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Fecal Microbiota Transplantation against Gut Colonization Using a Multidrug-Resistant Organism

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Abstract

Background: Fecal microbiota transplantation against gut colonization using a multidrug-resistant organism is a technique used to treat infections through normalizing the gut microbiota via fecal microbiota transplantation in patients with confirmed colonization by carbapenem-resistant *Enterobacteriaceae* (CRE) or vancomycin-resistant enterococci (VRE) based on a fecal culture test within the past one week. In this study, we aimed to determine the safety and effectiveness of this technique. *Methods:* The safety and effectiveness were assessed via a systematic review. A literature search was conducted using five Korean databases, such as KoreaMed, and international databases, including Ovid-MEDLINE, Ovid-EMBASE, and Cochrane Library. *Results:* Main results are described here. From the studies retrieved using the aforementioned search strategy, the remaining 581 studies were screened using the inclusion and exclusion criteria, resulting in the selection of nine studies for further consideration. In terms of safety, many studies reported deaths and adverse reactions associated with different causes. Fewer studies reported the rate of colonization; however, the effect of colony rate was inconsistent when compared to no treatment group. Additionally, none of the studies assessed the recurrence rate, a decrease in the prevalence of diseases related to infection by multidrug-resistant bacteria, and the quality of life. *Conclusion:* Fecal bacterial colonization for the decolonization of intestinal multidrug-resistant bacteria was evaluated using a technique that requires further research as there is insufficient literature evidence to validate its safety and efficacy in treating infections through normalizing the intestinal flora of patients with confirmed colonization by CRE or VRE.

Keywords

Fecal microbiota transplantation
Gut colonization
Multidrug-resistant organism

1. Introduction

Multidrug-resistant bacteria are a global issue, not only in Korea, and the World Health Organization has identified antibiotic resistance as a serious threat to public health. Among them, carbapenem-resistant *Enterobacteriaceae* (CRE) and vancomycin-resistant enterococci (VRE) can cause infections in vulnerable groups, resulting in complications, mortality, hospitalization, and increased medical costs, but there is no effective antibiotic treatment due to side effects of the drugs and the emergence of new resistant bacteria. If CRE or VRE is detected, but the patient has no symptoms from the infection, it is considered colonization, not infection. In these cases, antimicrobial treatment to decolonize is not indicated, and the patient is isolated to prevent transmission to others. However, once colonization has occurred, the bacteria cannot be negated for a considerable period of time, resulting in a long isolation period, which requires a lot of medical resources and causes inconvenience to the patient. Therefore, effective treatment for rapid decolonization is needed, but there are no reports to date [1].

Fecal flora transplantation is a procedure in which the fecal flora of a healthy person is transplanted into a patient, and the microbiota of the donor's normal stool restores the patient's diverse microbiota, thereby reducing intestinal colonization by multidrug-resistant organisms (MDROs) [2]. The technology has been reviewed as safe and effective by the New Medical Technology Assessment Committee and is being used off-label in medical institutions to treat patients with recurrent or unresponsive to conventional antibiotic therapy for *Clostridium difficile* infection. To date, there has been no systematic review of fecal flora transplantation for decolonization of multidrug-resistant bacteria in Korea, and this study aims to provide evidence through a systematic review of whether fecal flora transplantation is safe and effective for decolonization in patients with CRE or VRE colonization.

2. Materials and methods

2.1. Study design

This study used a systematic review to examine the safety and efficacy of fecal flora transplantation for colonization and decolonization of CRE or VRE in patients with confirmed colonization by stool culture. The systematic review was conducted according to the guidelines set out by the PRISMA group [3].

2.2. Literature search strategy

2.2.1. Key question

The primary question of this study is: "Is it safe and effective to treat infections by normalizing the patient's gut flora through fecal flora transplantation in patients whose stool culture confirms colonization with CRE or VRE?" and the Patient-Intervention-Comparison-Outcome (PICO) for the study is as follows. Patients were defined as those with colonization of CRE or VRE confirmed by stool culture, intervention was fecal flora transplantation, comparison was solid dietary therapy, and outcomes were safety: procedure-related deaths and adverse events, all-cause deaths and adverse events, and efficacy: colonization-related indicators (colonization rate, duration), recurrence rate, reduction in multidrug-resistant bacterial infection-related morbidity, and quality of life.

2.2.2. Literature search and selection process

The literature search was conducted on 10 January 2020 using five domestic databases including KoreaMed and international databases of Ovid-MEDLINE, Ovid-EMBASE, and the Cochrane Library. The search terms used in the literature search were constructed by deriving key conceptual terms from the target patients and interventions, and no language restrictions were placed on the search. Domestic databases were searched extensively using the search terms "fecal flora transplantation," "microbiota," and "transplantation," and then unnecessary articles were

manually excluded from the retrieved articles after confirming that the interventional procedure, fecal flora transplantation, was performed. International databases were selected by considering MeSH terms and the indexing structure of each database. A total of 725 articles were retrieved as a result of the domestic and international literature searches. Literature selection was performed independently by two reviewers for all retrieved articles. The primary inclusion/exclusion process involved reviewing titles and abstracts to exclude articles deemed irrelevant to the study, and the secondary inclusion/exclusion process involved reviewing the full text of articles to select articles that met the predetermined inclusion criteria.

The inclusion criteria were studies conducted in patients with colonization of carbapenem-resistant *Enterobacteriaceae* or vancomycin-resistant *Enterococcus faecalis* confirmed by stool culture, fecal flora transplantation for decolonization of multidrug-resistant bacteria in the intestine, and studies reporting at least one appropriate medical outcome, while the exclusion criteria were animal experimental and preclinical studies, non-printed studies, studies not published in Korean or English, studies with only abstracts, and grey literature such as theses and research reports. After applying the selection and exclusion criteria to 581 articles, excluding 144 duplicate searches, a total of 9 articles were included in the evaluation (**Figure 1**).

2.2.3. Evaluation of literature quality

The quality of the selected studies was assessed using the quality assessment checklist of the Scottish Intercollegiate Guideline Network (SIGN) in the UK. We selected essential items according to the type of study and rated them as '++' if almost all or all criteria were met and we were confident that the conclusions of the study or review would not be changed by the unmet part of the criteria, '+' if some criteria were met and we thought that the conclusions of the study would not be changed by the inadequate or unmet part, and '-' if almost all or all criteria were not met and we thought that the conclusions of the study would be changed. The levels of evidence based on the results of the quality assessment are shown in **Table 1**. The quality assessment was performed independently by two reviewers. We attempted to reconcile any discrepancies through discussion, but there were no inter-rater disagreements. Of the nine selected articles, one randomized clinical trial study was graded '1-',

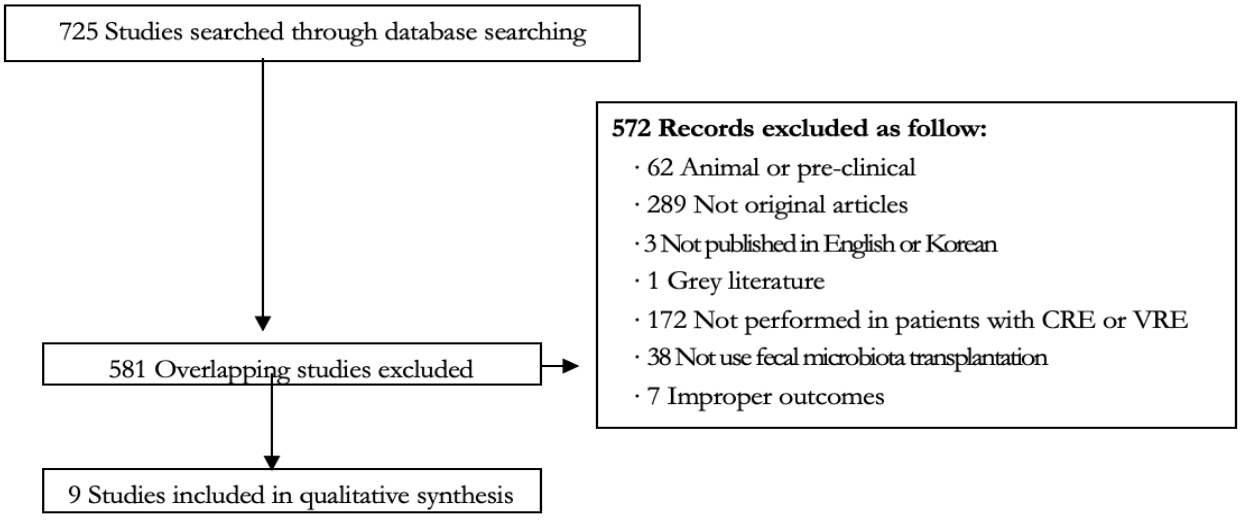

Figure 1. Flow chart of the literature selection process. Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; VRE, vancomycin-resistant enterococci.

one cohort study was graded '2+', and the remaining seven were case reports and did not receive a quality assessment. The recommendation grades based on the quality of evidence used in the studies are shown in **Table 2**.

2.3. Extract data

Data extraction was performed independently by two reviewers using a pre-established data extraction form for the selected articles. Data on safety and efficacy were extracted, along with the common content described in the literature and the characteristics of the study population that influenced the results.

3. Results

The articles selected to evaluate the safety and efficacy of fecal flora transplantation were all conducted internationally and comprised a total of nine studies, as shown in **Table 3**. The types of studies included one randomized clinical trial, one patient-controlled study, and seven case reports.

3.1. Safety

Safety was assessed by the indicators of procedure-related deaths and adverse events, and all-cause deaths and adverse events. Procedure-related deaths and adverse events were not identified in any comparative studies, and one single-arm study reported no events. For all-cause deaths and adverse events, the intervention group reported 5% (1/20) deaths, 19.0% (4/21) serious adverse events, 90% adverse drug reactions, and 57% diarrhea; the comparison group reported 11.8% (2/17) serious adverse events, 76.5% adverse drug reactions, and 20% diarrhea. Six of the seven single-arm studies reported death 5% to 20%, vomiting 5%, constipation 10%, diarrhea 10% to 100%, acute GvHD 10%, and sepsis 5%, and one reported no events (0%).

Table 1. SIGN criteria for the assignment of levels of evidence

Level	Description
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies
2+	High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2-	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
3	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
4	Expert opinion

Abbreviations: SIGN, Scottish intercollegiate guideline network; RCT, randomized control trial.

Table 2. SIGN criteria for the assignment of levels of grades of recommendation

Level	Description
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

Abbreviations: SIGN, Scottish intercollegiate guideline network; RCT, randomized controlled trial.

Table 3. Study characteristics of included study

Authors (year)	Patients (*n*)	Intervention		Comparator	Level of evidence	Safety	Effectiveness
		Route of infusion	Specimen				
Huttner (2019) [4]	ESBL-E and/or CPE (*n* = 39)	Capsules or through a nasogastric application	Frozen	No intervention	1-	Adverse event (90% vs. 76.5%), diarrhea (57% vs. 20%)	Decolonization rate (38% vs. 25%)
Saïdani (2019) [5]	CPE/A (*n* = 30)	Nasogastric tube	Not reported	No intervention	2+	Death (FMT: 1/20)	Decolonization rate (80% vs. 10%), decolonization period (3 days vs. 50.5 days)
Battipaglia (2019) [6]	CPE, VRE (*n* = 10)	Enema or via nasogastric tube	Fresh / frozen	-	3	Death (30%), bacteriemia without sepsis (20%), constipation (10%), diarrhea (20%), acute gut GvHD (10%), febrile neutropenia (20%)	Not applicable
Davido (2019) [7]	VRE (*n* = 8)	Nasoduodenal tube	Frozen	-	3	Not reported	Not applicable
Dinh (2018) [8]	CPE (*n* = 8) VRE (*n* = 9)	Nasoduodenal tube	Frozen	-	3	Death (5.9%)	Not applicable
Bilinski (2017) [9]	CPE, VRE (*n* = 20)	Nasoduodenal tube	Frozen	-	3	Death (5%), sepsis (5%), vomiting (5%), diarrhea (100%), abdominal pain (10%), ileus (10%)	Not applicable
Davido (2017) [10]	CPE, VRE (*n* = 8)	Nasoduodenal tube	Frozen	-	3	Death (12.5%)	Not applicable
Jang (2015) [11]	VRE (*n* = 1)	Nasoduodenal tube	Fresh	-	3	Diarrhea, fever, focal erythematous, edematous mucosa	Not applicable
Stripling (2015) [12]	VRE (*n* = 1)	Nasogastric tube	Not reported	-	3	Not reported	Not applicable

Abbreviation: ESBI, extended-spectrum beta-lactamases; CPE, carbapenemase-producing *Enterobacteriaceae*; VRE, vancomycin-resistant enterococci; FMT, fecal microbiota transplantation.

3.2. Validity

Efficacy was assessed by colonization rate, time to colonization, relapse rate, reduction in the incidence of multidrug-resistant bacterial infections, and quality of life. In the two comparative studies, the colonization rate was 38% to 80% in the intervention group and 10% to 25% in the comparison group, and the duration of colonization was a mean of 3 days in the intervention group and 50.5 days in the comparison group. No other studies were identified that reported recurrence rates, reductions in multidrug-resistant infection-related events, or quality of life.

4. Discussion

This study evaluated the safety and efficacy of fecal flora transplantation in normalizing the patient's gut flora in patients with stool culture-confirmed colonization of CRE or VRE. The selected literature consisted of only one randomized clinical trial and one patient-controlled study, which was insufficiently powered and underpowered to conclude the efficacy. When evaluating procedure-related adverse events, many of the patient-controlled studies reported deaths and adverse events after fecal flora transplantation from any cause [6,8-10], limiting the ability to analyze adverse events attributable to fecal flora transplantation. In addition, when planning the systematic review, we identified colonization rate as a quantitative indicator of efficacy to reduce the risk of patient-to-patient transmission of infection [13]; however, due to the small number of studies reporting colonization rate and the inconsistent effectiveness of colonization rate compared to no treatment, we were unable to identify evidence to support its use as a primary endpoint. Given the difficulty in identifying evidence of patient-to-patient transmission of resistant bacteria, the ultimate effect of fecal flora transplantation, it would be useful to systematically and continuously monitor post-transplantation colonization rates in future studies of the efficacy of fecal flora transplantation.

Limitations to demonstrating the safety and efficacy of fecal flora transplantation include the fact that the specific method of transplantation varies among the studies reviewed in this study, the exclusion of immunocompromised patients from the group of patients with high requirements for the procedure in actual clinical practice and the exclusion of immunocompromised patients from the selective literature [4,5,7-10], and the fact that no studies were identified that reported results on indicators such as recurrence rates, reduction in the incidence of multidrug-resistant bacterial infections, and quality of life. This may be due to the national approvals and regulatory guidelines for fecal flora transplantation yet to be standardized [14,15]. Therefore, based on the results of the literature review, the level of evidence for this technology was judged to be C, indicating that further research is still needed.

It has been argued that fecal flora transplantation should be viewed as a tissue or organ transplant under the EU Tissue and Cells Directive (EUTCD) because of the long-term effects of the transplanted flora on the human body [16,17], so the safety of this technology should be as rigorous as that of organ transplantation. Given this, the selection criteria for patients and donors are very important issues, and further evidence accumulation is needed.

Disclosure statement

The authors declare no conflict of interest.

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