LOPERAMIDE AND CODEINE THERAPY FOR ENTEROCUTANEOUS FISTULA : CASE SERIES

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ABSTRAK

Fistula enterokutan (Enterocutaneous Fistula/ECF) adalah hubungan abnormal antara saluran pencernaan intra-abdomen dan kulit atau luka. Keberadaan saluran ini menyebabkan cairan lambung atau usus bocor ke lingkungan eksternal. ECF dapat disebabkan oleh berbagai faktor, namun paling sering terjadi sebagai komplikasi pascaoperasi. Dalam seri kasus ini, disajikan dua kasus ECF yang ditangani menggunakan kombinasi loperamide dan codeine. Laporan Kasus 1: Seorang wanita berusia 46 tahun dengan obstruksi ileus total akibat Adenokarsinoma kolon transversum (grade rendah) cT4N1M1 (metastasis hati) menjalani laparotomi, adhesiolisis, dan hemikolektomi kanan ekstensif. Pemeriksaan pascaoperasi menunjukkan ECF dengan keluaran tinggi dan kebocoran anastomosis. Pasien distabilkan melalui koreksi elektrolit, nutrisi, antibiotik, serta terapi konservatif menggunakan loperamide, codeine, omeprazole, dan octreotide. Perawatan luka menggunakan vacuum-assisted closure (VAC). Laporan Kasus 2: Seorang wanita berusia 39 tahun dengan kanker ovarium stadium lanjut rekuren menjalani laparotomi dengan debulking. Luka pascaoperasi mengalami dehiscence yang berkembang menjadi ECF dengan keluaran rendah. Pasien dirawat dengan nutrisi, antibiotik, loperamide, codeine, dan omeprazole. Kantong kolostomi digunakan untuk perawatan luka. ECF merupakan kondisi kompleks yang sering kali berasal dari komplikasi bedah dan sulit diatasi. Seri kasus ini membahas terapi konservatif dengan loperamide dan codeine.

Kata kunci **:** fistula enterokutaneus, kodein, loperamide

ABSTRACT

Enterocutaneous fistula (ECF) is an abnormal connection between the intra-abdominal gastrointestinal tract and the skin or wound. The presence of this channel causes gastric or intestinal fluid to leak into the external environment. Enterocutaneous fistula can be caused by many factors, but most often occurs as a post-surgical complication[1,2]. In this case series, we present 2 cases of enterocutaneous fistula treated with a combination of loperamide and codeine. Case Report 1. A 46 year old woman suffering from total ileus obstruction ec Adenocarcinoma colon transversum moderately differentiated (Low grade) cT4N1M1 (liver metastases) underwent laparotomy surgery with surgical staging, adhesiolysis, and extended right hemicolectomy. Post-operative examination showed a high output enterocutaneous fistula with anastomotic leakage. The patient was stabilized with electrolyte correction, nutrition, and antibiotics. The patient was also treated conservatively with loperamide, codeine, omeprazole, and octreotide. Vacuum assisted closure (VAC) is used for patient wound care. Case Report 2. A 39 year old woman suffering from recurrent advanced stage ovarian carcinoma underwent laparotomy with debulking. In the wound after the laparotomy operation, dehiscence occurred which became a low output enterocutaneous fistula. The patient was stabilized with nutrition and antibiotics. The patient was also treated conservatively with loperamide, codeine, and omeprazole. Colostomy bag is used for patient wound care. Enterocutaneous fistula is a complex condition that most often results from surgical complications, and is a difficult condition to treat. In this case series we will discuss more about conservative therapy with a loperamide and codiene.

Keywords ***:*** *codeine, enterocutaneous fistula, loperamide*

INTRODUCTION

Enterocutaneous fistula (ECF) is an abnormal connection between the intra-abdominal gastrointestinal tract and the skin or wound. The presence of this channel causes gastric or

intestinal fluid to leak into the external environment. Enterocutaneous fistula can be caused by many factors, but most often occurs as a post-surgical complication (Cowan & Cassaro, 2023), (Ghimire, 2022). Enterocutaneous fistula is characterized by a relatively low incidence rate, with an estimated annual incidence of 1.87 per 100,000 people (Härle, 2023). From a demographic perspective, ECF tends to affect a predominantly female population, with an average age of 38 years (Ekani Boukar et al., 2023). More than 75% of all ECFs arise as postoperative complications, whereas approximately 15-25% are caused by abdominal trauma or occur spontaneously due to cancer, irradiation, inflammatory bowel disease (IBD), or ischemic or infectious conditions (Ghimire, 2022).

Enterocutaneous fistula requires a multidisciplinary approach because its management is a very long and complex process. ECF is associated with substantial morbidity and mortality. Mortality rates from ECF vary from 6% to 33% (Cowan & Cassaro, 2023). Meanwhile, leading institutions have reported morbidity rates due to ECF that are even higher, namely more than 85% (Dodiyi-Manuel & Wichendu, 2018). Sepsis, malnutrition, and dyselectrolythemia are the classic triad of complications that are highly likely to occur and are key in therapy (Ghimire, 2022), (Haack et al., 2014). A fistula is an abnormal connection between two epithelial surfaces. Anatomically, fistulas are divided into two categories, internal and external. An internal fistula is a connection between two internal structures. Some examples of internal fistulas are entero colitic, ileosigmoid, and aortoenteric. Alternatively, an external fistula forms a connection between internal structures and external structures. Examples are enterocutaneous, enteroatmospheric, and rectovaginal fistulas (Cowan & Cassaro, 2023). Enterocutaneous fistula is an abnormal connection between the intra-abdominal gastrointestinal tract (such as the stomach or intestines) with the skin or wound, thereby allowing gastric or intestinal fluid to leak to the outside world (Ekani Boukar et al., 2023).

Anything that creates a potential communication between the gut and the epidermis can lead to the development of an enterocutaneous fistula. A useful and commonly used acronym to remember the factors that lead to fistula formation is “FRIEND”(Cowan & Cassaro, 2023), (Haack et al., 2014). F (Foreign object), the presence of a foreign object, such as surgical sutures or pieces of intestine, can hinder the healing process. R (Radiation), Radiation therapy can cause damage to the intestines and increase the risk of ECF. I (Inflammation or infection), the presence of inflammatory bowel disease, such as Crohn's disease, can increase the risk of ECF, while infection of the fistula or surrounding tissue can delay healing and make closure more difficult. E (Fistula tract epithelialization), slow epithelialization of the fistula tract can hinder its closure. N (Neoplasm), the presence of neoplasm in the digestive tract can require surgery and allow ECF to occur, malignant cells in the area can complicate the process of closing the fistula. D (Distal obstruction), obstruction in the distal part of the injured intestine can increase intraluminal pressure and trigger perforation, apart from that the obstruction also prevents the closure of the fistula that has formed (Cowan & Cassaro, 2023), (Haack et al., 2014).

As mentioned previously, the most common cause of enterocutaneous fistula is iatrogenic and occurs in the postoperative period[1]. In both patients the cause of the fistula was a surgical procedure that experienced complications. Apart from that, based on analysis of the acronym risk factor FRIEND in both patients factor F or foreign objects in the form of sewing threads, E or slow wound epithelialization, N or neoplasms in the form of ovarian carcinoma and colon adenocarcinoma were found which were a risk for increasing the possibility of fistula formation. Physiologically, ECF can be classified based on the amount of output drained through the fistula. High-output fistulas drain more than 500 mL in 24 hours, medium-output fistulas between 200 to 500 mL in 24 hours, and low-output less than 200 mL in 24 hours (Cowan & Cassaro, 2023), (Ghimire, 2022). Monitoring the volume and character of the fistula outlet can guide the administration of nutritional therapy and resuscitation. Fistula output can

be documented to predict the likelihood of spontaneous closure and mortality rate 5. In the first case, through wound treatment using VAC, the fistula output was 600 mL (>500 mL) so it was classified as high output. Meanwhile, in the second case where the new wound was treated using a colostomy bag, the amount of fistula output was minimal (<200 mL) so it was classified as low output. The first step in patient management is stabilization. Patients are at high risk of electrolyte imbalance, sepsis, and malnutrition. Controlling these three factors is critical for survival (Cowan & Cassaro, 2023), (Kumar et al., 2011). Electrolyte imbalances should be corrected according to patient needs as indicated on laboratory evaluation (Cowan & Cassaro, 2023), (Kumar et al., 2011). The first patient with hypocalcemia was corrected with $CaCO_3$ 500 mg, in addition the hypoalbuminemia condition was corrected with albumin transfusion. The second patient had no detectable electrolyte problems.

Conservative management with anti-peristaltic agents and anti-secretory agents that target reducing fistula output and stimulating fistula closure is preferred as initial therapy with a success rate of between 5-20%. Despite having a success rate of fistula closure reaching 75-85%, surgery is the last treatment option for ECF (Ekani Boukar et al., 2023), (Dodiyi-Manuel & Wichendu, 2018), (Cano, 2014). It is very important for clinicians, especially surgeons, to understand this condition and the treatment options available. This case series discusses two patients with enterocutaneous fistulas treated with loperamide and codeine.

METHODS

The approach used in this case series is descriptive qualitative, namely reporting on enterocutaneous fistula patients. This case series is based on patients who were monitored from June 2022 to December 2023 at Prof Dr IGNG Ngoerah Hospital. Data was taken through history taking, physical examination and supporting examinations from two patients. The first patient was a 46 year old woman with high output enterocutaneous fistula ec susp leakage anastomosis. The second patient is a 39 year old woman with a low output enterocutaneous fistula ec susp suture dehiscence. Apart from that, patient medical records also play an important role. Next, the data obtained from the patient is analyzed to obtain an appropriate diagnosis and management. Then it is compared with theories or other similar research results.

RESULT

Case Report 1

Patient SB, a 46 year old Indonesian woman, is being treated at Prof Dr IGNG Ngoerah Hospital. The patient suffered from total obstruction ileus ec. Transverse colon adenocarcinoma moderately differentiated (Low grade) cT4N1M1 (liver metastases). The patient underwent laparotomy surgery with surgical staging, adhesiolysis, and extended right hemicolectomy. The patient also had a history of stage III C Ovarian Ca and had undergone TAH-BSO-Debulking and adhesiolysis one month previously. After the laparotomy operation, the patient experienced a high output enterocutaneous fistula. From the anamnesis, the patient complained of weakness and difficulty mobilizing. From vital signs examination, the patient's condition is stable. From the abdominal examination, it appeared that the post-operative wound was well maintained with an output of around 600 mL in 24 hours, in the form of feces with a liquid and dregs consistency. Laboratory examination revealed leukocytosis (19.69 10^9/L), hypocalcemia (Ca 6 mEq/L), hypoalbuminemia (Alb 2.2 gr/dL), with normal renal function blood urea nitrogen (BUN 12.5 mg/dL), serum creatinine (SC 0.57 mg/dL), and estimated glomerular filtration rate (eGFR 111.17 mL/minute). Nutritional therapy is given to patients enterally with honey and water 15 mL three times a day, as well as parenterally with NaCl 0.9%: Dextrose 5%: Kabiven (1:1:1) 20 drops per minute. To treat infections, patients are given

cefoperazone sulbactam 1 gram every 12 hours and metronidazole 500 mg every 8 hours. Calcium was corrected with $CaCO_3$ 500 mg every 8 hours orally and albumin was corrected with albumin transfusion until the albumin target was > 3gr/dL. The patient received conservative therapy in the form of omeprazole 40 mg every 12 hours IV, octreotide 200 mcg in D5%/NaCl 0.9% 100 cc finished in 15 minutes, loperamide 2 mg every 8 hours orally, and codeine 10 mg every 12 hours orally. The patient used vacuum assisted closure (VAC) for wound care. The patient underwent inpatient treatment for 30 days then was sent home with an outpatient plan to the surgical clinic to monitor the progress of his condition.

Case Report 2

The GAPM patient, a 39 years old Indonesian woman, was treated at Prof Dr IGNG Ngoerah Hospital. The patient suffered from recurrence of advanced stage ovarian carcinoma. The patient underwent laparotomy surgery with debulking. Previous history of Ovarian Ca and TAH-BSO was performed one year previously. In the post-operative laparotomy wound, the patient experienced a low output enterocutaneous fistula. From the anamnesis, the patient complained of weakness and pain in the surgical wound. From vital signs examination, the patient's condition is stable. From the abdominal examination, there was post-operative wound dehiscence, with muscle base, there was content with the impression of feces with minimal volume. On laboratory examination, no markers of infection or electrolyte disturbances were found. Nutritional therapy was given to the patient enterally with 100 cc of milk diet every 4 hours. To prevent infection, patients are given metronidazole 500 mg every 8 hours IV and ceftriaxone 1 g every 12 hours IV. The patient received conservative therapy in the form of omeprazole 40 mg every 12 hours IV, codeine 10 mg every 12 hours, loperamide 2 mg every 8 hours. Patients use a colostomy bag for wound care and calculating fluid production. The patient underwent inpatient treatment for 7 days then was sent home with an outpatient plan to the surgical clinic to monitor the progress of his condition.

DISCUSSION

Specifically, the etiology that causes the development of enterocutaneous fistula can be divided into surgical causes and spontaneous causes (Table 1) (Parrish, 2010).

Table 1. Causes of Enterocutaneous Fistula (Parrish, 2010)

Causes of surgical fistulas	Lysis of adhesions/Enterotomies
	Bowel resection for IBD
	Bowel resection for cancer
	Surgery on radiated bowel
	Unprepped bowel
Causes of spontaneous fistulas	Inflammatory bowel disease
	Diverticular disease
	Ischemic bowel
	Perforated ulcer
	Abdominal penetrating trauma
	Gynecological malignancies

Infection that leads to sepsis is a crucial problem that must be treated immediately or prevented in high-risk patients. Monitoring vital signs and laboratories is important to detect signs of infection. Broad spectrum antibiotics are recommended, and can be combined with different regimens (Cowan & Cassaro, 2023), (Kumar et al., 2011). In this case, the first patient showed visible signs of infection from leukocytosis. So the patient was given combination antibiotic therapy of cefoperazone sulbactam and metronidazole. Meanwhile, the second patient had normal examination results which did not show signs of infection, however, the condition of the fistula in the open wound and the conditions of treatment in the hospital had a high risk of causing infection. So the patient was given prophylactic therapy, namely metronidazole and ceftriaxone.

Nutrition is an important factor in ECF therapy. Most patients require parenteral nutrition, but some patients may be able to tolerate an enteral diet if the fistula is distal to the gastrointestinal tract and the output of the fistula is not improved by initiating feeding (Cowan & Cassaro, 2023), (Cano, 2014). In the first case, the patient was given nutrition from two enteral and parenteral routes simultaneously with NaCl 0.9%: Dextrose 5%: Kabiven intravenously and honey orally. This is because the patient cannot tolerate large amounts of enteral intake, so parenteral sources are needed to meet his nutritional needs. Meanwhile, the second patient received nutrition enterally with a milk diet.

Skin care by controlling or containing the fluid that comes out of the fistula is necessary to reduce local skin excoriation, inflammation, pain, and infection in the surrounding skin, thereby increasing the chances of healing[1]. Dressing with wet to dry gauze, use of a colostomy bag, suction wall, even assisted vacuum closure (VAC) are some of the therapy options (Dodiyi-Manuel & Wichendu, 2018). The skin care given to the patient was appropriate, namely the first patient used a VAC, while the second patient used a colostomy bag with their respective wounds well maintained.

The goal of medical therapy is conservative, namely acid neutralization and volume reduction, thereby reducing fistula output and encouraging spontaneous closure (Cowan & Cassaro, 2023), (Ghimire, 2022). Anti-peristaltic drugs, such as loperamide, diphenoxylate, and codeine are also effective in reducing the outcome of high-output fistulas by decreasing intestinal transit time (Cowan & Cassaro, 2023). In high-output fistulas, proton pump inhibitors (PPIs) and H2 blockers can be used to decrease gastric secretions and increase food transit time in the stomach (Cowan & Cassaro, 2023), (Ghimire, 2022). These drugs help reduce fistula output, especially in proximal fistulas or when there is high gastric secretion (Ghimire, 2022). Somatostatin, a 14 amino acid peptide hormone, inhibits pancreatic exocrine secretion by reducing the volume of pancreatic juice[2]. Octreotide, a somatostatin analog, has been studied extensively to control fistula output as well as accelerate fistula closure compared with patients on TPN alone (Ghimire, 2022).

In the case, the first patient received three types of conservative therapy, namely anti-peristaltic with a combination of loperamide codeine, inhibitor of gastric acid production with the PPI omeprazole, and anti-secretory with octreotide. Meanwhile, the second patient was given a combination of loperamide, codeine and omeprazole alone. Giving these conservative drugs requires careful consideration regarding the indications and side effects of treatment. It is hoped that there will be a reduction in fistula output and trigger spontaneous fistula closure through this conservative therapy.

There are some cases where immediate surgical correction may be necessary, however the majority of fistulas are treated non-operatively. This is because 90% of fistulas close by themselves within 5 weeks after medical treatment. There will usually be a waiting period of around 2 to 3 months before surgical correction is performed, allowing sufficient time for the fistula to close spontaneously. It also decreases the morbidity and mortality of surgical correction because the inflammatory condition is likely to have subsided[1]. Operating on a

fistula is fraught with difficulties, and there is a high risk of recurrence. The surgical approach may be difficult due to previous surgery and adhesions. As long as the bowel appears healthy, the best option is to excise the fistula tract and resect a small amount of associated bowel followed by anastomosis to restore bowel continuity. To reduce the recurrence rate, one must close the fascia where the fistula tract passes (Cowan & Cassaro, 2023), (Lee, 2012).

Recently, combination antiperistaltic administration with loperamide and codeine has been widely applied to treat enterocutaneous fistulas and other intestinal failures. Loperamide is a drug commonly used to treat enterocutaneous fistula. Loperamide works by slowing the movement of food through the intestines, thereby helping to reduce the amount of fluid and electrolytes lost through the fistula. This is especially important in patients with high-output fistulas. The recommended dose of loperamide for treating ECF is usually higher than the standard dose for treating diarrhea, due to reduced absorption in patients with intestinal failure. In patients with ECF, loperamide is often given in doses ranging from 2-24 mg daily, with an initial dose of 4 mg every 8-6 hours. The use of high doses of loperamide (above 16 mg daily) is supported by the British Association for Parenteral and Enteral Nutrition (BAPEN). Loperamide is not recommended for patients with gastric fistulas, as it slows gastric emptying and increases the risk of aspiration. Loperamide is excreted via the kidneys so it is contraindicated in patients with renal impairment, because it causes accumulation in the body. Additionally, high doses of loperamide can cause cardiac arrhythmias. Loperamide is a conservative therapy that is considered effective for ECF, but you still need to be careful when using it. In some literature and case reports it is stated that the efficacy of loperamide in reducing fistula outcomes increases when combined with codeine phosphate (Cowan & Cassaro, 2023), (Ghimire, 2022), (Jeremy Nightingale et al., 2018), (de Vries et al., 2017), (Rebollar, 2023), (Leicester, 2023).

The mechanism of action of codeine for enterocutaneous fistula (ECF) is to slow intestinal transit, thereby reducing fistula output. This is achieved by its anti-motility properties, which help reduce the movement of intestinal contents and minimize the amount of material expelled from the fistula. Codeine may also help relieve symptoms such as stomach pain, cramps, and diarrhea associated with ECF. The recommended dose of codeine for enterocutaneous fistula (ECF) is 15mg to 60mg every 8 hours (QDS), 30-60 minutes before meals. Please remember that codeine is a substance that can cause dependence. Its use over a long period of time or in high doses can cause an overdose, so careful consideration is needed regarding the dosage and monitoring. As with loperamide, codeine should be used with caution in patients with renal impairment and is contraindicated in patients with a glomerular filtration rate (GFR) less than 15 mL/menit (Lee, 2012), (de Vries et al., 2017), (Leicester, 2023), (Dumas et al., 2017).

At the British Intestinal Failure Centre, loperamide up to 40mg/day divided into 4 doses and codeine 240mg/day divided into 2 doses are used to successfully control refractory high-output fistulas (Dodiyi-Manuel & Wichendu, 2018), (Metcalf, 2019). This has been shown to decrease fistula output, increase spontaneous closure, and reduce hospital stays, but has never been shown to reduce mortality (Cowan & Cassaro, 2023). In the second case, the patient was given combination therapy with the same dose, namely loperamide 2 mg every 8 hours orally and codeine 10 mg every 12 hours orally. The dose given is still a low dose because it takes into account many factors related to the patient's condition. The patient had also been evaluated for kidney function and no abnormalities were found so it was not a contraindication. However, it is best to re-evaluate after further treatment.

The next intensive investigation that must be carried out is regarding the anatomical development of the fistula, and identifying complications such as stricture, abscess, or distal obstruction[2]. The evaluation regarding physiological features that can predict the rate of spontaneous closure includes the absence of sepsis, good nutritional status, and a low ratio of C-reactive protein to albumin. Conservative measures last a minimum of 4 weeks to allow

closure of the fistula 5. Criteria for the success of therapy cannot yet be assessed due to the short observation period, so it remains to be seen whether spontaneous closure of the fistula occurs or whether further surgical therapy is required for the patient. The length of stay (LOS) of ECF patients who received combination therapy with loperamide and codeine can be compared with the LOS of patients who did not receive this combination therapy. So it can be considered to assess the success of therapy.

The development of enterocutaneous fistula treatment is usually a complicated matter, resulting in prolonged hospitalization, pain, malaise, additional surgery, and major psychological disorders. Psychological sequelae, such as depression, anxiety, guilt, and hospitalization, may take months to resolve. These difficulties must be overcome with good communication and understanding between the patient, the patient's family, and related health workers (Ghimire, 2022)

CONCLUSION

Enterocutaneous fistula is a complex condition that most often results from surgical complications, and is a condition that is difficult to treat. In the case discussed are two patients with enterocutaneous fistulas who were treated with loperamide and codeine. The weakness of this study is the small number of samples studied, so a case series or further research is needed with a larger sample and a longer observation period regarding enterocutaneous fistula and the effectiveness of its therapy.

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