Low Molecular Weight Heparin Prevents the Progression of Precollapse Osteonecrosis of the Hip

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Background: *Hypercoaguable state has been indicated as a major risk factor in predisposing the idiopathic osteonecrosis of the hip. Furthermore, many studies have demonstrated that low molecular weight heparin (LMWH) can reverse the pathophysiology of the osteonecrosis of the hip in thrombophilic patients.*
Objective: *Determine whether LMWH can prevent the progression of idiopathic osteonecrosis of the hip.*
Material and Method: *A retrospective study of 36 patients who had bilateral idiopathic osteonecrosis with at least one hip in the pre-collapsed stage (Ficat & Arlet stage I-II) was conducted. In the study group, 18 patients (26 hips) received 6,000 units of Enoxaparin daily for 12 weeks. In the control group, 18 patients (23 hips) received no Enoxaparin. All patients were given radiographic evaluations every three months for a minimum of 24 months.*
Results: *At the last follow-up, 15 hips (57.7%) from the study group and five hips (21.7%) from the control group were observed to remain in the pre-collapse stage ($p = 0.042$). Coagulation disorder was observed in seven patients (38.9%) of the experimental group and five patients (27.8%) of the control group. One patient from the study group exhibited hematuria with spontaneous resolution after the course of Enoxaparin injection.*
Conclusion: *A progression rate of idiopathic osteonecrosis of the hip from the pre-collapse stage to the collapsed stage was found to be significantly lower in patients who received LMWH.*

Keywords: *Idiopathic osteonecrosis of the hip, Hypercoagulable state, Low molecular weight heparin, LMWH*

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A variety of surgical options, including core decompression, osteotomy, and vascularized bone graft, have been used to treat early stage idiopathic osteonecrosis of the hip with good midterm results[1-4]. It is noteworthy that pathogenesis of the disease may be reversed to provide patients with long-term functional hips. Hypercoagulability and others predisposing factors (such as steroids and alcohol intake etc.) have been reported as a major cause of microvascular thrombosis, finally resulting in osteonecrosis[4-17]. For this reason, many authors have reported the positive effect of anticoagulant[18-20], lipid lowering drugs[21], vasodilators[22,23], and bisphosphonate[24-26], but results remain controversial. Low molecular weight heparin (LMWH) has been studied in rats and shown a lesser degree of epiphyseal necrosis after cutting a periosteum at the femoral neck[19]. A clinical trial conducted by Glueck CJ reports 95% of pre-collapsed thrombophilic and/or hypofibrinolytic disorder-associated primary osteonecrosis hips did not progress further than Ficat stage I or II after receiving LMWH for 12 weeks, while 80% of the pre-collapsed corticosteroid-associated secondary osteonecrosis hips receiving identical treatment progressed to Ficat stage III or IV[20].

The authors hypothesized that LMWH is able to prevent or at least slow the progression of the idiopathic osteonecrosis of the hip, which may be associated with thrombophilia and/or hypofibrinolytic disorders.

Material and Method

All patients diagnosed with the idiopathic osteonecrosis of the hip that pass our inclusion/exclusion criteria were enrolled in the present study. Pelvic AP & frog-leg lateral radiographs and magnetic resonance imaging of both hips of the patients were assessed at screening. The inclusion criteria were age over 20 years, and bilateral idiopathic osteonecrosis of

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the hip with at least one side in the pre-collapsed stage (Ficat & Arlet stage 0-II). The exclusion criteria were history of steroids use, alcoholic intake of more than 400 mL/week, smoking, anticoagulant administration, hip trauma, any hip surgery, and the pathology in the pre-collapsed hip involving less than 25% as demonstrated by the MRI. Blood samples of all enrolled patients tested for thrombophilia (Factor V, Factor VIII, Protein C, Protein S and Anti thrombin III) were also recorded.

Thirty-six patients diagnosed of idiopathic osteonecrosis of the hips with 49 hips been in the pre-collapsed stage were reviewed. The patients were randomized into two groups, the study group consisted of 26 hips had been administered with 6,000 units of Enoxaparin daily for 12 weeks, and had been monitored for adverse effects (AE) every 4 weeks. Twenty-three hips in the control group had not received additional treatment. All patients had been radiographically evaluated with the pelvic AP and frog-leg lateral of the studied hips at 3, 6, 12, 18, and 24 months. The radiographic results were blindly evaluated by three orthopedic surgeons and two radiologists. The end point of the study was radiographic progression to a collapsed hip (Ficat & Arlet stage III & IV) or any surgical intervention required for pain intolerance and impairment of function. The procedures followed were in accord with the Helsinki Declaration of 1975. Institutional review board (IRB)/Ethics committee approval was obtained from Phramongkutklao hospital. Chi-square and Fisher's extract test were used to analyze the result with the p-value of 0.05.

Results

The demographic data are shown in Table 1. Of the 36 patients in the present study, 12 patients (33.3%) have had a hypercoagulable state. Of the 18 patients in the trial group, seven patients have had a hypercoagulable stage, compared to five out of 18 patients in the controlled group. The details were shown in a Table 2.

At 24 months follow-up, 15 hips (57.7%) from the study group remained precollapse stage, while only five hips (21.7%) in the control group remained precollapse stage ($p = 0.042$). In the study group, 10 out of 11 hips (90.9%) that were in the Ficat & Arlet stage 0 or I at the time of enrollment have not progressed beyond stage IIb, while only 5 out of 15 hips (33.3%) that were initially in stage IIa or IIb, had remained within stage IIb; Table 2.

There is major concern about bleeding disorder as an adverse reaction to LMWH. After 12 weeks of LMWH injection, one patient from the study group developed transient hematuria, which

Table 1. Demographic data of 36 patients with idiopathic osteonecrosis of the hip

	Study group (n = 18)	Control group (n = 18)
Age (years) ± SD	43.72±13.71	43.39±12.04
Gender	12 males & 6 females	13 males & 5 females
No. of hips	26 hips (13 right & 13 left hips)	23 hips (10 right & 13 left hips)
Thrombophilic profiles (No. of patients)	Normal (11) Thrombophilia (7)	Normal (13) Thrombophilia (5)
Ficat & Arlet classification staging (No. of hip)	Stage 0 (9 hips) Stage I (2 hips) Stage IIa (14 hips) Stage IIb (1 hip)	Stage 0 (9 hips) Stage I (2 hips) Stage IIa (8 hips) Stage IIb (4 hips)

Table 2. Comparison of the Ficat & Arlet staging at 2 years of follow-up between the study and control group

Initial stage of ON*	Study group (26 hips)		Control group (23 hips)		p-value
	Remain in precollapse stage	Collapse or surgery	Remain in precollapse stage	Collapse or surgery	
0-I	10	1	4	7	
IIa-IIb	5	10	1	11	
Total	15	11	5	18	0.042

* ON = osteonecrosis

spontaneously subsided. Otherwise, there were neither wound complications nor infections in the present study.

Discussion

Even though primary total hip replacement has been a very successful treatment for the hip with the osteonecrosis, concern remains regarding a high rate of revision[27,28]. It has been generally accepted that femoral head preservation is the goal for young patients suffering from hip osteonecrosis[29].

Animal studies[5,19,30,31] have demonstrated that occlusion of small venous vessels lead to increased femoral head intraosseous pressure. This decreases arterial flow and potentially leads to idiopathic osteonecrosis. Many studies in humans have shown evidence of thrombophilia and hypofibrinolysis as factors in pathogenesis of idiopathic osteonecrosis and Legg-Calve Perthes disease[1-20].

The authors result corresponds to a study by Glueck et al[20] but with a lesser percentage of success (57.7% vs. 95%), which may be due to a difference between the experimental group (idiopathic osteonecrosis vs. osteonecrosis associated with thrombophilic-hypofibrinolytic disorder). The progression of the idiopathic osteonecrosis of the hip without any intervention in other studies[32-34] has shown 20% progress to the collapsed stage, compared to 21.7% of our control group. The rate of progression was halved after receiving the LMWH as described.

Glueck et al[35] has reported 83% incidence of coagulation disorder in patients with the idiopathic osteonecrosis of the hip, however only 12 patients (33.3%) in the present study has been detected with the disorder. This may be due to the fact that only 5 thrombophilic profiles were tested in the present study, compared to additional polymerase chain reaction such as heterozygosity or homozygosity for Factor V Leiden, prothrombin gene, platelet glycoprotein IIIa A1/A2 mutation, and etc. for thrombophilic disorder and homozygosity for the 4G/4G mutation of the PAI-1 gene for hypofibrinolytic disorder in other studies[20,36,37]. Therefore, it is probable that there were more patients in our study having thrombophilic-hypofibrinolytic disorders. However, there was no statistically significant difference in the incidence of the disorders between the experimental and the control group, seven patients (38.9%) and five patients (27.8%), respectively. One potential clinical application is that LMWH can be administered to prevent progression of idiopathic osteonecrosis without any test for thrombophilia.

For the experimental group, 10 hips (90.9%) that were initially in either stage 0 or I were preserved in the precollapse stage at 2 years of follow-up compared to only five remaining pre-collapsed hips (33.3%) that were initially in either stage 2a or 2b. The result demonstrates that patients most likely to benefit from LMWH are those who have the idiopathic osteonecrosis of the hip in either Ficat & Arlet stage 0 or I.

There were some limitations inherent in the present study. The reliability of an intra and inter-observer on the radiographs, as well as the Ficat-Arlet classifications, were not determined, while the MRI assessment was questionable. As mention above, the patients had limited thrombophilic profiles analysis, so that some disorders affecting the response to LMWH administration might be hidden. The results were followed for at least 24 months; however, long-term results are still unknown. Further studies may be done using double-blinded randomized control trials with long term follow-up.

From the present study, it might be concluded that LMWH administration for the idiopathic osteonecrosis of the hip in pre-collapse stage can significantly prevent the progression of the disease in 24 months of follow-up. The result is particularly pronounced for hips with lesser severity of the disease including the hip with Ficat & Arlet classification stage 0 or I.

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Potential conflicts of interest

None.

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ผลของการใช้ยาป้องกันการแข็งตัวของเลือดต่อการป้องกันการดำเนินโรคในผู้ป่วยหัวข้อสะโพกตายระยะก่อนยุบตัว

ธไนนิธย์ โชตนภูติ, สมภพ ทองประเสริฐ, อาทิตย์ เหล่าเรืองธนา

วัตถุประสงค์: *สาเหตุของภาวะโรคหัวข้อสะโพกตายโดยไม่ทราบสาเหตุ (idiopathic osteonecrosis of femoral head) นั้น เป็นโรคที่มีภาวะสาเหตุจากหลาย ๆ ปัจจัย โดยได้มีการศึกษาพบว่าสาเหตุหลักเป็นจากภาวะที่เลือดแข็งตัวง่ายกว่าปกติ ซึ่งมีผล ทำให้การไหลเวียนโลหิตไปสู่กระดูกหัวข้อสะโพกน้อยลง การศึกษานี้มีสมมติฐานว่า LMWH สามารถป้องกันการดำเนินโรคของ ผู้ป่วยหัวข้อสะโพกตายโดยไม่ทราบสาเหตุระยะก่อนยุบ (1 และ 2) ไม่ให้เป็นมากขึ้นไปสู่ระยะหัวสะโพกยุบ (3 และ 4)*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลังของผู้ป่วยหัวข้อสะโพกตายโดยไม่ทราบสาเหตุ ที่อยู่ระยะก่อนยุบอย่างน้อย 1 ข้าง โดยได้ติดตามผลการรักษาในช่วงระยะเวลา 24 เดือน เปรียบเทียบกับกลุ่มที่ไม่ได้รับยา และมีการติดตามการคงอยู่ของ หัวข้อสะโพกด้วยภาพถ่ายรังสี pelvis AP และ frog leg lateral ทุก ๆ 3 เดือน จนกระทั่งครบ 24 เดือน*

ผลการศึกษา: *ผู้ป่วยกลุ่มที่ได้รับยาป้องกันการแข็งตัวของเลือด (Enoxaparin 6,000 units ต่อวัน นาน 12 สัปดาห์) นั้น สามารถป้องกันการดำเนินโรคไม่ให้เป็นมากขึ้นในระยะเวลา 24 เดือน ใน 15 ข้อสะโพก จาก 26 ข้อสะโพก คิดเป็น 57.70% เมื่อ เปรียบเทียบกับกลุ่มควบคุม สามารถป้องกันได้เพียง 5 ข้อสะโพก จาก 23 ข้อสะโพก หรือ คิดเป็น 21.73% ซึ่งมีความแตกต่าง อย่างมีนัยสำคัญทางสถิติ ($p<0.042$) โดยพบผู้ป่วย 1 ราย ที่มีภาวะเลือดออกในเดินปัสสาวะแทรกซ้อนจากการให้ยา enoxaparin แต่สามารถหายได้เองหลังจากการหยุดยา*

สรุป: *ยาป้องกันการแข็งตัวของเลือดน่าจะมีประโยชน์ และมีส่วนช่วยป้องกันการดำเนินโรคหัวข้อสะโพกตายระยะก่อนยุบ ไม่ให้เป็นมากขึ้นได้*
