Elevation of fibrin degradation product (FDP) values prevents the negative conversion of serum CRP values after total knee arthroplasty

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ABSTRACT

Background: It is essential as an orthopedic surgeon to diagnose prosthetic joint infection (PJI) at an early stage and to carry out precise treatment as well as preventing the deterioration of functional prognosis as much as possible. We suspected that PJI might have been caused because the negative conversion of creatinine reactive protein (CRP) has been prolonged after total knee arthroplasty (TKA) and patients with no serum CRP negative conversion have been treated with antibiotics to avoid the morbidity of PJI. The purpose of the present study is to investigate the factors associated with prolongation of the negative conversion of CRP, with the exclusion of PJI patients.

Methods: We performed a retrospective case control study at our institution from August 2014 to August 2016. We classified the patients into two groups based on whether it required ≥ 20 days (Group A, $n = 23$) or < 20 days (Group B, $n = 23$) for CRP levels to normalize. Serum D-Dimer and fibrin degradation product (FDP) values were measured at 1, 2, 5, 9, 12, 16, 19, 23, 26, and 30 days after TKA. Exclusion criteria include anticoagulant oral administration cases before TKA, venous thromboembolism (VTE) by postoperative lower limb venous echocardiography before and after TKA, CRP re-elevation cases, and patients with PJI. The cutoff points for D-dimer and FDP levels for screening tests were calculated from the receiver operating characteristic (ROC) curve.

Results: The ROC analysis of D-Dimer values at 30 days after TKA yielded an AUC of 0.891 (95% confidence interval (CI) 0.858–1.000), which indicates nearly an excellent test. The cutoff point of 22.1 $\mu\text{g}/\text{dl}$ for FDP value (Youden Index: 22.1 $\mu\text{g}/\text{dl}$) showed a sensitivity of 81.8% (95% CI 70.1–92.8) and a specificity of 80.0% (95% CI 67.9–89.1).

Conclusion: We revealed that CRP values of patient with an FDP level $\geq 22.1 \mu\text{g}/\text{dl}$ at 30 days after TKA necessarily showed negative conversion without antibiotic administration, when examining a patient with elevated serum CRP of minor criteria in the definition of PJI proposed by MSIS (other criteria do not apply).

Level of evidence: III

1. Background

Periprosthetic joint infection (PJI) after total knee arthroplasty (TKA) is a major complication¹ and remains a devastating and challenging complication after TKA.² Of decisive importance for the successful therapy of a PJI is an early and reliable diagnosis, which enables quick initiation of therapy and may make it possible to salvage the prosthesis.^{3,4} The standard serum C-reactive protein (CRP) is an acute phase protein produced in the liver and is elevated in case of inflammation or infection. The standard serum CRP assay is routine tests in the diagnostic workup for infection, while Bauer and Parvizi et al.^{5,6} described that if a suspected diagnosis PJI is already available clinically, the CRP values show better specificity. White J et al. revealed that

after TKA, the CRP value increases significantly and achieves its maximum value between the second and third postoperative day and then falls again to the normal level after 3–6 weeks in the case of a complication-free potential postoperative course.⁷ However, patients with no serum CRP negative conversion have been treated with antibiotics to avoid the morbidity of PJI. The Musculoskeletal Infection Society (MSIS) reported that there is a danger of administering antibiotics ineffectively for a long period of time, thus affecting the accuracy of PJI diagnosis.⁸ Therefore, we investigated whether there was any factor of delaying negative conversion of CRP after TKA except PJI.

Recently, Shahi A et al.⁸ reported that the serum D-Dimer test demonstrated better sensitivity, 89% and better specificity, 93%, for diagnosing PJI. D-Dimer of the coagulation marker is activated after TKA

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and has traditionally been used as a screening test for detecting venous thromboembolism (VTE). Perrier et al.⁹ reported that drilling, bone saw use, and bone excavation result in the long-term elevation of D-Dimer and fibrin degradation product (FDP) of fibrinolysis marker. When we examined retrospectively, we suspected that the coagulation marker would show high values as a result of delayed CRP negative conversion after TKA (without PJI and VTE); therefore, we hypothesized that patients with high level of D-Dimer and FDP values after TKA might delay the timing of CRP negative conversion. The purpose of the present study is to investigate the factors associated with prolongation of the negative conversion of CRP, with the exclusion of PJI patients.

2. Methods

We retrospectively researched the hospital database for a total of 121 patients who performed primary TKA for medial osteoarthritis of the knee from August 2014 to August 2016. Patients with the onset of PJI were not included. Out of 121 patients, 75 patients were excluded from this study due to anticoagulant oral administration before and after TKA, VTE with the use of lower limb venous echocardiography before and after TKA, re-elevation of CRP values, and morbidity of PJI (according to the diagnostic criteria of the Musculoskeletal Infection Society (MSIS)¹² (Fig. 1).

The 46 patients were divided into two groups: Group A: ≥ 20 days ($n = 23$) and Group B: < 20 days ($n = 23$), according to the number of days required for negative conversion of CRP values to occur (using 20.3 days: the mean duration of hospitalization after TKA in our hospital, as the reference value⁶). Particle enhanced immunoturbidimetric assay¹¹ (CRPL3; Roche Diagnostics) was used for the CRP analysis, with a detection limit of 0.3 mg/L and an extended measuring range of 0.3–350 mg/L, and was performed on a CP3000™ analyzer (Sekisui Medical, Tokyo Japan).

2.1. Surgical technique

All patients underwent measured resection performed by the same surgeon. The implants used were a NexGen CR-Flex (Zimmer-Biomet, Inc., Warsaw, IN) in 4 patients and a Journey 2 Bi-Cruciated Stabilized Knee System (Smith & Nephew, Inc. Memphis, TN) in 42 knees. The anesthesia method was a combination of conduction anesthesia

(femoral nerve and sciatic nerve block) and general anesthesia. Compression stockings and a foot pump were used during surgery to help prevent DVT, and a suction drainage was attached. From a day after TKA, the patients were allowed to walk without continuous passive motion. D-Dimer and FDP levels were measured at 1, 2, 5, 9, 12, 16, 19, 23, 26, and 30 days after TKA. The treatment algorithm of anticoagulation at our institute after TKA is shown in Fig. 2. Enoxaparin sodium started from a day after TKA, and lower limb venous echocardiography was performed at 9 and 16 days after TKA. Subcutaneous heparin calcium, intravenous heparin, or novel oral anticoagulant (NOAC) was selectively administered.

2.2. Statistical analysis

A power analysis of D-Dimer and FDP values revealed that sample size of 46 patients in each group would be required to allow for a detection of the difference between 18% and 17.5% (power = 0.75, 0.8, $\alpha = 0.05$, 0.05) with standard deviation of 20%. D-Dimer and FDP values at 1, 2, 5, 9, 12, 16, 19, 23, 26, and 30 days after TKA were compared between the two groups in each stratum using the Wilcoxon Matched Pairs Signed-Ranks Test. P values less than 0.05 were considered significant. We used receiver operating characteristic (ROC) curve analyses to determine the strength of serum D-dimer and FDP value for the reason of negative conversion of CRP. The ROC curve can be used to evaluate the effectiveness of serum D-Dimer and FDP value in the differentiation between $\geq$ postoperative 20 days and < 20 days (the number of days required for negative conversion of CRP values to occur). As the area under the curve (AUC) increases (to a maximum of 1), the indicator of negative CRP conversion strength improves. An AUC of 0.5 indicates a test with no indicator of negative CRP conversion strength, and a 0.9 or greater is considered an excellent test.¹² The Youden Index was used to determine the optimal cutoff point because this is the cutoff point that optimizes the anticoagulation marker's differentiating ability when equal weight is given to sensitivity and specificity.¹³ AUC values were compared between $\geq$ postoperative 20 days and < 20 days (the number of days required for negative conversion of CRP values to occur) using an approach proposed by Delong et al.¹⁴

Fig. 1. Flow diagram of illustrating patients' enrollment, allocation and analysis.

Fig. 2. Flow diagram of anticoagulant therapy after total knee arthroplasty at our institute.

3. Results

No significant difference was observed in age, gender, body weight, height, Knee Society Score, and range of motion between the two groups before TKA (Table 1). There was no significant difference about operation time between the two groups (The average operating time: Group A: 72.7 min, Group B: 78.9 min). The most delayed days of negative CRP conversion were 96 days in Group A and 19 days in Group B after TKA. The maximum value of D-Dimer after TKA was 30.2 $\mu\text{g}/\text{ml}$ in Group A and 18.7 $\mu\text{g}/\text{ml}$ in Group B. The maximum value of FDP after TKA was 68.2 $\mu\text{g}/\text{dl}$ in Group A and 42.1 $\mu\text{g}/\text{dl}$ in Group B (Table 2).

D-Dimer values for Group A were significant higher than Group B at 30 days after TKA ($p = 0.011$, $F = 3.053$, Table 3). FDP values for Group A were significant higher than Group B at 30 days after TKA ($p = 0.002$, $F = 4.216$, Table 4).

The ROC analysis of D-Dimer values at 30 days after TKA yielded an AUC of 0.891 (95% confidence interval (CI) 0.858–1.000), which indicates nearly an excellent test. The cutoff point of 22.1 $\mu\text{g}/\text{dl}$ for FDP value (Youden Index: 22.1 $\mu\text{g}/\text{dl}$) showed a sensitivity of 81.8% (95% CI 70.1–92.8) and a specificity of 80.0% (95% CI 67.9–89.1) (Table 5).

Table 1

Preoperative parameters.

Parameters	Group A (n = 23)	Group B (n = 23)	p -Value
Age	73.1 $\pm$ 7.1	74.2 $\pm$ 6.2	0.312
male/female	5/18	4/17	> 0.999
Weight (kg)	58.2 $\pm$ 10.2	54.9 $\pm$ 9.5	0.301
Height (cm)	151.9 $\pm$ 8.9	150.3 $\pm$ 9.4	0.399
Diagnosis (OA/RA)	23/0	23/0	> 0.999
Knee Society Score	37.9 $\pm$ 8.9	38.7 $\pm$ 10.1	0.372
Knee Function	42.3 $\pm$ 9.2	46.9 $\pm$ 11.1	0.184
Range of motion			
Extension	−9.8 $\pm$ 8.9	−10.8 $\pm$ 7.6	0.252
flexion	119.3 $\pm$ 13.4	122.8 $\pm$ 14.0	0.298

Table 2

Descriptive information regarding serum D-Dimer and FDP analysis.

		Min	Max	Median
D- Dimer ($\mu\text{g}/\text{ml}$)	Group A	1.0	30.2	19.7
	Group B	1.1	18.7	14.2
FDP ($\mu\text{g}/\text{dl}$)	Group A	3.3	68.2	48.1
	Group B	3.2	42.1	23.6

4. Discussion

To our knowledge, this is the first study to evaluate the role of serum FDP assessment as a factor for CRP negative conversion. Greidanus et al.¹⁵ reported that patients with a CRP level ≥ 13.5 mg/dl after TKA are more likely to develop PJI; therefore, removal of prosthesis and debridement may be required. However, in the present study, we confirmed that CRP values of patient with an FDP level ≥ 22.1 $\mu\text{g}/\text{dl}$ at 30 days after TKA necessarily showed negative conversion without antibiotic administration, when examining a patient with elevated serum CRP of minor criteria in the definition of PJI proposed by MSIS (other criteria do not apply).

The diagnosis of PJI has challenged surgeons since the advent of joint arthroplasty.¹⁶ Windisch C et al.³ reported that neither the absolute potential postoperative CRP value nor its course in the first 5 days after TKA is suitable for detecting an early infection: however, as in present case, we experienced a case of CRP negative conversion after TKA. There are several reasons for this diagnostic difficulty, including the absence of specific clinical signs and symptoms, the relative lack of accurate laboratory tests,^{17–19} while Vanderstappen C et al. revealed that intra-articular and serum CRP analysis showed a very high diagnostic strength of PJI²⁰; therefore, we plan to investigate correlation between intra-articular CRP analysis and FDP value.

There is evidence that preoperative CRP levels provide a predictive factor for infection after TKA and are an important tool of diagnosing PJI.^{21–23} In this study, preoperative CRP levels were normal values in 46 knees.

D-Dimer and FDP assessment results in fibrinolytic activities.^{24–26}

Table 3
Postoperative serum D-Dimer values.

	F statistic	Significance probability	Difference in mean	Two-sided significance	95% Confidence interval	
					lower	upper
Day.1	3.348	0.075	2.054	0.205	−1.167	5.276
Day.2	1.633	0.209	−3.467	0.478	−13.24	6.312
Day.5	0.698	0.408	−3.196	0.405	−10.86	4.476
Day.9	0.223	0.639	−0.395	0.833	−4.158	3.367
Day.12	1.148	0.290	0.568	0.756	−3.113	4.253
Day.16	8.598	0.006	1.976	0.172	−0.897	4.849
Day.19	0.180	0.674	1.599	0.298	−1.467	4.666
Day.23	2.703	0.110	2.243	0.082	−0.304	4.791
Day.27	1.280	0.270	2.724	0.136	−0.926	6.375
Day.30	3.053	0.095	5.366	0.011	1.355	9.378

Recently, Shahi A et al.⁹ found that serum D-Dimer is a promising marker for the diagnosis of PJI, and Rodelo JR et al.²⁷ reported that higher levels of D-Dimer were associated with increased 28- day mortality in patients with sepsis and emphasized the prognostic role of D-Dimer among septic patients. In the future, serum FDP analysis may have a strength for PJI diagnosis.

A first weakness of our study is that this was a retrospective study and certain values were missing owing to the absence of a standardized prospective study protocol. Next weakness is that the inadequate number of cases was assessed and patients with PJI and VTE after TKA were excluded. A third weakness of this study is that the parameters of this study are only standard hospital serum D-Dimer and FDP assay. A fourth weakness of this study is that according to MISIS definition of PJI, both ESR and CRP need to be elevated, however we did not measure and assess ESR in the present study. The last weakness of this study is that the groups were divided between the two based on 20.3 days, the mean duration of hospitalization after TKA in our institute.

5. Conclusions

The present study provided that CRP values of patient with an FDP level ≥ 22.1 $\mu\text{g/dl}$ at 30 days after TKA necessarily showed negative conversion without antibiotic administration, when examining a patient with elevated serum CRP of minor criteria in the definition of PJI proposed by MSIS.

Abbreviations

PJI: Periprosthetic joint infection; TKA: Total knee arthroplasty; CRP: C- reactive protein; MSIS: Musculoskeletal infection society; VTE: Venous thromboembolism; FDP: Fibrin degradation product; ROC: Receiver operating characteristic; AUC: As the area under the curve.

Table 4
Postoperative serum FDP values.

	F statistic	Significance probability	Difference in mean	Two-sided significance	95% Confidence interval	
					lower	upper
Day.1	3.099	0.086	4.456	0.201	−2.472	11.38
Day.2	1.534	0.223	−3.467	0.494	−13.24	6.312
Day.5	0.535	0.469	−4.776	0.463	−17.80	8.250
Day.9	0.994	0.325	−0.964	0.792	−6.392	8.321
Day.12	2.045	0.161	2.998	0.413	−4.334	10.33
Day.16	6.953	0.012	5.553	0.086	−0.830	11.93
Day.19	0.680	0.415	4.751	0.151	−1.820	11.32
Day.23	2.391	0.132	5.345	0.067	−0.403	11.09
Day.27	1.534	0.229	6.391	0.100	−1.328	14.11
Day.30	4.216	0.054	9.924	0.002	4.006	15.84

Table 5
Receiver operating characteristic curve analyses.

		Cut off value	Sensitivity (%)	Specificity (%)	AUC
Day.1	D-Dimer	2.8 $\mu\text{g/ml}$	66.7	60.0	0.571
	FDP	6.15 $\mu\text{g/dl}$	72.2	48.0	0.590
Day.2	D-Dimer	2.25 $\mu\text{g/ml}$	61.1	48.0	0.464
	FDP	6.95 $\mu\text{g/dl}$	55.6	56.0	0.469
Day.5	D-Dimer	5.10 $\mu\text{g/ml}$	77.8	48.0	0.397
	FDP	12.0 $\mu\text{g/dl}$	66.7	32.0	0.419
Day.9	D-Dimer	10.8 $\mu\text{g/ml}$	58.8	48.0	0.476
	FDP	21.6 $\mu\text{g/dl}$	64.7	48.0	0.534
Day.12	D-Dimer	12.2 $\mu\text{g/ml}$	61.1	56.6	0.529
	FDP	26.8 $\mu\text{g/dl}$	61.1	64.0	0.581
Day.16	D-Dimer	8.40 $\mu\text{g/ml}$	83.3	37.4	0.578
	FDP	22.1 $\mu\text{g/dl}$	61.1	54.5	0.601
Day.19	D-Dimer	9.15 $\mu\text{g/ml}$	76.5	57.1	0.625
	FDP	20.6 $\mu\text{g/dl}$	76.5	61.9	0.619
Day.23	D-Dimer	8.95 $\mu\text{g/ml}$	53.3	76.5	0.635
	FDP	15.8 $\mu\text{g/dl}$	66.7	64.7	0.688
Day.26	D-Dimer	7.6 $\mu\text{g/ml}$	53.3	33.3	0.561
	FDP	15.0 $\mu\text{g/dl}$	80.0	33.5	0.689
Day.30	D-Dimer	5.7 $\mu\text{g/ml}$	81.8	60.6	0.700
	FDP	22.1 $\mu\text{g/dl}$	81.8	80.0	0.891

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Availability of data and materials

The datasets used and/or analyses during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TK and TF designed the study and wrote the manuscript. TS, HI and

YM evaluated the data. All authors approved the final manuscript.

Ethics approval and consent to participate

The present study followed the Declaration of Helsinki and was approved by the local ethics committee of the Toho University Ohashi Medical Center, Tokyo, Japan.

Consent for publication

No applicable.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jor.2018.08.005>.

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