Executive Summary

Economic evaluation for procalcitonin test in patients with suspected sepsis

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▢ Introduction

Sepsis management has been emphasized due to the high hospitalization rate, mortality, and costs associated with sepsis. The latest guidelines for diagnosis and treatment of sepsis recommend using procalcitonin test, when determining whether to discontinue the use of antibiotics for patients who do not experience secondary infections following initial resuscitation of sepsis. Since unnecessary use of antibiotics can be minimized by using procalcitonin test, reduction in antibiotics-related complications, and further, effectiveness in reducing medical costs can be expected. However, there are no comparative studies on Korean patients with regards to this subject matter and economic evaluations on reduction in antibiotics treatment duration based on procalcitonin levels are also lacking.

Therefore, it is necessary to generate scientific evidence that procalcitonin test can safely reduce the duration of antibiotics treatment and whether this approach is feasible economically by identifying the effectiveness of procalcitonin test as an indicator to determine the treatment course of antibiotics in sepsis suspected or confirmed patients without secondary infections in Korea.

This study aimed to evaluate the clinical effectiveness on determining discontinuation of antibiotics based on procalcitonin levels in sepsis suspected patients and to conduct an economic analysis in order to provide evidence for policy- and decision-making related to procalcitonin test.

▢ Clinical effectiveness of procalcitonin test

Ⅰ. Systematic Review

In order to make a comparison between clinical effectiveness of procalcitonin-guided treatment on antibiotic use and effectiveness of routine care in sepsis patients, existing systematic reviews were used. A systematic review search was conducted using pre-established PICOTS-SD according to the methodology recommended by AHRQ of the US and the suitability of the searched studies was evaluated. Following the search strategy, a total of 134

cases were identified from various databases, such as EMBASE, Ovid-Medline, and KoreaMed, among which a final total of 7 reviews were selected based on the selection and exclusion criteria.

The selected systematic reviews were evaluated for suitability of literature selection and data extraction as well as comprehensiveness of the literature search using AMSTAR. Based on the quality evaluation, Prkno et al. (2013) was selected as the final candidate. Using the selected literature as the basis, search on clinical trials was conducted after adding ICU settings and randomized clinical trials to the selection criteria. Ultimately, one literature was selected as the final candidate through a process of primary/secondary selection and exclusion by two independent evaluators, and by including 7 clinical trials from precedent systematic reviews, a total of 8 clinical trials were included in the systematic review.

The risk of bias associated with the selected literature was assessed using RoB tool, while traditional and Bayesian meta-analyses were performed to compare the clinical effectiveness of procalcitonin-guided treatment on antibiotic use with routine care in sepsis suspected patients. According to the risk of bias assessment, since the characteristic feature of procalcitonin-guided treatment on antibiotic use made a double-blind difficult, most literature, with the exception of Jensen et al. (2011), were unclear on whether researcher blinding had been conducted. Meanwhile, traditional and Bayesian meta-analyses were used to quantitatively compare procalcitonin-guided treatment on antibiotic use with routine care.

The results of the two meta-analyses showed no statistically significant differences between the procalcitonin group and routine care group with respect to 28-day mortality, in-hospital mortality, length of stay in ICU, and length of stay in hospital; whereas, duration of antibiotics did show a significant difference between two groups. In the traditional meta-analysis, the procalcitonin group, compared to the routine care group, showed reduction of 2.43 days in the duration of antibiotics (95% CI: (-3.46, -1.40), p-value<0.0001), while in the Bayesian meta-analysis, posterior median of the

mean difference was estimated to be -2.39 (95% CrI: (-3.79, -1.13)). The posterior percentage of procalcitonin-guided treatment on antibiotic use reducing the duration of antibiotics use compared to routine care was shown to be 1.

Ⅱ. Prospective, multi-center, Randomized Controlled Trial

A prospective clinical trial was conducted from 4 tertiary hospitals (Seoul National University Hospital, Samsung Medical Center, Severance Hospital, and Seoul Asan Medical Center) in order to identify the influences on the duration of antibiotics and length of hospital stay in sepsis suspected or confirmed patients hospitalized in the ICU when decisions are made on discontinuing or changing antibiotics treatments based on procalcitonin levels.

In accordance with the selection and exclusion criteria, the patients registered for the clinical trial were randomly assigned to the procalcitonin or routine care group. At this time, a guideline was used to overrule cases involving even single violation of strong recommendation for antibiotics discontinuation, meaning continuing to use antibiotics for two more days and using antibiotics for two consecutive times despite recommendation for discontinuation of antibiotics administration, with such cases being excluded from per-protocol (PP) analysis. The patients registered for the clinical trial were monitored at 28-days after onset of sepsis, discharge from ICU, and discharge from hospital, and the number of days of using antibiotics was identified as the primary clinical outcomes, while 28-day mortality, in-hospital mortality, length of stay in ICU, and hospitalization costs were identified as the secondary outcomes.

In terms of clinical trial results, a total of 377 sepsis suspected patients had passed through the screening process for the selection criteria between May 2014 and June 2015, among whom, a total of 57 patients were registered for the clinical trial. In the procalcitonin group, 15 patients, out of 26 who were assigned to this group, were excluded from PP analysis due

to drop out or overrule, whereas in the routine care group, 3 out of 31 patients were excluded. As a result of comparing the baseline characteristics of patients assigned to the two groups, the overall distribution of baseline characteristics, such as age, severity, and medical history were shown to be similar.

The number of days using antibiotics indicated to be shorter in the procalcitonin group, for whom antibiotics discontinuation was determined according to procalcitonin levels, than that of the routine care group. Intent-to-treat (ITT) analysis showed that the number of days of antibiotics administration in the procalcitonin group was 12.24 days (sd=8.72) and 16.06 days (sd=10.4) in the routine care group, which indicated reduction of 3.82 days. However, the difference was not statistically significant (p=0.1479). On the other hand, PP analysis showed number of days of antibiotics administration in the procalcitonin and routine care groups to be 6.91 (sd=4.44) and 14.79 days (sd=9.37), respectively, showing significant reduction of 7.88 days of antibiotics administration in the procalcitonin group (p=0.0013). In terms of secondary indicators of length of stay in ICU and hospital, they were shown to be similar in both the procalcitonin and routine care groups by both ITT and PP analyses, while 28-day mortality, in-hospital mortality, utilization of mechanical ventilation, and treatment success rate were also shown to be similar between the two groups.

▢ Economic analysis of Procalcionin test

Ⅰ. Cost-Minimization Analysis

The fact that procalcitonin-guided withdrawal of antibiotics does not influence the final outcome, such as in-hospital and 28-day mortality was confirmed via systematic review and prospective clinical trial, and cost-minimization analysis was performed. Based on the data from two hospitals where prospective clinical trial was performed, 1-day medical cost, cost of procalcitonin test, antibiotics cost, and ICU cost for both the procalcitonin and routine care groups were extracted and compared.

Moreover, sensitivity analysis was performed using sepsis-related antibiotics costs from claims data of Health Insurance Review and Assessment (HIRA) and meta-analysis results from the systematic review.

The results of the cost-minimization analysis using values obtained from the prospective clinical trial showed that the average cost per sepsis hospitalization case in the procalcitonin and routine care group was 19.52 million and 26.84 million won, respectively, indicating the routine care group spent 7.32 million won more than the procalcitonin group. In addition, when only the procalcitonin and antibiotics costs were compared, the results also showed that the routine care group spent approximately 80,000 won more than the procalcitonin group.

Ⅱ. Budget Impact Analysis

Currently, procalcitonin test is a non-reimbursement item, and in consideration of being switched to a reimbursement item, budget impact analysis for years 2016 through 2018 was performed. By taking into account the number of reimbursements for procalcitonin tests and the substitution rate for the test being used in clinical settings, a total of 4 scenarios were examined, which were 2 reimbursements + substitution rate 10%; 2 reimbursements + substitution rate 20%, 3 reimbursements + substitution rate 10%, and 3 reimbursements + substitution rate 20%. Moreover, sensitivity analysis was also performed on when all sepsis antibiotics treatments are administered with minimal-cost antibiotics, when adequate reimbursement cost is applied for procalcitonin tests, and when the number of reimbursements for procalcitonin tests and the substitution rates increase.

It was confirmed in all of the scenarios considered that procalcitonin test had the effectiveness of budget savings compared to current routine care and changes in financial impact were sensitive to changes in the substitution rate. Procalcitonin test being reimbursed 2 times with substitution rate of 10% and being reimbursed 3 times with substitution rate 10% amounted to a budget savings effect of 21.6 billion and 21.4 billion won, respectively.

Moreover, procalcitonin test with substitution rate of 20% and being reimbursed 2 times versus 3 times was determined to amount to a budget savings effect of 47.6 billion versus 47.2 billion won compared to current routine care, respectively.

In all of the scenarios, the cost of procalcitonin test increased the financial burden in comparison to current status, but showed an overall budgetl savings effect by increasing the margin of budget savings associated with hospitalization and antibiotics cost, and there was a tendency for the substitution rate of using the test having a bigger financial impact than the number of imbursements for the procalcitonin test. A similar outcome was observed from the sensitivity analysis performed on antibiotics cost, reimbursement cost of procalcitonin test, number of reimbursements for the test, and substitution rate.

▢ Conclusions and Implications

Through a multi-center prospective randomized controlled trial conducted on sepsis suspected or confirmed patients admitted to ICU, it was confirmed that using procalcitonin test on Korean sepsis patients to determine treatment course of antibiotics was able to reduce the duration of antibiotics by approximately 8 days, in comparison to routine care, however, no statistically significant differences in mortality and length of hospital stay were indicated. The cost-minimization analysis demonstrated for each case of sepsis, using procalcitonin test to determine discontinuation of antibiotics treatment resulted in a cost savings effect of approximately 7.32 million won, in comparison to routine care. The present study also performed budget impact analysis with the assumption that procalcitonin test, which is currently a non-reimbursement item, will become a reimbursement item. It was shown that when the substitution rate of procalcitonin test was set to 10-20%, with the test being performed 2 to 3 times, it had a budget savings effect over current routine care.

This study is the first research to identify the clinical effectiveness of

procalcitonin test through a multi-center prospective randomized controlled trial conducted on sepsis patients and reflected the results in performing an economic analysis of current conditions in Korea. Therefore, the significance of the present study can be viewed as having provided evidence for policy- and decision-making related to procalcitonin test in Korea.

Sepsis, Procalcitonin, Antibiotics, Economic Evaluation, Randomized Controlled Trial

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