Fecal calprotectin level in differentiating between inflammatory and non-inflammatory diarrhea in patients with nosocomial diarrhea

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Study Protocol with Statistical Analysis Plan

Backgound/Rationale

Nosocomial diarrhea is defined as diarrhea that develops after 72 hours of hospitalization. This condition is common among hospitalized patients with reported prevalence of 14-21%. The causes of nosocomial diarrhea can be categorized into inflammatory and non-inflammatory causes. For inflammatory etiologies, the most concern is *Clostridium difficile* infection. Other infections such as cytomegaloviral enterocolitis can also occur because immune function can be suppressed during critical illness. Ischemic enterocolitis is another cause in the inflammatory group. The non-inflammatory causes include adverse effects of medications and tube-feeding diarrhea. Differentiating inflammatory diarrhea from non-inflammatory diarrhea is important. Investigations for distinguishing these two conditions are stool *C.difficile* toxin test and stool examination. Because the reported sensitivity of only 60-70% for C. difficile toxin test by EIA method, which is most widely used in many centers, and the diagnosis of CMV is based on pathological findings, inflammatory diarrhea cannot be excluded completely by the negative stool tests. Colonoscopy is still required in some cases. However, although colonoscopy is a low risk procedure, the risk may increase if performed in hospitalized patients, who may have many comorbidities. A noninvasive test that can better differentiate inflammatory from noninflammatory diarrhea could help physicians to perform colonoscopy more appropriately. Calprotectin is a protein found in human neutrophils, and it is released during active periods of inflammation of intestine. The sensitivity and specificity has been reported at 93% and 96%, respectively in differentiating inflammatory bowel disease from irritable bowel syndrome in outpatient setting. Hence, its benefit in differentiating inflammatory from noninflammatory diarrhea in nosocomial diarrhea is possible, but never been studied. In the present study, we aim

to study the efficacy of fecal calprotectin in distinguishing inflammatory nosocomial diarrhea from non-inflammatory nosocomial diarrhea. Furthermore, the level of fecal calprotectin has been reported to be associated with the degree of intestinal inflammation. It could have a role in determine prognosis of the patients.

Study design

The study is a prospective observational study performed at tertiary care center from June 2019 to June 2020.

Population

1. Sample size

In literature review, we found a study comparing fecal calprotectin levels between *C. difficile* associated diarrhea and antibiotic associated diarrhea. The median fecal calprotectin level in *C.difficile* associated diarrhea was 684.8 (range:203.7 to 1581.0) and the median level in antibiotic associated diarrhea was 66.5(range :23.1 to 145.7). Using Mann-Whitney U test with a standard normal of 1.96, alpha error of 5%, and power of 80%, the calculated sample size is 61patients in each group.

2. Study population

Inclusion Criteria:

1.Ageat least 18 years

2.Diarrhea more than 3 bowel movements per day which develops after 72 hours of admission

Exclusion Criteria:

1.Intraabdominal pressure more than 12 mmHg

2.Patient on chemotherapy with neutropenia (ANC less than 1,000/mm^3)

Study procedures

The patients with nosocomial diarrhea who are tested for *C.difficile* infection and stool examination will be recruited. Their leftover stool specimens about 100mg will be collected and frozen at -80 celsius degree until the end of study. All collected samples will be measured for calprotectin levels.

The inflammatory diarrhea is defined if

1) positive for *C. difficile* toxin or

2) stool WBC more than 5/HPF or

3) inflammatory mucosa or ulceration noted on colonoscopy

The noninflammatory diarrhea is defined if

1) negative for C. difficile toxin and

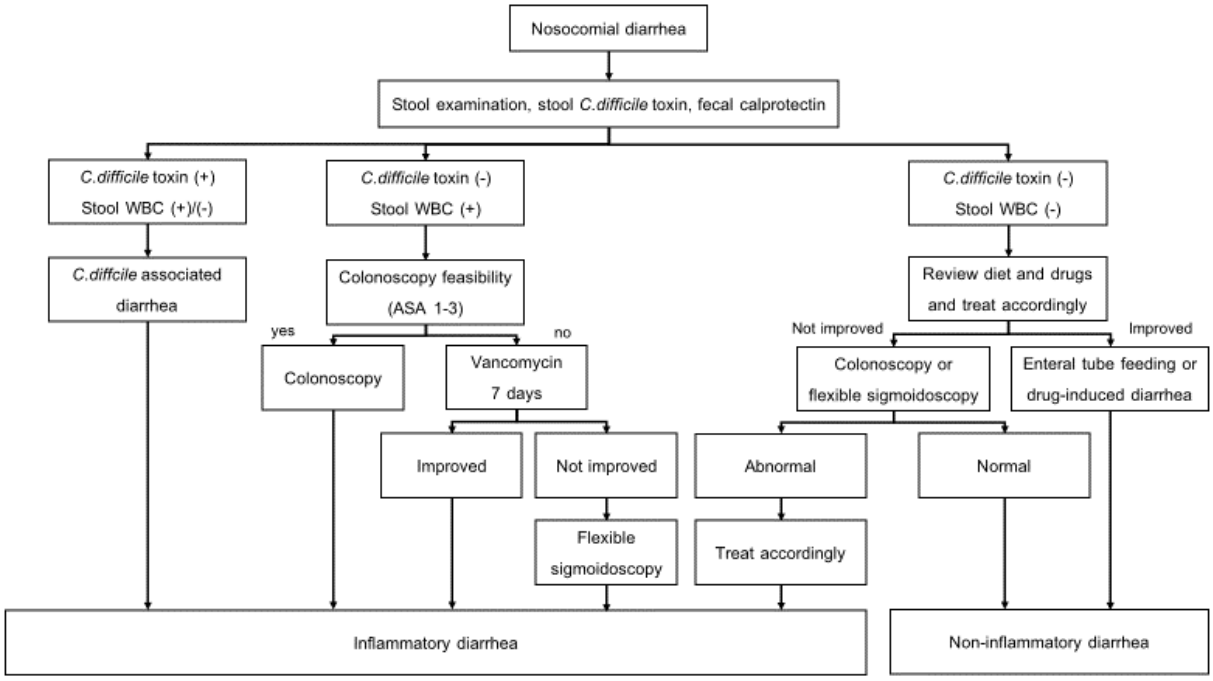
2) no WBC on stool examination and

3) dramatic and persistent response to diet adjustment

Or

4) no mucosal inflammation or ulceration if colonoscopy is performed

The management and enrollment flow chart is shown in Figure 1.



Data collection process

All patients are required to consent to the study. Their stool samples will be routinely sent for microscopic examination (cell count and parasites) and *C.difficile* toxin. Fecal calprotectin will be kept at -80 celsius degree and will be measured for fecal calprotectin at the end of study. The patients baseline characteristics, indication of hospitalization, treatment, and clinical progression will be obtained. All patients will be managed by primary physicians who do not know the results of fecal calprotectin level.

This protocol has been approved by Siriraj Institutional Review Board on January 24, 2019. The approval number is 718/2561(EC4).

Outcome Measures

Primary outcome: To determine the efficacy of fecal calprotectin in distinguishing inflammatory nosocomial diarrhea from non-inflammatory nosocomial diarrhea.

Secondary outcome: Correlation of fecal calprotectin levels and prognosis of hospitalized patients with nosocomial diarrhea.

The participants with nosocomial diarrhea were tested for C.difficile and stool examination or further colonoscopy for definite diagnosis group of diarrhea. Their leftover specimens will be kept until the end of the study. Then all collected stool specimens will be measured for calprotectin levels. Overall data collected of 147 participants will be completed analyzed about August 2020.

Statistical Analyses

The continuous data will be reported in mean and standard deviation or median and range as appropriate.

Categorical data will be reported in percentage or frequency.

Comparision of factors and patient characteristic between inflammatory and non-inflammatory diarrhea groups will be analyzed using independent t-test or Wilcoxon Rank Sum test for continuous variables, and chi-square test or fisher exact test for categorical variables.

Fecal calprotectin levels between inflammatory and non-inflammatory diarrhea will be shown in receiver operating characteristic curve(ROC). The best cut off will be calculated.

Correlation of fecal calprotectin levels and treatment outcomes, both univariate and multivariate analysis, will be analyzed by logistic regression.

P value < 0.05 will be considered statistically significant.

Adverse Event Information

This study only collects leftover stool samples without any intervention done to the patients. Therefore, there will be no additional risks to the patients apart from the standard care.

Limitations and Caveats

1.Some participants cannot undergo colonoscopy for definite diagnosis of nosocomial diarrhea due to risk of procedures. These patients will be excluded from the study.

2.Number of participants in two groups were not equal as this is an observational study.

Certain Agreements

The principal investigator is not an employee of the sponsor.

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