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Factors Affecting the Elevation of Inflammatory Markers before Primary Total Hip Arthroplasty 최 병 찬 2024년 2월

박 사 학 위 논 문

Factors Affecting the Elevation of Inflammatory Markers before Primary Total Hip Arthroplasty

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이 논문을 박사학위 논문으로 제출함

2024년 2월

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우선, 박사 과정 중 전반적으로 많은 조언과 가르침을 주신 이경재 교수님께 진심으로 감사의 마음을 드립니다. 논문을 작성하는 것이 익숙하지 않은 저에게 항상 중요한 부분을 짚어주시고 막히는 부분을 같이 고민해주신 덕분에 잘 마무리할 수 있었습니다. 그리고 논문의 중요성과 향후 저에게 삶의 방향성을 일깨워 주신 민병우 교수님, 석사 학위 후에도 지속해서 관심을 가지고 심사에 임해주신 배기철 교수님, 김범수 교수님께도 감사드립니다. 또한, 제가 박사학위 시작을 주저할 때, 적극적으로 권해주신 조철현 교수님께도 가슴 깊이 감사드립니다.

제가 전공의를 하면서 앞으로 고관절을 전공해야겠다고 마음먹었을 때 다른 대학의 고관절 전공 교수님들께서도 많이 기뻐해 주시고 환영해주셨던 것이 기억에 남습니다. 특히, 외부 심사위원이신 유기형 교수님께 많은 자리에서 환영해주시고 신경 써주신 것에 대해 진심으로 감사의 인사를 드립니다. 이번 기회로 교수님과 지속적이고 깊은 인연을 이어갈 수 있다면 이는 제 개인적으로 큰 영광이 될 것입니다.

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2024년 2월

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1. Introduction

Inflammatory reactions are host responses to threats in the form of infections or other injuries. The signs and symptoms of inflammatory reactions include changes in body temperature, heart rate, respiratory rate, and pain. Additionally, several laboratory findings can be used to evaluate and assess the severity of inflammatory reactions. Among them, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count are representative markers for screening systemic inflammation (1-4). CRP can induce a rapid response within a few hours of injury to the host (2). In cases of severe inflammation, plasma CRP levels can increase 1000-fold. Elevated ESR, which shows a slower response to inflammation compared to CRP, occurs within 24 - 48 hours after the onset of inflammation (3). WBC, particularly neutrophils, are recruited when an inflammatory reaction is initiated. A large number of neutrophils are consumed at the site of inflammation, leading to stimulation of the bone marrow to release significantly high numbers of immature neutrophils. WBC counts eventually increase, and neutrophils tend to be left-shifted under inflammatory conditions (5).

Although these markers are widely used for the detection of orthopedic infections, their clinical implications are not the same (1,4,6-8). Serum CRP levels show high sensitivity and acceptable specificity for the diagnosis of orthopedic infections. However, ESR and WBC count are known markers with relatively low sensitivity and specificity (1). Most orthopedic surgeons would agree that CRP level, ESR, and WBC count are useful markers for the detection of

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orthopedic infections. However, elevated levels of CRP and ESR can result not only from orthopedic infection or inflammation but also from trauma, the surgical procedure itself, or patient comorbidities. Numerous studies have investigated serial changes in the serum levels of various inflammatory markers after trauma or surgical procedures (4,9-12). In addition, the levels of inflammatory markers can be influenced by multiple chronic diseases and medical conditions, including autoimmune inflammatory disease (3), end-stage renal disease (13), and aging (14), without apparent infection.

As the popularity of total hip arthroplasty (THA) has increased recently, the number of patients with multiple comorbidities has also significantly increased. Therefore, personalized and optimized management of the perioperative complications of THA is essential for these patients. Abnormal levels of inflammatory markers are often detected in patients with multiple comorbidities before primary THA without a specific focus on infection. THA can be performed without delay when abnormal levels of inflammatory markers are caused by factors other than infection (15). However, elevated serum markers of infection before primary THA may cause hesitation among surgeons. Until now, determination of factors that affect the elevation of inflammatory marker levels before primary THA has been challenging. Performing THA depends on the surgeon's discretion and experience in cases where the levels of inflammatory markers are elevated.

This study aimed to examine the distribution of inflammatory markers and factors affecting the elevation of inflammatory marker levels before primary THA. This study hypothesized that elevated inflammatory marker levels could be caused by various preoperative diagnoses and comorbidities in patients before primary THA.

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2. Materials and Methods

This study was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (IRB No. 2023-08-019). A retrospective review of all patients who underwent elective THA at an outpatient clinic of a single institution between August 2018 and February 2022 was conducted. A total of 1,087 patients were preliminarily identified. The following patients were excluded: those who underwent any previous surgery on the ipsilateral hip joint, conversion of prior internal fixation to THA or revision THA, those with a follow-up period of one year, those with inadequate medical records for the evaluation of preoperative inflammatory markers, and those with other apparent focus on infection before THA. Patients who underwent simultaneous bilateral THA were also excluded to avoid bias originating from differences in hospital course and recovery patterns in the perioperative period (Figure 1).

A total of 511 patients were included in the study. The patients were divided into two groups: those with normal CRP values before surgery (group A, 432 patients) and those with an abnormal CRP value (group B, 79 patients). The thresholds for the upper limits of the normal were set to 0.5 mg/dL. Preoperative ESR, serum WBC, and neutrophil counts were also evaluated. Normal range of ESR was defined as 0 - 15 mm/h, and WBC count in blood was 10,000 × 10^3/uL.

Preoperative diagnoses of patients reviewed in this study were classified into four categories: Hip arthritis, osteonecrosis of the femoral head (ONFH), subchondral insufficiency fracture of the femoral head (SIFFH), and fused hip. Patients' medical records were also reviewed to determine underlying diseases known to be risk factors for elevated serum levels

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of inflammatory markers. Patients who had been diagnosed with a specific disease by an expert from a medical center before visiting our clinic or who had been diagnosed during the preoperative evaluation for primary THA were defined as having an underlying disease. Patients diagnosed with underlying diseases after primary total hip arthroplasty were excluded. The underlying diseases and medical histories of patients in the study group were classified as autoimmune inflammatory disease, diabetes mellitus, chronic kidney disease (with or without dialysis), history of cancer, organ transplantation, and history of contralateral hip arthroplasty.

Rheumatic diseases such as seropositive rheumatoid arthritis (SPRA), seronegative rheumatoid arthritis (SNRA), fibromyalgia, systemic sclerosis, Sjögren's disease, systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), gout, psoriasis, anti-neutrophil cytoplasmic antibody (ANCA)-associated disease, and henoch schonlein purpura (HSP) were included as autoimmune inflammatory diseases. Patients received counseling from a rheumatologist for medication adjustment before undergoing primary THA.

Blood glucose levels were checked for every patient, and the preoperative serum level of HbA1c with diabetes mellitus (DM) was also measured. Patients with high blood glucose levels who were not diagnosed with DM before surgery were counseled by an endocrinologist regarding the diagnosis and management of DM. Creatinine levels were measured in all patients. Patients with a result indicating over 1.30 were counseled by a nephrologist for management and assessment of chronic kidney disease (CKD).

In addition, histories of cancer, organ transplantation, and contralateral hip arthroplasty were evaluated because of their potential as risk factors for elevated inflammation marker levels. The preoperative WBC count in

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the urine (negative, 1+, 2+, and 3+) was checked, and patients were monitored for urinary symptoms. Symptomatic pyuria was assessed by an infectious disease specialist in patients with urinary symptoms and a positive urine WBC count.

Examination and comparison of the distribution of inflammatory markers, prevalence of preoperative diagnosis, and underlying diseases between the normal and abnormal CRP groups were performed. Statistical analyses were performed using SPSS software version 26 (IBM Corp., Armonk, NY, USA). The chi-square test or Fisher's exact test was used for categorical variables, including the prevalence of preoperative diagnosis and underlying diseases. Student's t-test was used for continuous variables such as inflammatory markers. Multiple logistic regression analysis was performed to determine factors affecting the elevation of inflammatory marker levels. Linear-by-linear association was used to analyze the association between CRP level and WBC count. Statistical significance was set at $p < 0.05$.

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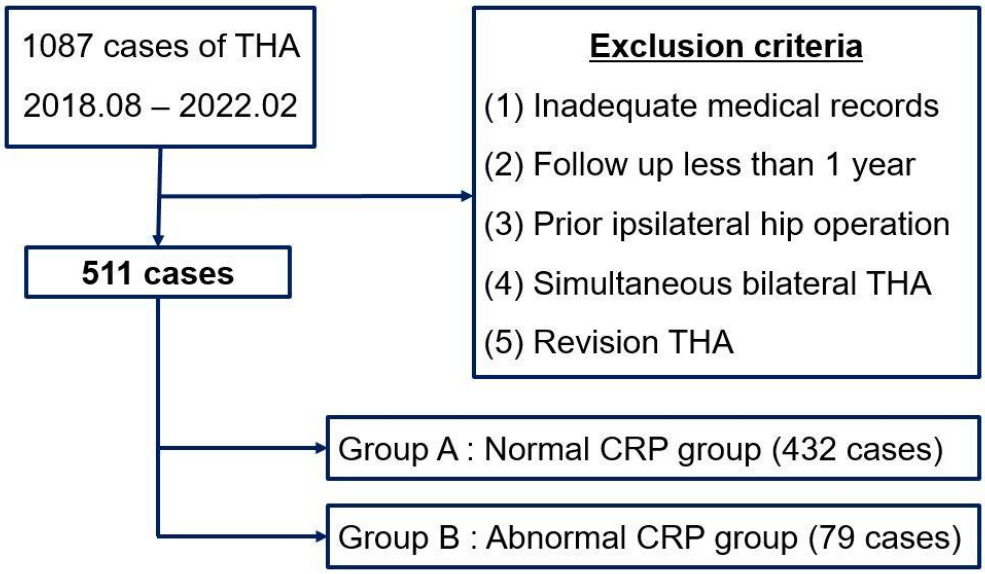

Figure 1. Patients enrollment flow chart. CPR: C-reactive protein; THA: total hip arthroplasty.

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3. Results

The prevalence of elevated CRP levels was 15.5%. The mean age of patients in the study cohort at the time of primary THA was 62.0 years (range: 23 - 93 years) and the mean body mass index (BMI) was 25.2 kg/m^2 (range: 16.7 - 39.0 kg/m^2). A total of 252 patients (49.3%) were male and 259 patients (50.7%) were female. The mean follow-up period was 25.2 months (range, 12 - 53 months). Incidence of PJI was two cases. one case in each group. The sex ratio and mean follow-up differed significantly between the two groups (Table 1).

A significantly lower mean CRP value was observed in group A (0.16 ± 0.13 mg/dL) compared with group B (1.44 ± 2.45 mg/dL) ($p < 0.001$). The mean ESR value showed significant difference (Group A: 25.91 ± 17.53 mm/hr vs Group B: 50.27 ± 28.57 mm/hr) ($p < 0.001$). The mean ESR value was abnormal in both groups. The mean WBC count in blood also showed a statistically significant difference (Group A: 6650 ± 1676 × 10^3/uL vs Group B: 7466 ± 2157 × 10^3/uL) ($p < 0.01$). The mean WBC count was within normal limits in both groups. Additionally, a significantly different proportion of neutrophils was observed between the two groups. (Group A: 58.06 ± 9.16% vs Group B: 63.28 ± 9.08%; $p < 0.001$) The mean WBC count and proportion of neutrophils were within normal range in both groups. The mean follow-up period was significantly longer in Group A B (A: 24.8 months vs B: 27.5 months; $p < 0.05$) (Table 2).

Group A included 225 cases (52.1%), 190 cases (44.0%), 16 cases (3.7%), and 1 case (0.2%) of hip arthritis, ONFH, SIFFH, and fused hip, respectively. Group B included 20 (25.3%), 53 (67.1%), and 6 (7.6%) patients with hip arthritis, ONFH, and SIFFH, respectively.

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Multivariate logistic regression analysis was performed to determine the factors affecting the elevation of inflammatory marker levels. Although the sex ratio differed significantly between the two groups, it was not a significant factor affecting the elevation of inflammatory marker levels ($p > 0.05$). The risk for elevation of CRP was higher for ONFH and SIFFH compared to hip arthritis (ONFH; Odds ratio (OR) = 3.03, 95% confidence interval (CI) = 1.73 – 5.28, SIFFH; OR = 4.85, 95% CI = 1.0 – 13.88). Both the results were considered statistically significant. (ONFH; $p < 0.001$, SIFFH; $p < 0.01$)

The prevalence of autoimmune inflammatory disease was higher in patients with high CRP levels (Group A: 24/432 (5.56%) vs. Group B: 16/79 (19.0%); $p < 0.001$, OR = 3.85) than in those with normal CRP levels. Descriptions of the autoimmune inflammatory diseases examined are shown in Table 3. Despite the slightly higher prevalence of DM in group B, the difference between the two groups was statistically insignificant (13.9% vs. 16.5%; $p > 0.05$). No significant difference in the mean HbA1c value was observed between the two groups (6.96 vs 7.55; $p > 0.05$). No difference in the prevalence of CKD was observed between the two groups (2.5% vs 3.8%, $p > 0.05$). Two patients from each group underwent dialysis. History of cancer (5.7% vs. 8.9%, $p > 0.05$), organ transplantation (0.9% vs. 0%, $p > 0.05$), and contralateral hip arthroplasty (18.1% vs. 20.3%, $p > 0.05$) was not significantly different between the groups (Table 4). No difference in the preoperative WBC count in the urine was detected between the two groups ($p > 0.05$) (Table 5).

Preoperative diagnoses of ONFH, SIFFH, and autoimmune inflammatory diseases as underlying diseases were identified as factors affecting the elevation of inflammatory marker levels.

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Table 1. Demographic Data

	Overall cases	Group A	Group B	p-value
Age (year)	62.1 ± 13.1	62.3 ± 13.0	61.1 ± 13.6	> 0.05
Gender (Male : Female)	252 : 259	202 : 230	50 : 29	< 0.05*
Height (cm)	160.3 ± 9.9	160.0 ± 9.9	161.9 ± 10.2	> 0.05
Weight (kg)	64.7 ± 12.3	64.5 ± 12.3	66.1 ± 12.7	> 0.05
BMI (kg/m^2)	25.13 ± 3.7	25.13 ± 3.7	25.13 ± 3.7	> 0.05
Follow-up period (months)	25.2 ± 10.1	24.8 ± 9.9	27.5 ± 10.9	< 0.05*
Incidence of PJI (case)	2	1	1	> 0.05

Values are presented as mean ± standard deviation. BMI: body mass index; PJI: Periprosthetic joint infection. *: Statistically significant ($p < 0.05$).

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Table 2. Inflammatory Markers of Group A and B

	Overall cases (n = 511)	Group A (n = 432)	Group B (n = 79)	p-value
CRP (mg/dL)	0.37 ± 1.1	0.16 ± 0.13	1.44 ± 2.45	< 0.001*
ESR (mm/hr)	29.63 ± 21.46	25.91 ± 17.53	50.27 ± 28.57	< 0.001*
WBC of blood ($\times 10^3$/uL)	6775 ± 1781	6649 ± 1676	7466 ± 2157	< 0.001*
Neutrophil count (%)	58.8 ± 9.3	58.1 ± 9.1	63.3 ± 9.1	< 0.001*

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell. *: Statistically significant ($p < 0.05$).

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Table 3. Autoimmune Inflammatory Disease Category

Autoimmune inflammatory disease	Group A (n = 24)	Group B (n = 16)
SPRA	9	1
SNRA	-	-
Fibromyalgia	1	-
Systemic sclerosis	-	1
Sjogren disease	-	1
SLE	2	2
AS	3	3
Gout	8	3
Psoriasis	1	3
ANCA associated disease	-	1
HSP	-	1

ANCA: anti-neutrophil cytoplasmic antibody associated disease; AS: ankylosing spondylitis; HSP: henoch schonlein purpura; SLE: systematic lupus erythematosus; SNRA: seronegative rheumatoid arthritis; SPRA: seropositive rheumatoid arthritis.

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Table 4. Multivariate Logistic Regression Analysis

	Overall cases (n = 511)	Group A (n = 432)	Group B (n = 79)	p-value	Odds ratio	95% CI
Demographics						
Gender (Male : Female)	252 : 259	202 : 230	50 : 29	> 0.05	0.742	0.43 - 1.28
Pre-op diagnosis						
Hip arthritis	245	225 (52.1%)	20 (25.3%)			
ONFH	243	190 (44.0%)	53 (67.1%)	< 0.001*	3.03	1.73 - 5.28
SIFFH	22	16 (3.7%)	6 (7.6%)	< 0.01*	4.85	1.70 - 13.88
Fused hip	1	1 (0.2%)	-	> 0.05	0	
Underlying disease						
Autoimmune disease	40	24 (5.56%)	16 (19.0%)	< 0.001*	3.85	1.91 - 7.77
DM	73	60 (13.9%)	13 (16.5%)	> 0.05	1.17	0.60 - 2.31
HbA1c		6.96 ± 1.1	7.55 ± 2.1	> 0.05	-	-
CKD/Dialysis	14/4	11/2 (2.5%)	3/2 (3.8%)	> 0.05	1.56	0.40 - 6.18
History of						
Cancer	32	25 (5.7%)	7 (8.9%)	> 0.05	1.51	0.62 - 3.72
Transplantation	4	4 (0.9%)	0 (0.0%)	> 0.05	0	0
Contralateral THA	94	78 (18.1%)	16 (20.3%)	> 0.05	1.13	0.61 - 2.09

CI: confidence interval; CKD: chronic kidney disease; DM: diabetes mellitus; ONFH: osteonecrosis of femoral head; SIFFH: subchondral insufficiency fracture or femoral head; THA: total hip arthroplasty. *: Statistically significant ($p < 0.05$).

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Table 5. Linear by Linear Association Analysis of Urine WBC

	Overall cases (n = 511)	Group A (n = 432)	Group B (n = 79)	p-value
Urine WBC				> 0.05
Negative	423	357 (82.8%)	66 (83.5%)	
1+	47	45 (10.4%)	2 (2.5%)	
2+	24	18 (4.2%)	6 (7.6%)	
3+	16	11 (2.6%)	5 (6.3%)	

WBC: white blood cell.

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4. Discussion

The findings of this study showed significant differences in the levels of all inflammatory markers, including CRP, ESR, and WBC, in the blood and neutrophil counts between the normal and abnormal CRP groups. ONFH, SIFFH, and autoimmune inflammatory diseases were significant factors affecting elevation of inflammatory marker levels.

It is important to note that despite significant differences in the levels of inflammatory markers (CRP, ESR, WBC count in the blood, and neutrophil count) between the two groups, only ESR was in the abnormal range in both groups. In contrast, the WBC and neutrophil counts were within the normal range in both groups. Only CRP was on the other side in terms of normal levels.

According to the MusculoSkeletal Infection Society criteria for the diagnosis of PJI, inflammatory markers are considered minor. The diagnosis of PJI is challenging and the reliability of inflammatory markers remains controversial (8,16,17). McArthur et al. (17) reported that 4% of PJI cases after total hip arthroplasty and total knee arthroplasty presented with normal levels of inflammatory markers. Huang et al. (16) and Parvizi et al. (18) reported culture-negative PJI in 7% - 12% of patients, despite other positive indicators of PJI. According to some studies, CRP can be useful for diagnosing periprosthetic or peri-implant infections after THA or conversion of prior internal fixation to THA (6,7,19-22). Huerfano et al. (20) maintained that a negative CRP value may be sufficient for revision THA in patients without other clinical or radiological findings suggesting infection. Gittings et al. (7) reported the effectiveness of preoperative CRP for screening infections before the conversion of internal fixation to THA, although occult infections could

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be overlooked. Ghanem et al. (19) suggested a CRP cutoff value of 1 mg/dL to distinguish PJI. This could be interpreted as a potential focus of infection in cases in which a marker of inflammation is abnormal before revision or conversion to THA. However, it is important to note that normal markers of inflammation cannot be used to rule out infection. Taken together, thorough consideration of multiple factors, including clinical, radiological, and laboratory findings (CRP, ESR, and culture of aspirated synovial fluid), is required for the accurate diagnosis of PJI. In this study, PJI development was observed in two cases. (one case in each group) Both patients underwent THA under the diagnosis of hip arthritis. They suffered from an acute hematogenous infection within six months after the operation. These findings suggest that the reliability of inflammatory markers for predicting the development of PJI before primary THA may not be significant.

The development of ONFH commonly involves marrow necrosis and edema of the adjacent bone marrow (23). Eventual progression to development of a subchondral fracture or collapse of a necrotic segment can occur, potentially inducing synovial inflammation that may result an elevation of serum inflammatory markers. In addition, SIFFH can cause diffuse bone marrow edema and synovial inflammation before rapidly progressing to hip arthritis (24). Therefore, theoretically, the elevation in inflammatory marker levels can be affected by both ONFH and SIFFH. However, there is a lack of literature regarding inflammation in patients with ONFH and SIFFH.

Several studies have reported outcomes and complications of THA in patients with autoimmune inflammatory diseases. Mäenpää et al. (25) found that high levels of CRP could be detected in patients with rheumatoid arthritis before primary or revision THA and a significant postoperative increase of CRP in these patients does not indicate

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complications. According to Aziz et al. (26), based on the national inpatients sample (NIS) database, the risk of acute perioperative complications after THA is higher in patients with lupus. That study reported a higher incidence of death (odds ratio 2.5) and stroke (odds ratio 4.0), but not of wound infection (odds ratio 0.9), after THA.

This study had several limitations. Only the outcomes of the short-term follow-up period were examined, indicating that the results might not accurately reflect long-term outcomes. The relationship between preoperative markers of inflammation and long-term outcomes remains uncertain. Histopathological analysis of frozen sections to determine neutrophil counts in a high-power field (HPF) is considered a useful tool for the diagnosis of PJI. Frozen section biopsy and tissue culture were performed for patients with high CRP levels or those with a high probability of infection based on intraoperative findings. Frozen histopathological studies or cultures were not performed for all patients included in this study and were therefore not available for statistical analysis. No growth was detected in the intraoperative tissue cultures of 72 cases. Frozen histopathologic study was also performed in five cases from the abnormal CRP group and the average neutrophil count in the high-power field (HPF) was 4.25 (range: 2 - 5 /HPF). In addition, the size of the abnormal CRP group (79 patients) and the number of PJI cases (2 patients) were small. In particular, the number of PJI cases was too small for statistical analysis, although no significant difference in the incidence of PJI was observed between the two groups. Thus, there is a potential for bias, and additional studies including a larger number of PJI cases may be required to determine whether preoperative inflammatory markers affect the development of PJI.

Despite these limitations, to the best of our knowledge, this is the first study to examine the distribution of preoperative inflammatory

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markers and factors affecting the elevation of inflammatory marker levels before primary THA.

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5. Summary

Elevated levels of inflammatory markers are commonly observed prior to primary THA. Regarding preoperative diagnosis, ONFH and SIFFH were significant factors affecting the elevation of inflammatory marker levels compared to hip arthritis. Regarding the underlying disease, auto-immune inflammatory disease was the only significant factor affecting the elevation of inflammatory marker levels. Additional studies are required to determine the relationship between preoperative inflammatory markers and development of PJI.

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Factors Affecting the Elevation of Inflammatory Markers before Primary Total Hip Arthroplasty

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(Abstract)

The objective of this study was to examine the distribution of inflammatory markers and factors affecting elevation of inflammatory marker levels before primary total hip arthroplasty (THA). A retrospective review of all THA cases from the out-patients' clinic between August 2018 and February 2022 was conducted. Comparison of the distribution of inflammatory markers, prevalence of preoperative diagnosis, and underlying diseases between the normal CRP group (group A) and the abnormal CRP group (group B) was performed. Significantly lower mean values were observed for all inflammatory markers in group A compared with group B. Preoperative diagnosis of osteonecrosis of the femoral head (ONFH) and subchondral insufficiency fracture of the femoral head (SIFFH) and autoimmune

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inflammatory disease as underlying disease were identified as factors affecting elevation of inflammatory marker levels. No difference in prevalence of other underlying disease was observed between the two groups. Elevated levels of inflammatory markers are commonly detected before primary THA. ONFH and SIFFH were significant factors affecting elevation of inflammatory marker levels compared to hip arthritis. Autoimmune inflammatory disease was significant factor affecting elevation of inflammatory marker levels. Additional study may be required to determine the relation of inflammatory marker levels with development of PJI.

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고관절 인공관절 전치환술 전 염증표지자 상승에 영향을 미치는 인자

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(초록)

본 연구의 목적은 염증 표지자의 분포를 조사하고 고관절 인공관절 전치환술 전 염증 표지자의 상승에 영향을 주는 인자를 조사함에 있다. 2018년 8월부터 2022년 2월 외래를 통해 내원한 고관절 인공관절 전치환술 환자를 C 반응 단백질의 수치가 정상인 군(A군)과 비정상인 군(B군)으로 분류하여 염증 표지자 수치, 수술 전 진단명, 환자의 기저진단을 후향적으로 비교, 분석하였다. 모든 염증 표지자 수치가 A 그룹의 환자에서 유의하게 낮았다. 로지스틱 회귀분석을 이용하여 분석했을 때 수술 전 진단명 중 대퇴골두무혈성괴사와 대퇴골두의 부전골절이 고관절염과 비교했을 때 염증 표지자의 상승에 영향을 미칠 수 있으며 환자의 기저질환 중 자가면역성 염증 질환이 염증성 표지자 상승에 영향을 미치는 유의한 인자였다. 결론적으로, 염증 표지자의 상승은 고관절 인공관절 전 치환술 전 드물지 않게 관찰되었다. 또한, 대퇴골두무혈성괴사와 대퇴골두의 부전골절이 고관절염에 비해

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염증 표지자의 상승에 영향을 줄 수 있으며 자가면역성 염증 질환이 수술 전 염증 표지자 상승에 영향을 미칠 수 있음이 확인되었다. 수술 전 염증 표지자의 상승과 수술 후 인공관절 주위 감염 발생의 연관성에 대해서는 추후 추가적인 연구가 필요할 것으로 보인다.

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