleeding, as well as intra-operative blood loss, was extremely common in this group. In Group II, 57 per cent of the unilaterally operated patients were transfused more than 4 units of whole blood, while 75 per cent of the bilateral cases received more than 8 units of blood, in sharp contrast to the other groups. Although the average amount of blood given to the Warfarin treated Group I patients was relatively small, these patients were noted to have a higher incidence of postoperative wound hematoma formation and larger hematomas than the Group III and IV patients. However, the rate of blood loss in hematoma formation was too gradual and the amount too small to result in an increase in the number of transfusions.

Discussion

Several clinical studies have demonstrated the efficacy of oral anticoagulants as thromboembolic prophylaxis in patients who have suffered hip fractures and other orthopaedic injuries[19,41,42,48] and similar success with Warfarin has also been demonstrated.[2,33] Fortunately there are several published series in which Warfarin has been used prophylactically in hip arthroplasty patients, and these series can be compared to our findings in Group I patients. Harris et al.[20] presented a controlled study of the use of Warfarin in mold arthroplasty patients. In their series, the treated patients had an incidence of thrombophlebitis of 7.1 per cent and of pulmonary embolism of 0 per cent compared to the control group in which the incidences were 34.3 per cent and 10.4 per cent respectively.

Low doses of heparin have been found to reduce dramatically the incidence of deep vein thrombosis, as detected by the ^{125}I-tagged fibrinogen technique, in postoperative patients.[17,18,27,29,34,50] Several clinical trials have demonstrated the efficacy of minidose heparin[44–47] and an excellent review of its use has recently been added to the literature.[49] Considering the evidence that many venous thrombi form during surgery,[15] low-dose heparin has a theoretical advantage over conventional anticoagulation in that it has been given preoperatively without hemorrhagic complications. Therefore, we thought this agent could be useful in the prophylaxis of thromboembolism in total hip patients. Unfortunately, low-dose heparin, as it was administered in these patients, was not a remarkably effective method of thromboembolism prophylaxis. In our study, the incidence of thrombophlebitis in those patients receiving low-dose heparin (Groups II, III and IV) was approximately 9 per cent, an incidence above that in the other series of prophylactically treated hip arthroplasty patients reviewed (Table 5) and above that in two other series[5,31] of untreated control patients (Table 2). The incidence of pulmonary embolism in Groups II and III of approximately 6 per cent is higher than that of all the other series of treated groups except that of Harris et al.[21] and is not markedly less than that found in many of the untreated series. A lower incidence of embolism was noted in Group 5 (2%), but as explained previously, we hesitate to consider this figure significant, considering the approximately 9 per cent incidence of thrombophlebitis in this group. We must emphasize, however, that it is extremely difficult to compare meaningfully various series of patients because of their differences in patient management and because of the possibilities of observer bias. Two factors may contribute somewhat to a higher incidence of thromboembolism in this series. In

contrast perhaps to other series, an attempt was made to include quite mild cases of phlebitis. Secondly, this series contained a rather high percentage of bilateral operations compared to other series. Several small series of total hip replacement patients have been presented in which low-dose heparin has been used. The results in each series have been discouraging.[4,11,28]

Past reports on low-dose heparin provide information that can be used to explain somewhat the poor results found in the use of that agent in total hip replacement patients. The mechanism of minidose heparin has been established by Yin and Wessler,[52–54] who have shown that very low levels of heparin, much lower than that needed to block the thrombin-fibrinogen reaction, can greatly augment the anticoagulation effect of the naturally occurring activated factor X inhibitor. They believe that administration of low-dose heparin preoperatively can, by this newly discovered mechanism of action, prevent the development of the "hypercoagulable state" thought to develop early in the postoperative course. Since minidose heparin does not usually affect the whole blood clotting time, it has been used according to fixed schedules by all investigators except Sharnoff,[44–47] who has used the Dale and Laidlow coagulometer to determine the dosage.

Recently, new sensitive assays have been developed, making it possible to measure extremely low heparin levels.[1,9,28] Kakkar et al.[28] demonstrated a precipitous drop in the heparin level during surgery in patients who were injected 5,000 units of heparin subcutaneously two hours preoperatively, in sharp contrast to healthy non-operated subjects, who attained a more sustained level after the same injection. No good explanation is available concerning the phenomenon, but Kakkar thought that total hip patients had an increased requirement for heparin compared to other surgical patients and that perhaps higher and more frequent doses were necessary. Gallus et al.[17] thought that three doses daily of 5,000 units of subcutaneous heparin was perhaps the reason for his lower rate of calf vein thrombosis in hip fracture and myocardial infarction patients compared to other series.

None of the low-dose heparin groups of the present study showed profound evidence of less thromboembolism compared to other series of total hip patients. Indeed the Group II patients demonstrated the hemorrhagic complications of administering 5,000 units two hours preoperatively. Studies using periodic heparin assays in low-dose heparin treated total hip patients would help determine the heparin dosage and interval preoperatively it should be given, as well as the most effective dosage and frequency postoperatively, without causing bleeding complications. It may well be advantageous to administer preoperative heparin between the 8 hours preoperatively of the Groups III and IV patients and the 2 hours preoperatively of the Group II patients. Low doses of heparin also may be more effective if started sooner postoperatively than the postoperative interval of 7 to 9 hours used in the present study. Furthermore, giving heparin 3 or 4 times daily, rather than only 2 a day, may be helpful.

In our experience, Warfarin was apparently more effective than any of the minidose heparin regimes employed. However, the disadvantages of daily prothrombin times, use perioperatively and wound hematomas were encountered in the use of Warfarin. We hope that after further investigation, a better regime of minidose heparin administration may be established for total hip patients so that these relatively high risk patients may have the same low incidence of thrombosis found in other types of heparin treated surgical patients, without the need for daily laboratory work to avoid hemorrhagic complications.

Anti-inflammatory agents, most notably phenylbutazone, have been used successfully in the treatment of thrombophlebitis. The adrenal corticosteroids, long known for their anti-inflammatory properties, have been found to decrease thrombophlebitis as well as other symptoms in patients with certain rather rare autoimmune diseases.[6,8,40] Hydrocortisone was, therefore, employed in addition to minidose heparin in the Group IV patients to determine the efficacy of glucocorticoids in the prophylaxis of thromboembolism. Steroids have been investigated concerning their possible effect on the blood fibrinolytic system. Although a decrease in the fibrinolytic activity of the blood of patients treated with corticosteroids has been observed,[23] contradictory work has demonstrated an increase in activity,[3] leaving us no conclusion presently as to the effect of steroids on the fibrinolytic system.

A study of the Group IV patients of the present study appears to show that hydrocortisone was not efficacious in the prevention of thrombophlebitis. Perhaps the best explanation for this result is that, according to Hume, Sevitt and Thomas,[22] the process of formation of deep venous thrombi is histologically noninflammatory. Therefore, anti-inflammatory agents are probably of little value in the prevention of venous thrombi, but are most likely useful only during the stage of organization and perivenous inflammation, long after the stage of thrombus formation. Further use of anti-inflammatory agents as thromboembolism prophylaxis is not recommended.

We therefore, do not recommend the use of low-dose heparin or hydrocortisone in the prophylactic treatment of thromboembolic disease associated with total hip arthroplasties.

References

1. Bonnar, J., Denson, K.W.E., and Biggs, R.: Subcutaneous Heparin and Prevention of Thrombosis. Lancet, 2:539-540, 1972.
2. Castle, M.E. and Orionion, E.A.: Prophylactic Anticoagulation in Fractures, J. Bone Joint Surg., 52A:521-527, 1970.
3. Chakrabarti, R., Fearnley, G.R. and Hocking, E.D.: Effect of Corticosteroid Therapy on Fibrinolysis in Patients with Inflammatory and Non-Inflammatory Conditions. Br. Med. J. 1:534-537, 1964.

4. Charnley, J.: Prophylaxis of Postoperative Thromboembolism. Lancet, 2:134-135, 1972.
5. Coventry, M.B., Nolan, D.R. and Beckenbaugh, R.D.: "Delayed" Prophylactic Anticoagulation: A Study of Results and Complications in 2,012 Total Hip Arthroplasties. J. Bone Joint Surg., 55A:1487-1492, 1973.
6. Crummy, C.S., Perlin, E. and Moquin, R.B.: Microangiopathic Hemolytic Anemia in Wegener's Granulomatosis. Am. J. Med., 51:554-548, 1971.
7. Culver, D., Crawford, J.S., Gardiner, J.H. and Wiley, A.M.: Venous Thrombosis after Fractures of the Upper End of the Femur. A Study of Incidence and Site. J. Bone Joint Surg., 52B:61-69, 1970.
8. Dines, D.E.: Polyarteritis Nodosa. Report of a Patient Receiving Long-term Anticoagulant Therapy. JAMA, 189:156-158, 1964.
9. Eika, C., Godal, H.C., and Kierulf, P.: Detection of Small Amounts of Heparin by the Thrombin Clotting-Time. Lancet, 2:376, 1972.
10. Evanski, P.M., Waugh, T.R. and Orofino, C.F.: Total Hip Replacement with the Charnley Prosthesis. Clin. Orthop., 95:69-72, 1973.
11. Evarts, C.M. and Alfidi, R.J.: Thromboembolism after Total Hip Reconstruction. JAMA, 225:515-516, 1973.
12. Evarts, C.M.; DeHaven, K.E.; Nelson, C.L.; et al.: Interim Results of Charnley-Muller Total Hip Arthroplasty, Clin. Orthop., 95:193-200, 1973.
13. Evarts, C.M. and Feil, E.J.: Prevention of Thromboembolic Disease after Elective Surgery of the Hip. J. Bone Joint Surg., 53A:1271-1280, 1971.
14. Field, E.S., Nicolaides, A.N., Kakkar, V.V. and Crellin, R.Q.: Deep Vein Thrombosis in Patients with Fractures of the Femoral Neck. Br. J. Surg., 59:377-379, 1972.
15. Flanc, C., Kakkar, V.V. and Clarke, M.B.: The Detection of Venous Thrombosis of the Legs Using ^{125}I-labeled Fibrinogen. Br. J. Surg., 55:742-747, 1972.
16. Flanc, C., Kakkar, V.V. and Clarke, M.B.: Postoperative Deep-Vein Thrombosis. Effect of Intensive Prophylaxis. Lancet, 1:477-478, 1969.
17. Gallus, A.S.; Hirsh, J.; Tuttle, R.J.; et al.: Small Subcutaneous Doses of Heparin in Prevention of Venous Thrombosis. N. Engl. J. Med., 288:545-551, 1973.
18. Gordon-Smith, I.C., LeQuesne, L.P., Grundy, D.J.; et al.: Controlled Trial of Two Regimes of Subcutaneous Heparin in Prevention of Postoperative Deep-vein Thrombosis. Lancet, 1:1133-1135, 1972.
19. Hamilton, H.W., Crawford, J.S., Gardiner, J.H. and Wiley, A.M.: Venous Thrombosis in Patients with Fracture of the Upper End of the Femur. J. Bone Joint Surg., 52B:268-288, 1970.
20. Harris, W.H., Salzman, E.W., and DeSanctis, R.W.: The Prevention of Thromboembolic Disease by Prophylactic Anticoagulation. J. Bone Joint Surg., 49A:81-89, 1967.
21. Harris, W.H., Salzman, E.W., DeSanctis, R.W. and Coults, R.D.: Prevention of Venous Thromboembolism Following Total Hip Replacement. JAMA, 220:1319-1322, 1972.
22. Hume, M., Sevitt, S. and Thomas D.P.: Venous Thrombosis and Pulmonary Embolism, p. 26. Cambridge, Massachusetts, Harvard University Press, 1970.
23. Isacson, S.: Low Fibrinolytic Activity of Blood and Vein Walls in Venous Thrombosis. Scand. J. Haematol., Suppl. 16:1-29, 1971.
24. Johnston, R.C. and Larson, C.B.: Results of Treatment of Hip Disorders with Cup Arthroplasty. J. Bone Joint Surg., 51A: 1461-1479, 1969.
25. Johnston, R.C.: Clinical Follow Up of Total Hip Replacement. Clin. Orthop., 95:118-126, 1973.
26. Kakkar, V.V., Howe, C.T., Nicolaides, A.N., et al.: Deep Vein Thrombosis of the Leg. Is there a "High Risk Group." Am. J. Surg., 120:527-530, 1970.
27. Kakkar, V.V., Nicolaides, A.N., Field, E.S., et al.: Low Doses of Heparin in Prevention of Deep-Vein Thrombosis. Lancet, 2:669-671, 1971.
28. Kakkar, V.V., Spindler, J., Flute, P.T., et al.: Efficacy of Low Doses of Heparin in Prevention of Deep-Vein Thrombosis After Major Surgery. A Double-blind, Randomized Trial. Lancet, 2:101-106, 1972.
29. Lahnborg, G., Friman, L., Bergstrom, K. and Lagergren, H.: Effect of Low-Dose Heparin on Incidence of Postoperative Pulmonary Embolism Detected by Photoscanning. Lancet, 1:329-331, 1974.
30. Langenskiold, A. and Paavilainen, M.L.: Total Replacement of 116 Hips by the McKee-Farrar Prosthesis. A Preliminary Report. Clin. Orthop., 95:143-150, 1973.
31. Lazanksi, M.G.: Complications Revisited. The Debit Side of Total Hip Replacement. Clin. Orthop., 95:96-103, 1973.
32. Moczynski, G., Abraham, E., Barmada, R. and Ray, R.D.: Evaluation of Total Hip Replacement Arthroplasties. Clin. Orthop., 95:213-216, 1973.
33. Neu, L.T., Jr., Waterfield, J.R. and Ash, C.J.: Prophylactic Anticoagulant Therapy in the Orthopedic Patient. Ann. Intern. Med., 62:463-467, 1965.
34. Nicolaides, A.N., Desai, S., Douglas, J.N., et al.: Small Doses of Subcutaneous Sodium Heparin in Preventing Deep Venous Thrombosis After Major Surgery. Lancet, 2:890-893, 1972.
35. Patterson, F.P. and Brown, C.S.: The McKee-Farrar Total Hip Replacement. Preliminary Results and Complications of 368 Operations Performed in Five General Hospitals. J. Bone Joint Surg., 54A:257-275, 1972.
36. Pinto, D.J.: Controlled Trial of an Anticoagulant (Warfarin Sodium) in the Prevention of Venous Thrombosis Following Hip Surgery. Br. J. Surg., 57:349-352, 1970.
37. Ring, P.A.: Complete Replacement Arthroplasty of the Hip by the Ring Prosthesis. J. Bone Joint Surg., 50B:720-731, 1968.
38. Rosengarten, D.S. and Laird, J.: Effect of Leg Elevation on the Incidence of Deep-Vein Thrombosis After Operation. Br. J. Surg., 58:182-184, 1971.
39. Rothermel, J.E., Wessinger, J.B. and Stinchfield, F.E.: Dextran 40 and Thromboembolism in Total Hip Replacement Surgery. Arch. Surg., 106:135-137, 1973.
40. Rowell, N.R. and Cotterill, J.A.: Relapsing Polychondritis. Br. J. Dermatol., 88:387-390, 1973.
41. Sevitt, S.: Venous Thrombosis and Pulmonary Embolism. Their Prevention by Oral Anticoagulants. Am. J. Med., 33:703-716, 1962.
42. Sevitt, S. and Gallagher, N.G.: Prevention of Venous Thrombosis and Pulmonary Embolism in Injured Patients. A Trial of Anticoagulant Prophylaxis with Phenindione in Middle-aged and Elderly Patients with Fractured Necks of Femur. Lancet, 2:981-989, 1959.
43. Sevitt, S. and Gallagher, N.G.: Venous Thrombosis and Pulmonary Embolism. Br. J. Surg., 48:475-489, 1961.
44. Sharnoff, J.G.: Prevention of Thromboembolism. Bull. New York Acad. Med., 49:655-660, 1973.
45. Sharnoff, J.G.: Results in the Prophylaxis of Postoperative Thromboembolism. Surg. Gynecol. Obstet., 123:303-307, 1966.
46. Sharnoff, J.G. and DeBlasio, G.: Prevention of Fatal Postoperative Thromboembolism by Heparin Prophylaxis. Lancet, 2:1006-1007, 1970.
47. Sharnoff, J.G., Kass, H.H. and Mistica, B.A.: A Plan of Heparinization of the Surgical Patient to Prevent Postoperative Thromboembolism. Surg. Gynecol. Obstet., 115:75-79, 1962.
48. Tubiana, R. and Duparc, J.: Prevention of Thrombo-Embolic Complications in Orthopaedic and Accident Surgery. J. Bone Joint Surg., 43B:7-15, 1961.
49. Wessler, S. and Yin, E.T.: Theory and Practice of Minidose Heparin in Surgical Patients. Circulation, 47:671-676, 1973.
50. Williams, H.T.: Prevention of Postoperative Deep-Vein Thrombosis with Perioperative Subcutaneous Heparin. Lancet, 2:950-952, 1971.
51. Wilson, P.D., Jr., Amstutz, H.C., Czerniecki, A., et al.: Total Hip Replacement with Fixation by Acrylic Cement. A Preliminary Study of 100 Consecutive McKee-Farrar Prosthetic Replacements. J. Bone Joint Surg., 54A:207-236, 1972.
52. Yin, E.T. and Wessler, S.: Evidence for a Naturally Occurring Plasma Inhibitor of Activated Factor X: Its Isolation and Partial Purification. Thromb. Diath. Haemorr., 21:398-401, 1969.
53. Yin, E.T., Wessler, S. and Stoll, P.J.: Rabbit Plasma Inhibitor of the Activated Species of Blood Coagulation Factor X. Purification and Some Properties. J. Biol. Chem., 246:3694-3702, 1971.
54. Yin, E.T., Wessler, S. and Stoll, P.J.: Biological Properties of the Naturally Occurring Plasma Inhibitor to Activated Factor X. J. Biol. Chem., 246:3703-3711, 1971.