PHENYTOIN TO IMPROVE HEALING OF ENTEROCUTANEOUS FISTULA : A CASE REPORT

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ABSTRAK

Fistula enterokutan adalah komunikasi abnormal antara usus dan kulit. Fistula enterokutan paling sering berkembang sebagai komplikasi pasca operasi operasi usus. Berbagai penelitian telah menunjukkan bahwa fenitoin dapat meningkatkan penyembuhan luka dan menginduksi fibrosis yang lebih cepat. Kami menyajikan kasus fistula enteroketan pasca-eksplorasi laparatomi dan adhesi usus lisis yang diobati menggunakan fenitoin. Fistula enterokutan (ECF) mewakili kondisi klinis yang menantang yang sering menyebabkan morbiditas yang berkepanjangan dan peningkatan biaya perawatan kesehatan. Manajemen ECF biasanya melibatkan dukungan nutrisi, drainase, dan, dalam beberapa kasus, intervensi bedah. Namun, proses penyembuhan fistula ini bisa lambat dan rumit oleh berbagai faktor seperti infeksi, kekurangan gizi, dan penyembuhan jaringan yang buruk. Laporan kasus ini mengeksplorasi penggunaan fenitoin, antikonvulsan yang dikenal karena peran potensialnya dalam penyembuhan luka, sebagai terapi tambahan untuk meningkatkan proses penyembuhan fistula enterokutan. Pasien dalam laporan ini mengalami ECF kronis setelah operasi perut dan menunjukkan penutupan parsial meskipun manajemen konvensional. Fenitoin diberikan sebagai bagian dari rejimen terapeutik, dan perbaikan penting dalam penutupan fistula diamati. Kasus ini memberikan bukti awal yang menunjukkan bahwa fenitoin mungkin memiliki efek menguntungkan pada penyembuhan luka, terutama dalam kasus di mana perawatan tradisional gagal mempercepat penutupan. Mekanisme yang diusulkan melibatkan modulasi sintesis kolagen dan aktivitas fibroblas, yang penting untuk perbaikan jaringan. Sementara studi lebih lanjut diperlukan untuk memvalidasi temuan ini, kasus ini menyoroti potensi fenitoin sebagai pilihan pengobatan alternatif untuk meningkatkan penyembuhan fistula enterokutan, terutama pada pasien dengan kasus refrakter.

Kata kunci : *enterocutaneous fistula, laparatomy, phenytoin*

ABSTRACT

Enterocutaneous fistulas are abnormal communications between the bowels and skin. Enterocutaneous fistulas most commonly develop as a post operative complication of bowel surgery. Multiple studieshave shown that phenytoin can promote wound healing and induce faster fibrosis. Wepresenting a case of enterocutaneous fistula post-exploratory laparatomy and lysis bowel adhesion which treated using phenytoin.Enterocutaneous fistulas (ECFs) represent a challenging clinical condition that often leads to prolonged morbidity and increased healthcare costs. The management of ECFs typically involves nutritional support, drainage, and, in some cases, surgical intervention. However, the healing process of these fistulas can be slow and complicated by various factors such as infection, malnutrition, and poor tissue healing. This case report explores the use of phenytoin, an anticonvulsant known for its potential role in wound healing, as an adjunctive therapy to improve the healing process of an enterocutaneous fistula. The patient in this report presented with a chronic ECF following abdominal surgery and demonstrated partial closure despite conventional management. Phenytoin was administered as part of the therapeutic regimen, and notable improvements in the fistula closure were observed. This case provides preliminary evidence suggesting that phenytoin may have a beneficial effect on wound healing, particularly in cases where traditional treatments fail to accelerate closure. The proposed mechanism involves the modulation of collagen synthesis and fibroblast activity, which are essential for tissue repair. While further studies are needed to validate these findings, this case highlights the potential of phenytoin as an alternative treatment option for enhancing the healing of enterocutaneous fistulas, particularly in patients with refractory cases.

Keywords *: enterocutaneous fistula, laparatomy, phenytoin*

INTRODUCTION

A fistula is defined as an abnormal communication between twoepithelialized surfaces. The communication occurs between twoparts of the GI tract or adjacent organs in an internal fistula(e.g., enterocolonic fistula or colovesicular fistula). An external *fistula* (e.g., enterocutaneous fistula or rectovaginal fistula) involves the skin or another external surface epithelium. Over 80% of enterocutaneous fistulas represent iatrogeniccomplications that occur as the result of enterotomies or intestinalanastomotic dehiscences. Previous studies have confirmed the ability of phenytointo promote wound healing. Enterocutaneous fistulas (ECFs) are a significant clinical challenge, often resulting from surgical procedures, inflammatory bowel disease, or traumatic injury. These abnormal connections between the gastrointestinal tract and the skin can lead to serious complications, such as malnutrition, sepsis, and prolonged hospitalization. ECFs are notoriously difficult to treat, with healing being slow and unpredictable in many cases. Conventional management focuses on nutritional support, infection control, and, if necessary, surgical intervention. However, despite these efforts, the healing process can be prolonged, leading to a considerable burden on both patients and healthcare providers.

Recent studies have explored various pharmacological and non-pharmacological approaches to accelerate the healing of enterocutaneous fistulas. Among these, phenytoin, an anticonvulsant drug traditionally used in the management of seizures, has shown potential beyond its primary indication. Phenytoin has been observed to promote wound healing in various clinical settings, possibly due to its effects on cellular processes such as fibroblast activity, collagen synthesis, and tissue regeneration. Its role in improving wound healing has garnered interest, particularly in the context of chronic and complex wounds like ECFs. This case report aims to present the successful use of phenytoin in improving the healing of an enterocutaneous fistula in a patient who had previously experienced prolonged and difficult management. By documenting this case, we seek to explore the possible mechanisms through which phenytoin may influence wound healing and offer a novel approach to treating ECFs. The patient's clinical course, treatment regimen, and outcomes will be discussed in detail, providing valuable insights into the therapeutic potential of phenytoin in this challenging clinical scenario.

In conclusion, the use of phenytoin as an adjunctive treatment for enterocutaneous fistulas is an emerging area of interest that warrants further investigation. This case report highlights the need for continued research into alternative therapies that may improve the management and healing of complex wounds, ultimately reducing patient morbidity and healthcare costs. Through a better understanding of phenytoin's potential benefits, clinicians may be able to offer more effective and timely interventions for patients suffering from this difficult condition.

CASE REPORT

Eleven y.o male children experiencingfecal leak from the abdominal drain during day-6 of post-exploratory laparatomy and adhesiolysisindicated by general peritonitis and severe adhesion caused by perforative appendicitis. The patient was already in liquid diet (milk) through the post-operative care. Physical and laboratory examination showed no sign of peritonitis nor sepsis. Based on these findings, the patient was diagnosed with enterocutaneous fistula. We decided toremove the drain & converting into stoma bag and prescribethe patients with phenytoin injection with 2.5 mg/kg dose twice a day. During day-2 of phenytoin treatmet the output was reduced andno sign of peritonitis nor sepsis. The patient allowed to be outpatient and prescribed with phenytoin orally, liquid diet (milk) & follow-up visit next week. The

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patient's parent also educated to record the output and the fistula characteristic daily. During the weekly follow-up, the parent's record revealed fistula's closure in day-5 of outpatient care.

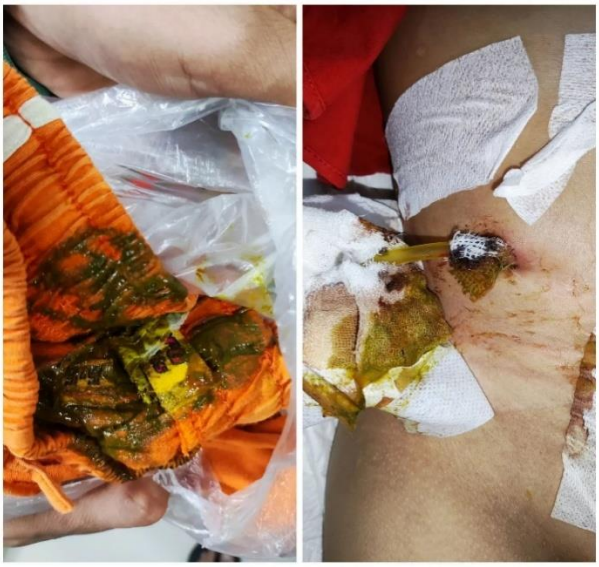

Figure 1.Fecal Leak From The Abdominal Drain

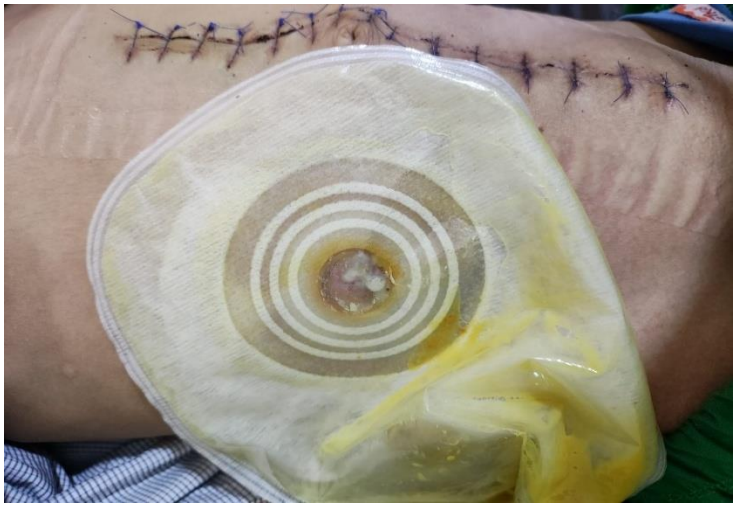

Figure 2. Covering Fistula with Stoma Bag

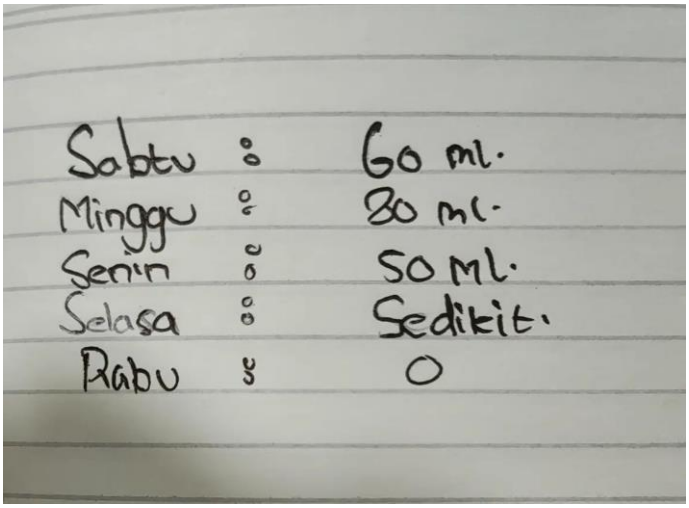

Figure 3. Parents Note Revealed Fistula's Closure in Day-5 Of Outpatient Care

RESULT AND DISCUSSION

Enterocutaneous fistulas are abnormal communications between the bowels and skin. Enterocutaneousfistulas that drain less than 200 mL of fluid per dayare known as *low-output fistulas*, whereas those that drain morethan 500 mL of fluid per day are known as *high-output fistulas*.Over 80% of enterocutaneous fistulas represent iatrogeniccomplications that occur as the result of enterotomies or intestinalanastomotic dehiscences. Fistulas that arise spontaneouslywithout antecedent iatrogenic injury are usually manifestations of progression of underlying Crohn's disease or cancer. Iatrogenic enterocutaneous fistulas usually become clinically evident between the fifth and tenth postoperative days. Fever, leukocytosis, prolonged ileus, abdominal tenderness, and wound infection are the initial signs. The diagnosis becomes obvious when drainage of enteric material through the abdominal wound or through existing drains occurs. These fistulas are often associated with intra-abdominal abscesses.

CT scanning following the administration of enteral contrast is the most useful initial test. Leakage of contrast material from the intestinal lumen can be observed. Occasionally, contrast administered into the intestine does not demonstrate the fistula tract. A *fistulogram*, in which contrast is injected under pressure through a catheter placed percutaneously into the fistula tract, may offer greater sensitivity in localizing the fistula origin. Initial treatment isconservative, including resuscitation, sepsis control, localmanagement of fistula output, nutritional support,pharmacotherapy and radiologic investigations. The finaltreatment, if necessary, is restorative surgery. Careful replacement of the losses of fluid and electrolytes isessential and is often accompanied by CVP (central venouspressure) monitoring. Continued monitoring of ongoing lossesand replenishment is essential. Patients with high output andproximal fistulas develop significant metabolic acidosis,which may need intravenous sodium bicarbonateadministration.

Control of sepsis: Tachycardia, persistentfever, and leukocytosis indicate active infection. Treatmentwith broad-spectrum antibiotics and local drainage ofabscesses (if present) may have to be done. Most deep orintraperitoneal collections are best treated by imaging guideddrainage. Open surgical drainage may have to be done if theabscess is not accessible. The fistula may need to becompletely exteriorized to the skin level to prevent furtherintra-abdominal fluid collection. The overall objective is to increase the probability of spontaneousclosure. Nutrition and time are the key componentsof this approach.Most patients will require TPN; however, atrial of oral or enteral nutrition should be attempted in patientswith low-output fistulas originating from the distal intestine.

Timing of Surgical Intervention. Most surgeons would pursue2 to 3 months of conservative therapy before consideringsurgical intervention. This approach is based on evidence that90% of fistulas that are going to close do so within 5 weeks andalso that surgical intervention after this time period is associatedwith better outcomes and lower morbidity. Over 50% of intestinal fistulas close spontaneously. Presence ofcomponents in the form of foreign bodies, radiation,inflammation, infection, inflammatory bowel disease,epithelization of the fistula tract, neoplasms, distalobstructions, and steroids (FRIENDS) are indicationfor surgical intervention. Phenytoin drug has long been known as an antiseizuredrug is currently reported from several studiesshowing it had a therapeutic effect on wound healingand speed up fibrosis.This has been supported by many studies and studies thatreported since decades. Several studies have shown theadvantages of therapeutic effect of the administration ofphenytoin on healing burns, trauma wounds, venousstatic ulcers.

Several studies have shown that phenytoin can improve wound healing Phenytoin's mechanism for accelerating wound healing is still not fully understood, but several theories have been proposed. The mechanisms by which phenytoin induces wound healing include stimulating fibroblast proliferation, increasing angiogenesis, increasing granulation tissue

formation, decreasing collagenase activity, increasing collagen deposits, inhibiting glucocorticoid activity, decreasing exudate in wounds and inhibiting antibacterial activity either directly or indirectly by affecting cells, inflammation and neovascularization. There is also evidence that phenytoin may play a role in the healing of pilonidal sinus fistula and wounds and that such a positive effect on wound healing can be applied to the healing of gastrointestinal fistulas.In another study, it was found that phenytoin could reduce levels of MMP-1, MMP3, MMP-9, and TNF-α but did not decrease IL-6, whereas IL-6 could increase fibroblast proliferation and collagen synthesis.This mechanism becomes the basis for its application in ECF cases, with an increase in the number of fibroblasts, angiogenesis, and collagen synthesis.

Jabeer et al report a case of pancreatic fistula managed with oral phenytoin. The oral phenytoin promote the fistula closure.Sugiarto et al conducted an animal randomized control study to evaluate the effect of oral phenytoin and vitamin C therapy on enterocutaneous fistula healing. They found an increasing number of fibroblast in phenytoin + vitamin C group. Suggesting this treatment had a stimulating effect on fibroblast proliferation which supporting healing process.This finding was also highlighted by Bachtiar et al study which implying an increased number of fibroblast and angiogenesis in phenytoin treated group.

CONCLUSION

This finding suggested the benefit of phenytoin treatment in managing enterocutaneous fistula. However, further studies are still needed. In this case report, we have highlighted the potential of phenytoin as an adjunctive therapy in improving the healing of enterocutaneous fistulas. The patient demonstrated significant improvement in fistula closure and wound healing after the introduction of phenytoin as part of the treatment regimen. Although traditionally used for its anticonvulsant properties, phenytoin’s ability to enhance wound healing through mechanisms such as fibroblast activation, collagen production, and tissue regeneration appears promising in the context of complex wound management. The positive clinical outcome in this case suggests that phenytoin could be a valuable option for promoting the healing of ECFs, especially when conventional treatments alone are insufficient.

However, it is important to note that this case report represents a single instance, and further clinical studies are necessary to better understand the broader applicability and safety profile of phenytoin for enterocutaneous fistula healing. Randomized controlled trials and larger cohort studies will be essential to confirm these findings and elucidate the precise mechanisms underlying phenytoin’s effects on wound healing. Nevertheless, this case provides valuable insights into an alternative therapeutic approach that could potentially improve patient outcomes, reduce hospitalization times, and ultimately enhance the quality of care for individuals suffering from enterocutaneous fistulas. As the medical community continues to explore innovative treatments for complex wound healing, phenytoin may emerge as an important tool in the management of ECFs.

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