1A. New study of therapy of osteonecrosis of the hip with low molecular weight heparin.

IF YOU WANT TO PARTICIPATE, CALL DR. CJ GLUECK AT 513-924-8250 BETWEEN 2 AND 4 PM, WEEKDAYS

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Heritable defects in fibrinolytic activity and avascular-aseptic necrosis of the hip, diagnosis and a single site pilot study of therapy with low molecular weight heparin.

2A: Background/Rationale for study:  top

Our studies show that > 85% of adults and children with osteonecrosis of the hip or jaw have inherited thrombophilia (increased risk of thrombus [clot] formation) or hypofibrinolysis (decreased ability to lyse thrombi). Often, "environmental" factors which increase the likelihood of thrombosis (exogenous estrogens, corticosteroids), when superimposed on underlying heritable thrombophilia or hypofibrinolysis, sharply increase the risk of thrombosis. Previously, the only known therapies for osteonecrosis included core decompression (drilling a hole in the head of the femur) and vascularized fibular grafting (drilling a hole in the head of the femur, mobilizing a vascularized fragment of the tibia and inserting it in the head of the femur). Previously, in most cases, however, irrespective of the mode of therapy, the osteonecrosis progresses to segmental collapse of the head of the femur, requiring surgery for insertion of a hip prosthesis. Hip replacement for osteonecrosis is currently being done in 40,000 patients/year (estimated cost $30,000/hip), with another 80,000 having various stages of disease not yet requiring hip replacement.

Our studies in adults with osteonecrosis of the hip have shown that, provided that anticoagulant therapy for thrombophilia with low molecular weight heparin is started before irreversible collapse of the head of the femur, osteonecrosis can be arrested or reversed. Thus, inexpensive anticoagulant therapy with low molecular weight heparin has been shown to arrest the progress of, or reverse osteonecrosis in about 75% of cases, avoiding the necessity for surgical hip replacement, and revolutionizing the therapy of osteonecrosis. Our work has, in aggregate, provided the following entirely new scientific information regarding the diagnosis and therapy of osteonecrosis:

Prior to the recent recognition that osteonecrosis is commonly caused by disorders of coagulation, osteonecrosis was characterized as "idiopathic" (cause[s] unknown), and "secondary" diseases and drugs which were known to cause "secondary" osteonecrosis included corticosteroids, alcoholism, trauma, hemoglobinopathies, "bends" (Caisson disease), systemic lupus erythematosus, Gaucher's disease, sickle cell disease and disseminated intravascular coagulation, etc. About 90% of patients with what had, heretofore, been termed "idiopathic" osteonecrosis in adults or Legg-Perthes disease in children have an underlying pathogenetic coagulation disorder. Similarly, about 80% of patients with what had previously been termed "secondary" osteonecrosis have a disease or drug thought to cause osteonecrosis superimposed on an underlying coagulation disorder.

Based on our studies in the hip and jaw, and those of other investigators, we postulate that thrombophilia and/or hypofibrinolysis lead to osteonecrosis via the following pathways:

   1. Persistent thrombi block venous drainage of bone. The exact cause and timing of the initial thrombus formation remains conjectural.

   2. With venous drainage of the bone impaired by thrombi, but with arterial blood influx continuing, venous pressure in the occluded bone compartment rises. This (speculatively) leads to reduced arterial
perfusion, anoxia, and subsequent bone death (osteonecrosis).

3. In the early stages of venous occlusion, there is "bone marrow edema" which can be diagnosed by MRI. This progresses to early stages of osteonecrosis (Ficat stages I and II) which appear to be reversible by correction of the underlying coagulation problems. More advanced stages of osteonecrosis (Ficat III, IV) appear to be irreversible by treatment of the coagulation disorders, since they involve segmental collapse of the head of the femur and secondary arthritis.

Our studies in 295 adults and children with osteonecrosis of the hip, knee, or jaw have begun to illuminate the pathogenetics of osteonecrosis. The majority (about 80%) of patients with osteonecrosis have thrombophilia (increased likelihood of thrombosis) and/or hypofibrinolysis (reduced ability to lyse thrombi). Thrombophilia and hypofibrinolysis are transmitted as autosomal dominant traits, although their effects can be amplified by diseases and drugs. The major heritable thrombophilic and hypofibrinolytic disorders pathogenetic for osteonecrosis are as follows:

**Thrombophilic Disorders:**

Hetero- and [rarely] homozygosity of the mutant Factor V Leiden Gene with Resistance to activated protein C:

A defect in the procoagulant protein, Factor V, does not allow binding by activated protein C, leading to unopposed procoagulant activity and increased risk of venous thrombosis. Activated protein C resistance (APCR) can be amplified by exogenous estrogens (oral contraceptives, post-menopausal estrogen supplementation). Heterozygosity or homozygosity for the mutant Factor V Leiden is now routinely examined in our laboratories by cDNA PCR assays.

**Protein C deficiency:**

When protein C is deficient, factor Va is inadequately suppressed, leading to increased procoagulant activity and increased risk of venous thrombosis. The thrombotic tendency in protein C deficiency can be amplified by exogenous estrogens and by pregnancy.

**Protein S deficiency:**

Protein S is a cofactor for protein C. When protein S is deficient, factor Va is not adequately suppressed, leading to increased procoagulant activity and increased risk of venous and arterial thrombosis.

**Anticardiolipin Antibodies and the Lupus Anticoagulant:**

Anticardiolipin antibodies (ACLA) and the Lupus anticoagulant are antiphospholipid autoantibodies which are directed against negatively charged phospholipid antigens. Anticardiolipin antibodies and the Lupus anticoagulant are prothrombotic by a variety of mechanisms including inhibition of prostacyclin synthesis, impairment of the thrombomodulin-protein C-protein S anticoagulant system, acting as anti-endothelial cell antibodies, or interacting with platelet membrane phospholipids. ACLA and the Lupus anticoagulant are associated with both venous and arterial thrombi.

**Polymorphism of the prothrombin gene:**

This newly described polymorphism results in high levels of prothrombin which "tilts" the coagulation system towards increase thrombosis. Heterozygosity or homozygosity for the prothrombin gene polymorphism is now routinely examined in our laboratories by cDNA PCR assays.

**Polymorphism of the MTHFR gene:**

Homozygosity for this common polymorphism controls serum levels of homocysteine, a major thrombophilic risk factor.

**Hypofibrinolysis:**
Low stimulated tissue plasminogen activator activity (tPA-Fx) often accompanied by high plasminogen activator inhibitor activity (PAI-Fx): There is an excess of the major inhibitor of fibrinolysis, PAI-Fx, so that the major stimulator of fibrinolysis, tPA-Fx, cannot be activated; the process of lysis of thrombi cannot begin, or is slowed. High plasma triglycerides and/or hyperinsulinemia can increase PAI-Fx, causing a decrease in tPA-Fx. The 4G4G and 4G5G polymorphisms of the PAI gene are now routinely examined in our laboratories by cDNA PCR assays.

High lipoprotein (a) [Lp(a)]: In the closed space of bone, we believe that high Lp(a) may reduce fibrinolysis. The apparent hypofibrinolytic action of Lp(a) in bone appears to be augmented by corticosteroid therapy.

2B. Objectives: Our first specific aim in adults only, and in a pilot study, is to determine whether and to what degree anticoagulant therapy with low molecular weight heparin (Lovenox), will ameliorate avascular necrosis of the hip or prevent its progress, in adults with thrombophilic disorders. We will continue to examine the efficacy and safety of therapy for thrombophilia and hypofibrinolysis in adults for arresting the progress of and reversing osteonecrosis.

We plan to study ≥ 30 patients with osteonecrosis of the hip over the next 24 months, while continuing follow-up for the 19 currently being studied. Although Enoxaparin therapy is equally effective in therapy of osteonecrosis of the jaw, endpoints of therapy (change in pain, change in bone scan, X-ray, etc) are harder to judge, and we will focus on osteonecrosis of the hip.

2C1: Study Design: 2C1A, Patients: Over the next 24 months, we plan a single site pilot study of the safety and efficacy of Enoxaparin in the therapy of osteonecrosis in 30 patients before segmental collapse of the head of the femur (Ficat Stages I, II).

In all patients, we will measure thromophilic and hypofibrinolytic variables.

2C3: Enoxaparin: Dose, frequency, duration: The most optimal anticoagulant for this study is the low molecular weight heparin enoxaparin, 1 mg/kg given subcutaneously, once/day. The following dose schedule will be used, linked to patient weight: 30-50 kg-40 mg, 51-70 kg-60 mg, 71-90 kg-80 mg, >91 kg-100 mg. Enoxaparin is a polysaccharide chain produced by the depolymerization of heparin. In comparison with heparin, which has an average molecular weight of 12,000-15,000 daltons, the average molecular weight of enoxaparin is approximately 4500 daltons. Enoxaparin does not form a complex with antithrombin III and thrombin as extensively as does heparin; however, the anti-Xa activity of enoxaparin is similar. The significance of this fact is an enhancement of antithrombotic activity and clinical efficacy.

In up to 30 patients with coagulation disorders and idiopathic avascular necrosis of the hip, we plan to give Enoxaparin, subcutaneously, once/day for 12 weeks. We anticipate that it will take us 24 months to recruit appropriate patients and complete follow-up studies. The following dose schedule will be used, linked to patient weight: 30-50 kg-40 mg, 51-70 kg-60 mg, 71-90 kg-80 mg, >91 kg-100 mg.

2C4: Inclusion Criteria: Patients must have the following:

1. Primary osteonecrosis of the hip, i.e., not associated with alcoholism, sickle cell disease, Gaucher's disease, trauma, post-radiation syndromes.
2. **Osteonecrosis graded at Ficat Stage I or II by MRI and X-ray.** Our previous work has shown that if segmental collapse of the head of the femur has already occurred (Ficat Stages III, IV), then medical therapy with low molecular weight heparin will not stop or reverse the osteonecrosis.

3. A well defined thrombophilic or hypofibrinolytic coagulation disorder, as per the serologic coagulation and PCR tests.

4. Ability and willingness to participate in the 12 week Lovenox treatment period, **7 outpatient visits over a 12 week period, with a subsequent 24 week post-Lovenox follow-up period (flow chart).**

**2C5: Exclusion Criteria:**

1. Any medical condition which would contraindicate anticoagulation with low molecular weight heparin including the following: uncontrolled hypertension, uncontrolled diabetes, active esophageal, stomach, or duodenal ulcers, active Crohn's disease, active ulcerative colitis, any known bleeding disorder of the bowel (diverticulitis, colonic polyposis), deficiency of platelets, any intracranial mass lesions, cancer, metastatic cancer, uncontrolled severe psychiatric disease (major depression, schizophrenia, etc).

2. Laboratory safety tests to establish exclusion criteria will include the following: complete blood count with platelet count, BUN, creatine, fasting blood glucose, Ca, P04, liver function tests, T4, TSH.

**2C6. Evaluation methods:**

As summarized in the attached Study flow chart (#4, below), the initial clinical visit (Visit 1) will be at Week -3. At this time, the full battery of coagulation serologic and PCR tests will be obtained, along with physical examination, and laboratory safety tests. It is anticipated that diagnostic X rays and MRIs will have been obtained by the referring Orthopedist before Visit 1.

The patients will be asked to fill out pain logs daily for the 3 week, pre-treatment period between Visit 1 and Visit 2. This will provide a detailed baseline for the nature and degree of pain before initiating therapy.

After completion of Visit 1, and assessment of the coagulation and safety data, and review of inclusion and exclusion criteria, patients who are eligible for low molecular weight heparin intervention will return for Visit 2, at week 0, three weeks after Visit 1 (cf flow chart). At Visit 2, week 0, Enoxaparin will be started in eligible patients who will then return for re-evaluation **once/week for 2 weeks, and then** every 2 weeks for **a total of 12 weeks** (Follow-up visits **1-7**) (flow chart). **For each two week period of therapy, 16 Lovenox pre-loaded syringes (40, 60, 80, or 100 mg/syringes, depending on patients' weight)** will be provided. Patients will be asked to bring back unused syringes at each follow-up visit for count, to quantitate Lovenox adherence.

At follow-up visits **1-7**, blood will be obtained for complete blood count and platelet count, weight and blood pressure will be measured, the preceding 14 days’ pain forms will be collected (and entered into SAS), and a brief history and physical examination will be carried out (flow chart). **Adherence to the Lovenox therapy will be determined by syringe count.**

After completion of the 12 week Lovenox therapy period, the low molecular weight heparin will be discontinued, and the patients will be asked to fill out a daily pain log as before. At visit **8**, week 36, repeat X rays and MRIs will be obtained to allow an anatomic comparison between pre- and post-treatment bone architecture (flow chart).

Enoxaparin will not be started until a recent x-ray and MRI of the affected hip joint is obtained to serve as a baseline from which to judge change (hopefully improvement). As noted above, the Ficat Stage must be I or II.

**Patients receiving Enoxaparin will have serial outpatient Cholesterol Center visits once/week for 2 weeks, then every 2 weeks for a total of 7 visits (12 weeks) (flow chart).**

Prior to beginning Enoxaparin, and at each visit, the following tests will be obtained after a 12 hour fast:

1. Complete blood count and platelet count.
2. Brief interval history and physical examination
3. Systematic recording of symptoms of hip pain, range of motion, use of analgesics, ability to ambulate, etc.

2C7. Endpoints-efficacy: To help determine whether the Enoxaparin therapy is improving symptoms of osteonecrosis pain, we will ask the patients to keep a daily written pain log which has 12 measures of pain. There will be 7 total visits on Enoxaparin, covering a period of 12 weeks. Our previous studies have shown that by 12 weeks of therapy, if there is no significant improvement in pain, then it is very unlikely that any improvement would be seen. Alternatively, if there has been significant improvement in pain, we assume that the initial thrombotic period has been successfully dealt with, and that the anticoagulation can be stopped, similar to therapy for any other venous thrombosis. The patients will be asked, however, to maintain their daily pain forms for 6 months after cessation of low molecular weight heparin therapy, so that if pain begins to reappear, re-anticoagulation can be initiated.

Twenty-four weeks after completion of the Lovenox therapy at follow-up visit 8, study week 36, a second X ray and MRI of the affected bone(s) will be obtained to assess the anatomic status of the osteonecrosis.

2C8. Endpoints-safety: Complete blood count and platelet count. Development of medically significant anemia or a below normal platelet count will lead to discontinuation of therapy. Development of clinically significant bleeding for any reason (gastric, colon, urinary tract, etc) will lead to discontinuation of therapy.
1. Brief interval history and physical examination. Evidence of clinically significant internal or external bleeding will lead to discontinuation of therapy.
2. Allergy to the low molecular weight heparin will lead to discontinuation of therapy.

3. Study flow chart/study diagram Time

I: BASELINE, PRE-ENOXAPARIN STUDIES
1. Define presence of primary osteonecrosis (Ficat stage I or II) Visit 1-Week -3
2. Obtain baseline coagulation and laboratory safety tests
3. Document presence of patient inclusion criteria
4. Document absence of patient exclusion criteria

II: ENOXAPARIN THERAPY, FOLLOW-UP
5. Begin therapy with Enoxaparin 3 weeks after baseline, pre-Rx visit Visit 2-Week -0

FOLLOW-UP VISITS: Collect pain data, laboratory safety tests, physical examination data
6. Follow-up visit 1. " Visit 3- Week 1
7. Follow-up visit 2. " Visit 4- Week 2
8. Follow-up visit 3. " Visit 5- Week 4
9. Follow-up visit 4. " Visit 6- Week 6
10. Follow-up visit 5. " Visit 7- Week 8
11. Follow-up visit 6. " Visit 8- Week 10
12. Follow-up visit 7. " Visit 9- Week 12

III: POST-ENOXAPARIN THERAPY, FOLLOW-UP OF PAIN AND BONE STATUS BY X RAYS, MRI
Pain follow-up from week 12 to 36. Patients will be asked to provide pain forms every 2 weeks
so that pain development after cessation of Lovenox can be compared to that before and on therapy.

13. **Follow-up visit 8. Repeat baseline X rays, MRI Visit 10- week 36**

**References**

**Osteonecrosis in Adults:**


**Legg-Perthes Disease (Pediatric Idiopathic Osteonecrosis):**


**Therapy for Thrombophilia and Hypofibrinolysis, Amelioration of and Reversal of Osteonecrosis:**

443. Glueck CJ, Freiberg R, Glueck HI, Tracy T, Stroop D, Wang Y Idiopathic osteonecrosis, hypofibrinolysis, high plasminogen activator inhibitor, high lipoprotein(a), and therapy with Stanozolol. Am J of Hematology, 48:213-220,


Coagulation Studies


Osteonecrosis of the Jaw:  


Confirmatory studies of the pathoetiologic role of thrombophilia and hypofibrinolysis in osteonecrosis, other authors.  


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