Clinical Article
J Korean Neurosurg Soc 65 (6) : 834-840, 2022
https://doi.org/10.3340/jkns.2022.0126
pISSN 2005-3711 eISSN 1598-7876

Comparison of Inflammatory Markers Changes in Patients Who Used Postoperative Prophylactic Antibiotics within 24 Hours after Spine Surgery and 5 Days after Spine Surgery

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Objective : C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count are inflammatory markers used to evaluate postoperative infections. Although these markers are non-specific, understanding their normal kinetics after surgery may be helpful in the early detection of postoperative infections. To compliment the recent trend of reducing the duration of antibiotic use, this retrospective study investigated the inflammatory markers of patients who had received antibiotics within 24 hours after surgery according to the Health Insurance Review & Assessment Service guidelines and compared them with those of patients who had received antibiotics for 5 days, which was proven to be non-infectious.

Methods : We enrolled 74 patients, divided into two groups. Patients underwent posterior lumbar interbody fusion (PLIF) at a single institution between 2019 and 2020. Group A included 37 patients who received antibiotics within 24 hours after the PLIF procedure, and group B comprised 37 patients who had used antibiotics for 5 days. A 1 : 1 nearest-neighbor propensity-matched analysis was used. The clinical variables included age, sex, medical history, body mass index, estimated blood loss, and operation time. Laboratory data included CRP, ESR, and WBC, which were measured preoperatively and on postoperative days (POD) 1, 3, 5, and 7.

Results : CRP dynamics tended to decrease after peaking on POD 3, with a similar trend in both groups. The average CRP level in group B was slightly higher than that in group A; however, the difference was not statistically significant. Multiple linear regression analysis revealed operation time, number of fused levels, and estimated blood loss as significant predictors of a greater CRP peak value (r^2=0.473, p<0.001) in patients. No trend (a tendency to decrease from the peak value) could be determined for ESR and WBC count on POD 7.

Conclusion : Although slight differences were observed in numerical values and kinetics, sequential changes in inflammatory markers according to the duration of antibiotic administration showed similar patterns. Knowledge of CRP kinetics allows the assessment of the degree of difference between the clinical and expected values.

Key Words : C-reactive protein · Erythrocyte sedimentation rate · Antibiotics · Spine · Surgery.

• Received : May 31, 2022 • Revised : July 21, 2022 • Accepted : August 10, 2022
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INTRODUCTION

Surgical site infections (SSIs) after spine surgery are common, and rates of deep infection range from <1% to 2%, with wide variability observed between studies involving different surgical procedures, patient demographics, sample size, and duration of antibiotic usage[14,16,23,24].

Prompt recognition and differentiation of other infections in the postoperative course are important to prevent seeding of the discs, vertebrae, and paraspinal structures. However, the early detection of postoperative infection can be difficult to differentiate from a normal postoperative course because various indicators of infection, including fever, pain, and leukocytosis, are commonly present without SSIs[6]. Among these indicators, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count are routinely assessed and evaluated to distinguish between normal and infectious postoperative courses at many institutes[1]. Although these markers are not specific indicators of infection, understanding the normal kinetics after spinal surgery may aid the early detection of postoperative infection. Many studies have investigated sequential changes in inflammatory markers while continuing prophylactic antibiotic administration after spinal surgery and have suggested abnormal kinetics of CRP or procalcitonin as the basis for the early detection of SSIs[4,7,15].

Recently, the Health Insurance Review & Assessment Service (HIRA) in Korea proposed guidelines[20] for the use of prophylactic antibiotics for spinal surgery within an appropriate period (within 24 hours postoperatively). Growing evidence supports the guidelines for prophylactic antibiotics, but many studies indicate that 24 hours of prophylactic postoperative antibiotics may entail additional risks, including antibiotic resistance, without providing a preventive benefit in patients undergoing orthopedic procedures[5,12,19].

This study aimed to assess the normal postoperative kinetics of CRP, ESR, and WBC count after spine surgery with instrumentation and compare individuals whose antibacterial prophylaxis was discontinued within 24 hours (HIRA guidelines) versus 5 days postoperatively. Moreover, variables of the patients and spine surgery, which are specific determinants of the kinetics of inflammatory markers, were evaluated.

MATERIALS AND METHODS

Patients and data selection

We retrospectively reviewed posterior lumbar interbody fusion (PLIF) performed by a single surgeon at a single institute between 2019 and 2020 for the treatment of degenerative pathology in patients aged >20 years, with a minimum 6-month follow-up, with approval from the Institutional Review Board of Kyung Hee University Hospital (2021-12-073). We excluded traumatic, oncologic, and autoimmune disorders; procedures for the treatment of revision; and spinal infections. The patients were stratified into two groups : 1) those who had received 24 hours of postoperative antibiotics including preoperative antibiotics and 2) those who had received preoperative antibiotics, which they continued for 5 days postoperatively. Five days is the routine antibiotic course for instrumented spinal surgery at our institute, tailored to the period for postsurgical hemovac removal, and is used when there are no infectious signs, such as sustained fever and local tenderness and redness. To control for confounding variables that affect the kinetics of inflammatory markers, we performed propensity score matching. Propensity-matched variables included age, sex, body mass index, comorbidities, fused level, operative time, and estimated blood loss.

HIRA guidelines and antibiotic regimens

The HIRA in Korea recommends limiting the administration of broad-spectrum antibiotics and shortening the administration period as much as possible to prevent indiscriminate use and antibiotic resistance. Patients had received 24 hours of postoperative antibiotics (group A) were in accordance with the 9th edition of the HIRA guidelines, and the type of antibiotic and duration of administration were limited (Fig. 1). Antibiotic regimens consisted of 1st or 2nd cephalosporin only, and prophylactic antibiotic administration was initiated within 1 hour prior to incision and discontinued within 24 hours postoperatively. In our institute, all subjects received intravenous cefazedone (1st cephalosporin; 1 g/8 hours) as a prophylactic antibiotic. The guidelines included 18 types of surgery, and patients <18 years old, those who had used antibiotics for preoperative infections, and those who had undergone emergency surgery were excluded. Patients who received a blood transfusion of ≥4 units within 24 hours after surgery were also excluded.

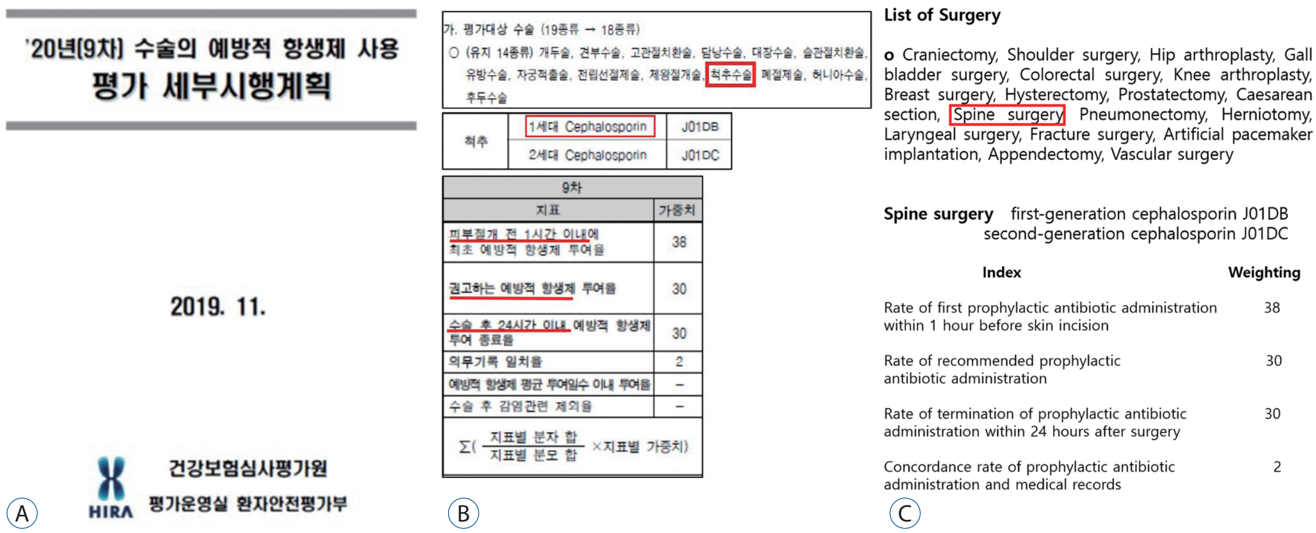

Fig. 1. The 9th edition of the Health Insurance Review & Assessment Service guidelines[20] (A). The type of antibiotic and duration of administration are limited (B). The English version of the Health Insurance Review & Assessment Service guidelines (C).

Inflammatory markers

Blood specimens were collected before surgery and on postoperative days (POD) 1, 3, 5, and 7. The serum CRP level was determined using the latex agglutination method, and its normal value is <0.5 mg/dL. ESR was determined using a manual test with a Westergren sedimentation rate tube, and its normal range is <20 mm/h. The WBC count was assessed using an automatic cell counter. All blood specimens were obtained at 6 A.M. for each subject.

Statistical analyses

Normal kinetics for inflammatory markers was defined as a sequential change : an increase after surgery until a peak value was reached, followed by a decrease. Peak values of inflammatory markers were based on measurements from subjects with a normal CRP level (<0.5 mg/dL), ESR (<20 mm/h), or WBC (4–10×10^3/mm^3) who was proved to be non-infection. Univariate analysis, including Mann-Whitney U and Student's t-tests, was performed to ascertain variables for inclusion in the multivariate analysis. Subsequently, the Pearson correlation test and multiple regression analysis were performed to determine the significant relationship and influence of each variable. Statistical significance was set at $p<0.05$.

RESULTS

Patient demographics and determination of peak CRP

A total of 74 patients who met the inclusion criteria were included in the present study. Patient demographics, surgical data, and hospitalization information are shown in Table 1. A postoperative peak for CRP was observed in 68 patients (88.3%); however, ESR and WBC counts could not be determined on POD 7. The mean preoperative CRP value was 0.69±1.36 mg/dL (values <0.5 mg/dL were assumed to be 0.5 mg/dL), and the peak CRP values were 11.43±6.97 mg/dL and 12.79±7.31 mg/dL in groups A and B, respectively ($p<0.05$), and occurred 3.14±0.92 days postoperatively ($p<0.05$). Mean preoperative ESR and WBC counts were 14.3±13.1 mm/h and 7.4±3.1×10^3/mm^3, respectively.

Univariate analysis revealed no variables as significant determinants of the ESR and WBC count peak values. For the peak CRP value, univariate analysis identified the estimated blood loss, number of fused levels, operation time, and preoperative CRP level ($p<0.05$) in the multivariate analysis. Estimated blood loss was nonmonotonic; therefore, the highest quartile of blood loss (≥1000 mL) was treated as a formal variable. The linear regression test based on these variables was statistically significant (r^2=0.473, $p<0.001$). Significant predictors of higher postoperative peak CRP levels included estimated blood loss >1000 mL ($p<0.05$), number of fused lev-

 https://doi.org/10.3340/jkns.2022.0126

Table 1. Characteristics of enrolled patients after propensity score matching

	Antibiotics, 24 hours (group A, 37)	Antibiotics, 5 days (group B, 37)	Standardized mean difference	*p*-value
Age (years)	62.2±12.4	60.9±14.1	0.10	0.34
Female	21 (56.8)	23 (57.5)	0.05	0.72
BMI	26.2±3.2	26.7±3.4	0.08	0.32
Comorbidities				
Hypertension	17 (45.9)	19 (47.5)	0.03	0.45
Diabetes mellitus	6 (16.2)	7 (17.5)	0.10	0.14
COPD	4 (10.8)	5 (12.5)	0.09	0.22
CKD	2 (5.4)	2 (5.0)	0.04	0.38
IHD	1 (2.7)	1 (2.5)	0.02	0.75
No. of fused level	2.2±1.1	2.3±1.0	0.07	0.32
Operative time (minutes)	173.2±110.4	181.8±121.3	0.04	0.44
Estimated blood loss (mL)	429.5±281.2	446.1±301.7	0.07	0.21

Values are presented as mean±standard deviation or number (%). BMI : body mass index, COPD : chronic obstructive pulmonary disease, CKD : chronic kidney disease, IHD : ischemic heart disease

Table 2. Predictors of greater postoperative peak CRP

	OR (95% CI)	*p*-value
Age (years)	0.883 (0.477–1.323)	0.43
Female sex	0.974 (0.871–1.148)	0.14
BMI	1.235 (0.957–1.521)	0.42
Hypertension	1.388 (1.143–2.014)	0.11
Diabetes mellitus	1.119 (0.984–1.423)	0.57
COPD	1.274 (0.678–1.723)	0.28
CKD	1.421 (0.792–1.934)	0.54
IHD	1.398 (0.991–1.832)	0.61
No. of fused level	1.891 (1.653–2.018)	<0.001
Operation time (minutes)	1.470 (1.332–1.591)	0.03
Estimated blood loss (mL)	1.585 (1.329–1.733)	0.02
Preoperative CRP (mg/dL)	2.133 (1.873–2.411)	0.03

CRP : C-reactive protein, OR : odds ratio, CI : confidence interval, BMI : body mass index, COPD : chronic obstructive pulmonary disease, CKD : chronic kidney disease, IHD : ischemic heart disease

els ($p<0.001$), operation time ($p<0.05$), and preoperative CRP level ($p<0.05$) (Table 2). CRP values were normalized to the percentage of the peak value and POD was normalized to the number of days after the peak. The CRP value was eliminated with first-order kinetics ($r^2=0.68$, $p<0.01$), indicating that a constant proportion was eliminated per unit time, and the curve fitted to normalized data revealed a half-life of 2.9 days. A curve fit could not be performed for ESR and WBC counts.

Sequential changes of inflammatory markers

In group A, the mean preoperative CRP value was 0.69±1.36 mg/dL, which increased to 2.57±3.98 mg/dL on POD 1. On POD 3 and 5, it increased sharply to 10.72±10.14 mg/dL and 6.48±7.76 mg/dL, respectively. On POD 7, it showed a decreasing trend and was measured to be 3.72±4.81 mg/dL. In addition to CRP, the quantitative changes in ESR and WBC count are shown in Fig. 2.

In group B, the mean preoperative CRP value was 0.61±1.49 mg/dL, which increased to 2.83±4.24 mg/dL on POD 1. On POD 3 and 5, the CRP value increased sharply to 11.39±10.09 mg/dL and 7.31±9.14 mg/dL, respectively. On POD 7, it showed a decreasing trend and was measured to be 4.09±5.13 mg/dL. All markers are shown in Fig. 2, similar to those in group A. In group A, antibiotics were not administered after POD 1; therefore, the inflammatory markers of groups A and B were compared with their respective values on POD 3 to 7, but there were no statistically significant differences (all $p>0.05$).

Wound infection

Three cases of postoperative SSIs were identified during the study period. These cases were excluded from this study; however, one case in group A and two in group B. The CRP level showed a decreasing trend after reaching the first peak value before rising again. WBC count and ESR showed a continu-

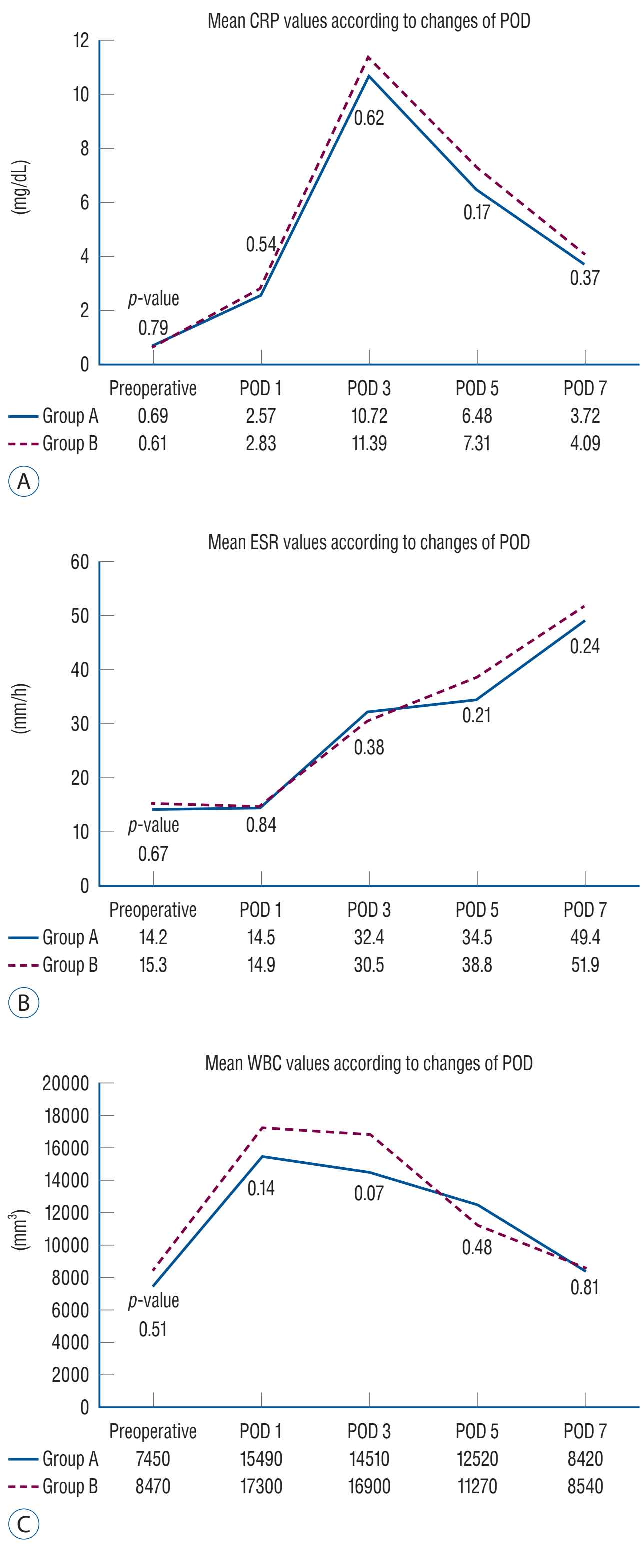

Fig. 2. The changes of mean C-reactive protein (CRP) level (A), erythrocyte sedimentation rate (ESR) (B), and white blood cell (WBC) count (C) preoperatively and on postoperative days (POD) 1, 3, 5, and 7, with comparisons between groups A and B. *p*-values are shown below the line graph.

ous increasing trend, and the WBC count decreased to within the normal range at the time of discharge. The time to reach the peak value and the quantitative value differed significantly by patient. Because there were few cases, the numerical changes and differences could not be analyzed.

DISCUSSION

Although many attempts have been made to decrease postoperative infectious complications, including sterilization methods, surgical techniques, and availability of advanced antibiotics, SSIs remain an unexpected complication that occurs after spine surgery. Consequently, perioperative use of antibiotics is routinely performed after spine surgery to prevent SSIs.

However, the overuse of antibiotics has resulted in increased opportunistic infections, the emergence of multidrug-resistant pathogens, and other adverse effects[2,8,9]. In Korea, that the discontinuation of postoperative prophylactic antibiotics is recommended within 24 hours after surgery, according to HIRA guidelines. The wound associated with spinal surgery is classified as a clean wound, which refers to an uninfected operative wound in which no inflammation is encountered and there is no gastrointestinal, respiratory, or urogenital tract in entered[3].

There have been many reports on the use of prophylactic antibiotics in spinal surgery. Hellbusch et al.[10] evaluated 269 patients who underwent lumbar fusion and received either a postoperative-only dose of antibiotics or extended 10-day regimen. The infection rate was 4.3% in the preoperative-only group and 1.7% in the 10-day antibiotic group (p>0.25). In a study of 1597 patients undergoing lumbar surgery who received either 24 hours (464 patients) or 5–7 days (1133 patients) of postoperative antibiotics, Kanayama et al.[12] reported no significant difference between the two groups in terms of infection rate. Although limited by their underpowered sample sizes and heterogeneous control groups, several studies have reported that postoperative antibiotic regimens have no added benefit in preventing SSIs[5,10-12].

CRP, ESR, and WBC count have been used to evaluate the status of infection, and several studies have reported the usefulness of inflammatory markers and suggested that a combination of normal kinetics can predict the absence of infection after elective surgery[7]. Among them, CRP value is more reliable than ESR and WBC count for monitoring the effectiveness of treatment for spinal infection[13]. Understanding normal postoperative kinetics is crucial for detecting trends that deviate from normal kinetics. In the postoperative course, many studies have described the normal kinetics of CRP as entailing a rapid rise, a peak value on POD 2 or 3, followed by a sharp decrease, and then a gradual decrease with normalization by POD 14[17,18,21].

In this study, we presented the peak value and half-life of CRP (as normal postoperative CRP kinetics after the peak) and postoperative sequential changes in CRP value, ESR, and WBC count for both groups. First, CRP is eliminated using first-order kinetics, meaning that a constant proportion is eliminated per unit time[22]. The curve fitted to the normalized data revealed a half-life of 2.9 days. The fit of the curve was acceptable (r^2=0.68, p<0.01). This result seems to be consistent with that of a previous study on the normal postoperative kinetics of CRP in spinal surgery. Our results are also consistent with those of previous studies in which CRP normalized by POD 14–21, considering the calculation of the half-life of CRP. In addition, multivariate analysis considering nonsurgical factors, including estimated blood loss, number of levels fused, operation time, and preoperative CRP level, were factors that could affect the peak CRP value. Considering these factors, it is important to estimate the peak CRP value and half-life in clinical practice. Second, the postoperative sequential changes (quantitative) in inflammatory markers were compared between the two groups. As mentioned above, the peak values of ESR and WBC count could not be determined by laboratory tests on POD 7; however, a normal postoperative course was confirmed through the overall change in values. Although there was a difference in the average values of inflammatory markers by POD in the two groups, there was no significant difference in the pattern of rapid increase followed by a gradual decrease from POD 3–5. Our results confirmed that the duration of antibiotic administration did not have a significant effect on changes in inflammatory markers in patients with a normal postoperative course.

This study had some limitations. First, postoperative inflammatory markers were routinely evaluated until POD 7. Therefore, the peak values of ESR and WBC count could not be determined, and a half-life model of CRP could not be substituted for the results of POD 14 days or longer, when postoperative changes returned to normal (preoperative level). Unfortunately, we conducted laboratory tests until POD 7. However, since most patients were discharged from the hospital on POD 7–10, it was difficult to conduct the test while they were in the hospital. Second, for patients who underwent PLIF only, the changes in inflammatory markers were greater than those of other spinal surgeries, such as lumbar decompression only, discectomy, and anterior cervical surgery. Third, the sample size was small because propensity-matched analysis was performed; however, this allowed for more precise comparisons.

Nevertheless, the postoperative change prediction model was presented through the peak CRP value and half-life, which was a peculiarity of this study. Moreover, the use of antibiotics within 24 hours after spinal surgery showed no significant differences in the incidence of infection complications and postoperative sequential changes, including peak values, compared to patients who received antibiotics for 5 days.

CONCLUSION

Although there were slight differences in numerical values and kinetics, sequential changes in inflammatory markers according to the duration of antibiotic administration showed similar patterns. Knowledge of CRP kinetics allows the assessment of the degree of difference between the clinical and expected values.

AUTHORS' DECLARATION

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : SBK; Data curation : GY; Formal analysis : MKC; Methodology : MKC; Project administration : SBK; Visualization : MKC; Writing - original draft : GY; Writing - review & editing : MKC

Data sharing

None

Preprint

None

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