CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 435, pp. 164–170

Enoxaparin Prevents Progression of Stages I and II Osteonecrosis of the Hip

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In a prospective pilot study, we hypothesized that enoxaparin (60 mg/day for 12 weeks) would prevent progression of Stages I and II osteonecrosis of the hip associated with thrombophilia or hypofibrinolysis or both over ≥ 108 weeks of followup versus untreated historic controls, with different treatment responses in primary versus corticosteroid-associated secondary osteonecrosis. Patients with one or more thrombophilic-hypofibrinolytic disorder and Ficat Stages I or II osteonecrosis of at least one hip were included. A blinded committee interpreted anteroposterior and frog-leg lateral radiographs at entry in the study and every 36 weeks to ≥ 108 weeks. Maintenance of the disease at Stages I and II versus progression of the osteonecrosis to Stages III and IV requiring total hip replacement was the major end point. Sixteen patients had primary osteonecrosis (25 hips; 13 Stage I, 12 Stage II), and 12 had secondary osteonecrosis (15 hips; five Stage I, 10 Stage II). With no Enoxaparin-related complications, 19 of 20 hips (95%) with primary osteonecrosis were unchanged from Stages I and II osteonecrosis at ≥ 108 weeks; 12 of 15 hips (80%) with secondary osteonecrosis progressed to Stages III and IV osteonecrosis. In primary osteonecrosis at ≥ 108 weeks, survival of 95% hips, or 76% (19/25 hips, based on intent to treat), compared favorably with untreated historical controls (approximately 20% 2-year survival), comparable to 20% survival in secondary hip osteonecrosis. Enoxaparin may prevent progression of primary hip osteonecrosis, decreasing the incidence of total hip replacement.

Received: July 14, 2004
Revised: August 27, 2004; November 10, 2004
Accepted: January 10, 2005
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One author (CJG) has received funding from the Jewish Hospital Medical Research Council.
Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.
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DOI: 10.1097/01.blo.0000157539.67567.03

Level of Evidence: Therapeutic study, II-1 (prospective cohort study)

Thrombophilia or hypofibrinolysis or both have been associated with development of osteonecrosis.[4,9–12,17,18,27,43] Osteonecrosis also secondary to corticosteroid use, alcoholism, and systemic lupus erythematosus.[17] Investigators have found a sequence of venous thrombosis with outflow obstruction mediated by thrombophilia or hypofibrinolysis or both, leading to increased intraosseous venous pressure, reduced arterial flow, and hypoxia that seems to be important in the development of ischemic osteonecrosis.[5,10,12,17,18,20,22,24,29,30] If continued venous thrombotic osseous events mediate progression of osteonecrosis, anticoagulation[10,12] with enoxaparin for the same duration as used in deep venous thrombosis of leg veins[31] might slow, or even reverse, ischemic osteonecrosis. Even after radiographic diagnosis of osteonecrosis, provided that doses of enoxaparin or warfarin sodium are started during Ficat[1] Stages I or II disease, we think that osteonecrosis may be arrested or possibly reversed,[10–12] therefore allowing the patient to avoid hip replacement. Our pilot studies with warfarin sodium and stanozolol for treatment of osteonecrosis of the hip[10–12] showed that if pain relief was not obtained after 12 weeks, it was not realized by therapy continuing until 16–24 weeks. No benefit was obtained by treating Ficat Stage III or Stage IV osteonecrosis.[10–12]

The ultimate goal of treatment of osteonecrosis of the hip is preservation of the femoral head, but, as recently summarized by Lieberman ". . . development of successful strategies to treat this disease has been difficult to do because osteonecrosis is associated with numerous different diseases and neither the etiology nor the natural history have been delineated clearly."[23] Also, as reported by Assouline-Dayan et al ". . . management of osteonecrosis is primarily palliative and does not necessarily halt or retard the progression of the disease. Treatment options focus on repairing the secondary changes that develop in the femoral head and not on reversing the primary pathology."[2]

Given the limitations in the available armamentarium for treatment of osteonecrosis,[6,8,14,16,21,33,37–39,42] our hypothesis was that enoxaparin would prevent progression of Stages I and II osteonecrosis associated with thrombophilia or hypofibrinolysis or both compared with untreated historic controls,[14,21,38] and that treatment responses would differ in primary osteonecrosis versus osteonecrosis secondary to corticosteroid use.

MATERIALS AND METHODS

The prospective research study was approved by the Food and Drug Administration (FDA) and the Institutional Review Board at the Jewish Hospital; signed informed consent was obtained.

Patients with one or more thrombophilic-hypofibrinolytic disorder and Ficat Stages I or II osteonecrosis of at least one hip were included in the study. Patients with one Ficat Stage I or Stage II hip who had previous surgery on the other hip also were included, with the study end point being assessed only in the unoperated hip (Tables 1–3). Enoxaparin 60 mg/day was given for the first 12 weeks of the study. A blinded committee interpreted anteroposterior (AP) and frog-leg lateral radiographs at entry in the study and every 36 weeks to ≥ 108 weeks. Maintenance of Ficat Stages I and II versus progression to Stages III and IV or total hip replacement (THR) was the primary end point.

After determining eligibility of the patients (as described below), enoxaparin (60 mg/day in a preloaded syringe) was self-administered subcutaneously for 12 weeks, with serial hip radiographs taken every 36 weeks to ≥ 108 weeks (Tables 1–3). Adherence to the enoxaparin regimen was determined by syringe count at weekly followups. The enoxaparin dose (60 mg/day) and duration (3 months) were the maximums allowed by the FDA. Enoxaparin (60 mg/day) has been used successfully for thrombosis prophylaxis in hip surgery.[41] Conventional prophylactic and therapeutic doses of enoxaparin are 1.5 mg/kg/day and 1 mg/kg twice per day, respectively.[25] In the context of venous thrombosis, anticoagulation usually is given for 6 months,[19,35,36] with a minimum of 3 months.[31]

All patients receiving enoxaparin had weekly followups for 12 weeks with physical examination, complete blood count, and platelet count. Clinically significant bleeding, development of anemia, thrombocytopenia, or allergy to enoxaparin were established as criteria to stop treatment.

Exclusionary criteria included previous hip surgery including core decompression, alcoholism, and enoxaparin contraindications (uncontrolled hypertension, gastrointestinal and/or urinary tract bleeding, cerebral artery and/or venous malformations, inflammatory bowel disease, and platelet count < 140,000). Every patient seen who met our inclusion and exclusion criteria was entered in the study.

We characterized osteonecrosis as primary or secondary to long-term high-dose corticosteroid use because this is currently the predominant clinical and clinical research designation.[10–12,17,18,27]

Before entry in the study, AP and frog-leg lateral radiographs and magnetic resonance imaging (MRI) scans of both hips were taken to determine eligibility (Tables 1, 2). Magnetic resonance imaging was used to help verify the clinical diagnosis of osteonecrosis, and no attempt was made to quantify the extent of femoral head involvement by MRI.[34] Consensus Ficat staging[1] was done by our four-person orthopaedist-radiologist committee blinded to patients' clinical status, age, and hip pain symptoms (Tables 1, 2). The committee developed a unanimous final judgment on each Ficat stage with no concurrent attempt to quantitate intraobserver or interobserver variation.

TABLE 1. Ficat Stages[1] of Hips of 16 Patients with Primary Osteonecrosis

Patient Number	FICAT Stage (right [R])			FICAT Stage (left [L])			FICAT Stage on Followup (weeks)				
	Entry	*36 Weeks*	*Change*	*Entry*	*36 Weeks*	*Change*	*72*	*108*	*144*	*180*	*216*
1	RII	RI	NC	LI	LI	NC				RI, LI, NC	
2	RII	RII	NC	LII	LII	NC			RII, LII, NC		
3	RIII–IV	RIII–IV	NC	LI	LI	NC				LI, NC	
4	RI	RI	NC	LI	LI	NC				RI, LI, NC	
5	RIII	RIII	NC	LI	LI	NC					LI, NC
6	RI	RI	NC	LI	LI	NC				RI, LI, NC	
7	RIII	RIII	NC	LI	LI	NC					LI, NC
8	RII	RII	NC	LII	LII	NC				RII, LII, NC	
9	RI	RI	NC	LI	LI	NC		RI, LI, NC			
10	RII	RII	NC	LII	LII	NC			RII, LII, NC		
11	RI	RI	NC	LII	LI	NC					
12	RII	RII	NC	LIII	LIII	NC		RII, NC			
13	RI	RI	NC	LII	LTHR	worse					
14	normal	normal	NC	LII	LTHR	worse					
15	RIII	RIII	NC	LII	LII	NC			LTHR, RTHR		
16	RI	RI	NC	LTHR				RI, NC			

NC = no change; N = normal; R = right; L = left; THR = total hip replacement

TABLE 2. Ficat Stages[1] of Hips of 12 Patients with Secondary Osteonecrosis

Patient Number	FICAT Stage (right)			FICAT Stage (left)			FICAT Stage on Followup (weeks)			
	Entry	*36 Weeks*	*Change*	*Entry*	*36 Weeks*	*Change*	*72*	*108*	*144*	*180*
1	RIII	RIII	NC	LI	LI	NC				LI, NC
2	RII	RII	NC	LII	LII	NC		RII, LII, NC		
3	RII	RIII	worse	LII	LIII	worse				
4	RIV	RIV*	—	LI–II	LTHR	worse				
5	RII	RII	NC	LIII	LTHR	worse	RTHR			
6	RII	RTHR	worse	LIII	LTHR	worse				
7	RI–II	RIII	worse	LI	LIII	worse	LTHR, RTHR			
8	RII	RII	NC	normal	normal	NC		RIII, worse		
9	RI	RIII	worse	LTHR			RTHR			
10	RIII	RIII	NC	LII	LIII	worse	LIII			
11	RIII	RIII	NC	LII	LIII	worse				
12	RII	RIII	worse	normal	normal	NC	RIII			

NC = no change; R = right; L = left; THR = total hip replacement; * = vascularized fibular graft on right hip

Before entry in the study, blood was obtained from the patients for polymerase chain reaction and serologic measurement of thrombophilia and hypofibrinolysis.[3,4,9,13] The blood samples were obtained while the patients were seated and between 8:30–9:30 AM after an overnight fast. For entry into the study, one or more of the following indicators was required. For thrombophilic disorders these included: heterozygosity or homozygosity for the Factor V Leiden, prothrombin gene, or the platelet glycoprotein IIIa A1/A2 mutations; homozygosity for the C677T MTHFR mutation; anticardiolipin antibodies; lupus anticoagulant; deficiency in proteins C, S, or antithrombin III; homocysteine > 13.5 umol/L (95th percentile of normal); and resistance to activated protein C. For hypofibrinolytic disorders these included: homozygosity for the 4G/4G mutation of the PAI-1 gene; plasminogen activator inhibitor activity > 21.1 U/mL (95th percentile of normal); and Lp(a) > 35 mg/dL.

The major study outcome measure was progression from Ficat Stages I or II osteonecrosis to Stages III or IV osteonecrosis and/or THR over ≥ 108 weeks (Tables 1–3). This is a firm radiologic end point. If the study end point was reached, then followup stopped; if osteonecrosis had not progressed from Ficat Stages I or II at 108 weeks, then followup continued to ≥ 180–216 weeks (Tables 1–3). During 20–24-months, progression from Ficat Stages I or II to III or IV in untreated historic controls[14,21,38] was compared with progression in our patients (Fig 1). Other outcome measures included comparison of progression at ≥ 108 weeks for patients with primary versus secondary osteonecrosis (Table 3), and any enoxaparin complications.

Using our outcome data and estimates of treatment effects, power and sample size calculations for future blinded placebo-controlled trials were done. Progression from Stages I and II to Stages III and IV was compared in patients with primary versus secondary osteonecrosis (Table 3) using chi square analysis or Fisher's exact test when cell size was < 5.

RESULTS

Eighteen men and 10 women with one or more familial or acquired thrombophilic or hypofibrinolytic disorder or both and Ficat Stages I or II osteonecrosis of at least one hip were included (Tables 1, 2). There were another 14 patients referred for the study who did not fulfill these criteria. Sixteen patients (age 45 ± 8 years; five women, 11 men; 13 Caucasians, three African-Americans) had primary osteonecrosis (25 hips; 13 Stage I, 12 Stage II)

TABLE 3. Changes in Ficat Stage during Followup in Patients with Primary and Secondary Osteonecrosis

Osteonecrosis	≥ 108 Weeks	≥ 72 Weeks	≥ 36 Weeks	Intent to Treat ≥ 108 weeks
Primary	13 patients, 20 hips		3 patients, 5 hips	
16 patients, 25 hips	19 (95%) no change		3 (60%) no change	19 (76%) no change
	1 (5%) worse		2 (40%) worse	6 (24%) worse
				p < .01
Secondary	3 patients, 4 hips	5 patients, 6 hips	4 patients, 5 hips	
12 patients, 15 hips	3 (75%) no change			3 (20%) no change
	1 (25%) worse	6 (100%) worse	5 (100%) worse	12 (80%) worse

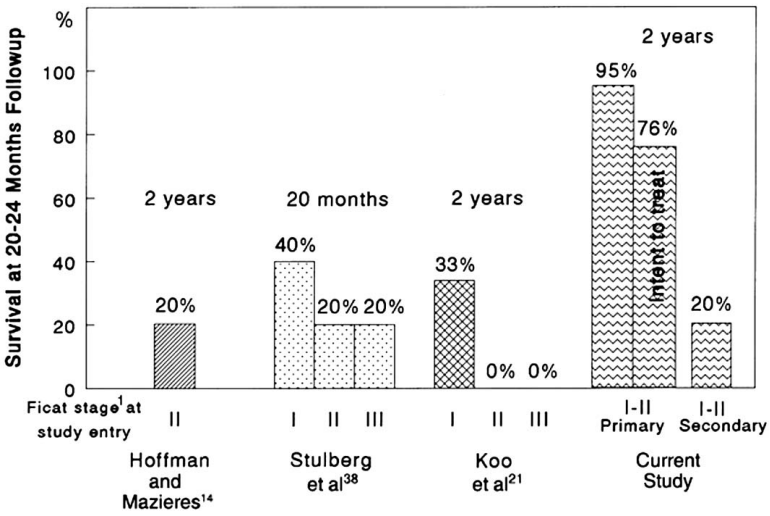

Fig 1. The percent of hip survival is shown at 20–24 months followup in untreated historic controls[14,21,38] with entry Ficat[1] Stages I and II osteonecrosis, and at 24 months followup in the current patients with pretreatment Ficat Stages I and II primary and secondary osteonecrosis.

(Table 1). Of the five women with primary osteonecrosis, three took exogenous estrogens at first diagnosis, which were stopped 3 weeks or more before blood sampling. The mean ± standard deviation (SD) of the duration of time from initial diagnosis to participation in the current study was 6 ± 4 months. Twelve patients (age, 36 ± 9 years; five women, seven men; 11 Caucasians, one African-American) had osteonecrosis secondary to long-term, high-dose corticosteroid use (15 hips; five Stage I, 10 Stage II) (Table 2). Six of these 12 patients continued using corticosteroids during the study. Two patients with secondary osteonecrosis had systemic lupus erythematosus. No women with secondary osteonecrosis were taking exogenous estrogens. The mean ± SD duration of time from initial diagnosis to participation in the current study was 6 ± 3 months.

Patients with primary osteonecrosis were older ($p = 0.013$) than those with secondary osteonecrosis, but did not differ by gender or race. At entry in the study, the distribution of patients with Ficat Stages I and II (13 and 12 respectively in primary osteonecrosis; five and 10 respectively in secondary osteonecrosis) did not differ ($p = 0.33$).

Thirteen patients with primary osteonecrosis (20 hips) had followup for ≥ 108 weeks or more (mean, 161; range, 108–216 weeks), and three patients (five hips) had followup for 36 weeks (Tables 1, 3). If osteonecrosis had not progressed from Ficat Stages I and II at 108 weeks, then longitudinal followup continued to ≥ 180–216 weeks (Tables 1, 3). Patient 11 (Table 1) was lost to followup at 36 weeks. Patient 13, on worsening of left hip osteonecrosis, stopped followup at 36 weeks despite no change in his right hip (Table 1). Patient 14 progressed to Ficat Stages III and IV osteonecrosis and THR at 36 weeks (Table 1).

Of the 12 patients with secondary osteonecrosis, three patients (four hips) had followup for ≥ 108 weeks, five patients (six hips) had followup for ≥ 72 weeks, and four patients (five hips) had followup for ≥ 36 weeks (Tables 2, 3). The much shorter followup in the patients with secondary osteonecrosis was attributable to progression from Ficat Stages I and II to Stages III and IV osteonecrosis or THR, when longitudinal followup stopped, because study outcome had been realized.

At ≥ 108 weeks or more of followup (mean, 161 weeks; range, 108–216 weeks) in 13 patients (20 hips) with primary osteonecrosis, 19 hips (95%) had no change from Ficat Stages I and II osteonecrosis (Tables 1, 3) (Fig 1). Based on intent to treat, even if one assumes that all five hips in the three patients with primary osteonecrosis with followup less than 108 weeks had progressed to Ficat Stages III and IV osteonecrosis (Table 3), 19 of 25 hips (76%) were preserved (Table 3) (Fig 1). At ≥ 108 weeks followup in patients with primary osteonecrosis, preservation of 95% of hips (76% based on intent to treat), compares favorably with untreated historic controls of approximately 20% with 2 years hip preservation (Fig 1).

At ≥ 108 weeks, in 12 patients with secondary osteonecrosis, only three of 15 hips (20%) had osteonecrosis that remained at Ficat Stages I and II, whereas 12 (80%) had osteonecrosis that had progressed to Ficat Stages III and IV (Tables 2, 3) (Fig 1). This 20% 2-year hip preservation is the same as untreated historic controls (Fig 1).

At ≥ 108 weeks of followup, the percent of hips remaining at Stages I and II in patients with primary osteonecrosis (95%) was much greater ($p < 0.001$) than in patients with secondary osteonecrosis (20%) (Table 3). Based on intent to treat, at ≥ 108 weeks followup,

the percent of hips remaining at Stages I and II in patients with primary osteonecrosis (76%) was much greater ($p < 0.01$) than in patients with secondary osteonecrosis (20%) (Table 3).

There were no bleeding episodes, anemia, or thrombocytopenia reported.

DISCUSSION

Current osteonecrosis treatments include core decompression,[16,21,33,37,38] core decompression with bone grafting,[37] electrical stimulation,[37] osteotomy,[42] vascularized fibular grafting,[6] and THR.[8,14,32,39] Total hip replacement relieves pain and restores hip function,[2,8,14,23,32,39] but there is a high revision rate in patients in younger age groups, who most commonly have osteonecrosis.[8,32]

Successful strategies for treatment of osteonecrosis are difficult to develop,[23] do not reverse primary pathologic features of osteonecrosis,[2] may not halt progression to segmental collapse,[2] and all have certain limitations.[6,8,14,21,32,33,37–39,42] In this frame of reference, our hypothesis was that enoxaparin (60 mg/day for 12 weeks) would prevent progression of Stages I and II osteonecrosis associated with thrombophilia or hypofibrinolysis or both during at least 108 weeks followup, compared with untreated historic controls,[14,21,38] and that there would be different treatment responses in patients with primary versus corticosteroid-associated secondary osteonecrosis. Our goal was preservation of the femoral head[23] by reversing primary (coagulation) pathologic features of osteonecrosis.[2]

Our rationale was grounded on associations of thrombophilia or hypofibrinolysis or both with osteonecrosis of the hip[9–12,17,27,43] and with Legg-Calve-Perthes' disease in childhood described in some[4,7,40] but not all[15] studies. Experimental models of osteonecrosis[5,22,24,29,30] and of Legg-Calve Perthes' disease[24] posit venous occlusion as a primary event, followed by increased intraosseous pressure, reduced arterial inflow, ischemia, and infarction. Thrombophilia or hypofibrinolysis or both, by promoting deep osseous venous thrombosis, may initiate this cascade.[10–12,17,18,27,43] Anticoagulation, by blocking continued venous and arterial thrombosis, and by promoting clot lysis, might slow the progression, or even reverse, the process of osteonecrosis by ameliorating ischemia and allowing healthy reossification.

In our study, in patients with primary osteonecrosis at 108 weeks $\geq$ followup, 95% of hips were preserved at Ficat Stages I and II, and 76% were preserved based on the intent to treat population. This compares very favorably with untreated historic controls in which the 20–24-month survival of the hips with Ficat Stages I and II osteonecrosis was approximately 20% (Fig 1).[14,21,38] However, at $\geq$ 108 weeks in our study, 20% preservation of hips with Ficat Stages I and II secondary osteonecrosis was the same as the 20% hip survival in historic controls,[14,21,38] (Fig 1) and was much less ($p < 0.01$) than in hips with primary osteonecrosis (20% versus 76%). Enoxaparin was well tolerated and was not associated with any clinical or laboratory complications.

Hoffman and Mazieres[14] reported that 80% of hips with Ficat Stage II osteonecrosis collapse within 2 years of diagnosis. Stulberg et al[38] studied 55 hips in 36 patients, ½ having core decompression, and ½ having conservative, nonsurgical treatment. By 20 months in the nonoperative group, 40% of hips with Stage I osteonecrosis had survived, 20% of hips with Stage II osteonecrosis had survived, and 20% of hips with Stage III osteonecrosis had survived (Fig 1).[38] Koo et al[21] assessed outcomes of osteonecrosis in 37 hips (33 patients). At 24 months, of 22 hips with Ficat Stage I osteonecrosis, there was 33% survival; of 11 hips with Stage II osteonecrosis, there was 0% survival; and of four hips with Stage III osteonecrosis, there was 0% survival (Fig 1).[21] The percentage of patients in these studies with primary and secondary osteonecrosis[14,21,38] is not known, and it is possible that our comparison of outcomes of patients with primary osteonecrosis versus these historic controls[14,21,38] represents comparisons of primary versus secondary osteonecrosis.

Results of our study suggest that enoxaparin has promise for treatment of primary osteonecrosis when initiated at Ficat Stages I or II, before segmental collapse of the femoral head. However, in osteonecrosis secondary to corticosteroid use, enoxaparin did not alter progression[14,21,38] to Ficat Stages III or IV. We think that synergistic effects of thrombophilia or hypofibrinolysis or both[4,9–12,17,18,43] and corticosteroid use renders osteonecrosis unresponsive to enoxaparin therapy. We did not address whether or when a second anticoagulation treatment course is appropriate. Given the apparent benefit with a subprophylactic dose of enoxaparin (mandated by the FDA), we think that benefit might be augmented using the standard prophylactic dose (1.5 mg/kg/once per day), the therapeutic dose (1 mg/kg/twice per day), or warfarin titrated to an international normalized ratio of 2.0–2.5. Duration of therapy also needs to be examined, because anticoagulation of thrombophilia-associated thrombosis is often 6–12 months or greater.

In the absence[10–12] of any 2-year followup data regarding enoxaparin efficacy and safety in patients with Ficat Stages I and II osteonecrosis, we chose to do an unblinded pilot study. If 20% of hips are preserved at 2 years followup in untreated osteonecrosis,[14,21,38] and estimating that 40%, 60%, and 76% hip preservation (as in our study) represent significant treatment outcomes, at alpha = .05

and power = 80%, 91, 28, and 15 hips respectively would be required in treatment and placebo groups in a blinded study.

An optimal study of anticoagulation in patients with thrombophilia or hypofibrinolysis or both and Ficat Stages I and II primary osteonecrosis would be double blind, with placebo and enoxaparin injections. Questions which need to be examined include the following: should the enoxaparin dose be greater, as much as a full anticoagulant dose of 1 mg/kg every 12 hours; how long should the enoxaparin be given; and what is the role of retreatment? If osteonecrosis can be stopped short of segmental collapse, we think that it takes years for revascularization and reossification to occur. Therefore, much longer followup is important to permit better understanding of the role of enoxaparin in primary osteonecrosis caused by thrombophilia or hypofibrinolysis or both.

A second limitation of our study involves consensus judgment regarding progression of osteonecrosis from Ficat Stages I and II to Stages III and IV by a four-person committee that read the radiographs, despite their being blinded to the clinical information and therapy of the patients. Reliability of classifying Ficat stages by radiographs is not very good (low kappa values),[26] and staging by MRI probably is less effective.[28]

In primary osteonecrosis associated with thrombophilia or hypofibrinolysis or both, if enoxaparin is started during Ficat Stages I and II osteonecrosis, we postulate that osteonecrosis may be safely arrested or possibly reversed, potentially avoiding surgical intervention for the patient. Anticoagulation seems appealing in patients with primary osteonecrosis, but must be shown to be superior to the risks of osteoporosis and the rare heparin-induced thrombocytopenia. Future studies also might examine warfarin, which has a well-known long-term risk profile.

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