

Intravenous Phenytoin: Potential New Therapy for Gastrointestinal Fistulae

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Abstract Gastrointestinal fistulae are among the most devastating complications of gastrointestinal surgery and can be lethal. Fistula tract healing consists of several processes, including cell migration and formation of a new extracellular matrix. Multiple studies have demonstrated that phenytoin can promote wound healing and induce faster fibrosis. We postulate that the positive effects of phenytoin can be used to enhance fibrosis of the fistula tract. We treated 16 patients who had developed GI fistulae as a complication of surgical intervention. Five patients developed external small intestinal fistulae, 3 patients developed colonic fistulae, 3 patients developed pancreatic fistulae, 1 patient developed a biliary fistula and 4 patients developed gastrocutaneous fistulae. Patients were started on IV phenytoin for the first 4 days and subsequently switched to oral phenytoin for a total of ten days. A significant drop in output was noticed 3-4 days after treatment. The fistulae healed in a short period averaging 8 days without the need for a surgical intervention in 13 patients (81%), but failed to heal in three patients. **Conclusion:** intravenous phenytoin may have a positive effect on the treatment of fistulae. Prospective studies are needed to validate this potential effect of phenytoin on fistula healing.

Keywords: *gastrointestinal, fistulae, surgery, phenytoin*

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1. Introduction

A frequently observed and undesirable side effect of phenytoin is gingival hyperplasia [1]. This side effect results from the growth of connective tissue. Multiple medical reports have promoted the use of phenytoin to enhance wound healing [2,3]. Gastrointestinal fistulae are one type of wound that heals by fibrosis. Based on the notion that phenytoin enhances fibrin deposition, we used phenytoin in the management of external gastrointestinal fistulae. The mechanism by which phenytoin promotes wound healing is not fully understood; however, several theories have been proposed. These theories include the stimulation of fibroblast proliferation, enhancing the formation of granulation tissue, decreasing collagenase activity, the inhibition of glucocorticoid activity, direct and indirect antibacterial activity induced by activating inflammatory cells and neovascularisation [4,5]. Evidence also exists that phenytoin may play a role in anastomotic healing [6,7]. Based on these findings, we used systemic phenytoin for the treatment of 16 different external gastrointestinal fistulae.

2. Method and Results

Our study involved 16 patients who developed postoperative external gastrointestinal fistulae at the King

Fahd Military Medical Complex-Dhahran between October 2007 and November 2011. The study group was composed of 13 men and 3 women with a median age of 43 years (range: 21 to 66 years). All patients had previously been maintained on conservative treatment with parenteral nutrition or enteral feeding for an average of two weeks. After no improvements were observed, systemic phenytoin administration was initiated.

The aetiology of the fistulae is presented in Table 1. Four patients exhibited gastrocutaneous fistulae post-laparoscopic sleeve gastrectomy, one patient had a biliary fistula post-laparoscopic cholecystectomy, five possessed enterocutaneous fistulas four post small bowel surgery due to penetrating traumas and one due to Crohn's disease, three had pancreatic fistulae two post pancreatic necrosectomy and one post pancreatectomy and three had colocutaneous fistulae post left hemicolectomy due to diverticulitis.

Table 1. Types of fistulas

Fistula type	no. of pts
Gastro-Cutaneous	4
Biliary	1
Enterocutaneous	5
Pancreatic	3
Colocutaneous	3

Initially, standard conservative management was applied to all patients, which included the use of intravenous fluid resuscitation, improving the nutritional status either by parenteral nutrition or enteral feeding (in

gastrocutaneous fistulae patients using jejunostomy) and broad spectrum antibiotics. Patients who failed to exhibit any response after 14 days of conservative management were included in this study, however, all of the enterocutaneous fistulae were treated for 6 weeks initially and whom failed were subjected to the study. Initially, we used intravenous phenytoin at a dose of 100 mg TID for three days. Subsequently, we switched to oral phenytoin 100 mg TID. Four days after initiating, we observed a significant drop in output of the fistulas and noted a change in the coloration of the fistulas output to a frothy whitish drainage especially in the pancreatic and gastric fistulae group. We continued to administer phenytoin for ten days unless side effects like neutropenia developed, which occurred in one patient who was subsequently withdrawn out of the study. Surprisingly, in three patients exhibiting necrotizing fasciitis at the site of the fistula due to faecal and small bowel contents, the infection resolved, and the wound healed in an average of two weeks. Among the sixteen patients, three failed conservative management. One of these patients possessed a notably short tract of less than one cm, another had Crohn's disease and was on Azathioprine, and the third possessed a drain that was stuck against the leaking area along the gastric wall after sleeve gastrectomy. The patients failing conservative management were all managed surgically or interventionally.

3. Discussion

The formation of a gastrointestinal fistula represents a relatively infrequent yet serious condition. Despite treatment, morbidity and mortality are particularly high. The potential sequelae of gastrointestinal fistulae include fluid collection, abscess formation, haemorrhage, sepsis, malnutrition, and death [8]. In addition, fistulae frequently prolong hospital stays and inflict a considerable psychological burden on patients due to the negative body image impact. Physical effects notwithstanding, fistulae are associated with complex issues of personal hygiene and wound care, pain, delay in returning to normal activities, and expenses associated with prolonged hospitalisation.

The aetiology, epidemiology, and classification of gastrointestinal fistulae are complex. The majority of fistulae develop as a complication of abdominal surgery, trauma, disease, intra-abdominal abscesses, malignant disease, or radiotherapy [9].

The mainstay management of GI fistulae is conservative.

Conservative treatment is comprised of supportive measures to stabilize the patient. These measures include the provision of adequate drainage plus cutaneous protection, fluid/electrolyte balance, nutritional replacement and bowel rest via enteral or parenteral nutrition, and wound care and antibacterial therapy in patients with signs of systemic sepsis or local inflammation with pain [10]. The end result of successful treatment is the healing of the tract by fibrosis.

Phenytoin (diphenyl hydantoin or Dilantin) is a highly effective and widely prescribed anticonvulsant agent used in the treatment of grand mal seizures and psychomotor epilepsy. The side effects of phenytoin continue to create

significant morbidity. Common side effects include gingival hyperplasia, coarsening of the face, and hirsutism. In dermatology, phenytoin has been used to treat ulcers, epidermolysis bullosa, and inflammatory conditions. The mechanism of phenytoin appears to involve its ability to inhibit collagenase [1].

Phenytoin has been investigated as a treatment for more than 100 diseases. A Medline search in November of 2002 revealed that 12,860 articles concerning phenytoin have been published since 1966. In dermatology, phenytoin has been investigated for the treatment of ulcers, epidermolysis bullosa, and inflammatory conditions. Numerous allergic, proliferative, and idiosyncratic cutaneous side effects have been reported with its use [1]. This review summarizes the uses, mechanisms, and cutaneous side effects of phenytoin.

Researchers have investigated the effects of phenytoin on a cellular level. In a portion of patients with epidermolysis bullosa, the levels of collagenase are increased [3]. Phenytoin inhibits collagenase in vitro [2]. By inhibiting collagenase activity, phenytoin has been theorized to stabilize collagen fibrils and thus decrease blister formation [4]. Phenytoin modulates connective tissue metabolism and cell proliferation in human skin fibroblast cultures [5]. When fibroblasts are embedded within freely contracting, relaxed, type I collagen matrices, the fibroblasts are insensitive to phenytoin. However, if fibroblasts are grown in collagen matrices that are nonretracting and under tension, phenytoin stimulates cell proliferation and inhibits collagenase activity [6]. Patients with epidermolysis bullosa treated with phenytoin exhibited lower levels of inflammatory mediators, such as arachidonic acid in the plasma and erythrocyte phospholipids, than did untreated epidermolysis bullosa patients [8].

Phenytoin has been studied (generally with inadequate controls) in the healing of pressure ulcers, venous stasis ulcers, diabetic ulcers, traumatic wounds, and burns [11].

Used topically, phenytoin appears to enhance healing without side effects. This compound's wound-related pharmacology has been investigated [12]. Phenytoin increases gene expression of the platelet-derived growth factor B chain in macrophages and monocytes [13]. Healthy granulation tissue appears earlier with phenytoin than with conventional saline dressings [14]. Phenytoin may promote wound healing through multiple mechanisms, including the stimulation of fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism, and antibacterial activity [15]. Phenytoin appears promising in enhancing the healing of decubitus ulcers [16,17]. In a comparison involving 47 patients with stage II decubitus ulcers, treatment with phenytoin, DuoDerm® dressings or triple antibiotic ointment applications all resulted in a reduction in the number of ulcers. However, the phenytoin group demonstrated more rapid results in all aspects of ulcer healing [18]. Similarly, one study suggested that phenytoin may be superior to honey as a topical agent in the treatment of chronic ulcers [19].

Topical phenytoin was used with positive effects during the Iran-Iraq war when other resources were limited. In Iran, topical phenytoin was reported to play a role in treating 19 wounds caused by missiles and 6 refractory ulcers in civilians. In Iraq, it was reported that topical

phenytoin in the treatment of war-related decubitus ulcers resulted in prompt pain relief, decreased wound exudates and bacterial contamination, enhanced granulation-tissue formation, and decreased healing time [20,21]. Such results could make phenytoin a useful agent in countries with limited access to more expensive wound-care therapies. Phenytoin suppresses the production of cortisol. Specifically, phenytoin induces the liver cytochrome P450 enzyme system and stimulates steroid clearance [22]. Phenytoin can also induce adrenal suppression.

Given these enhancing effects of local phenytoin on wound healing, we hypothesised that such a positive effect could be enhanced when used in a systemic manner and used it to help closure of gastrointestinal fistula tract. The healing process of GI fistula tracts occurs mainly in the form of fibrosis of the tract. Using this fact, we used phenytoin intravenously and orally to enhance the rapid closure of the fistula tract. We assume that gingival hyperplasia after the use of phenytoin occurs because of the frequent gingival injury during teeth brushing. We assume that the increase in fibrin deposition by fibroblasts is not systemic but rather at the area of inflammation or injury. Such an effect was very clear in the cases described above. In the three cases that failed conservative treatment, two were taken for surgical management. Although we anticipated extensive fibrosis, fibrosis was present only at the areas of the fistula tract; the rest of the peritoneal cavity contained soft peritoneal adhesions.

The treatment guidelines for adults with traumatic brain injury from the American Academy of Physical Medicine and Rehabilitation, the Brain Trauma Foundation, and the American Academy of Neurology recommend the use of phenytoin for the prophylaxis of early post trauma seizures [23]. The anticonvulsant mechanism is not clear, although several cellular actions have been described, including effects on ion channels, active transport, and general membrane stabilization (Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation, 1998). However, this action might be a healing effect of contused brain tissue, rather than the effect of phenytoin on the ionic channels. Such a theory is difficult to prove, and accordingly, further studies are needed.

4. Conclusions

Clinical studies using phenytoin therapy suggest that phenytoin may be useful for the treatment of both acute and chronic wounds of various aetiologies. Such an encouraging effect was also observed in our study in treating gastrointestinal fistulae using systemic phenytoin therapy. Although these results are encouraging, the efficacy of systemic phenytoin therapy has yet to be confirmed by double-blind placebo-controlled studies. Large, controlled studies are needed to confirm the benefits of systemic phenytoin in GI fistulae of varied aetiologies.

Competing Interests

Drs. Saed Jaber, Bader Tayara, Basma Fallatah, Hassan Yami, and Mahmoud Abdelmoeti have no conflicts of

interest or financial ties to disclose, the authors declare no conflicts of interest to the authorship and/or of the publication of this case report. Similarly, the authors received no financial support for the research and /or the authorship of this research.

Author's Contribution

Saed A Jaber, MD, designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Basma M Fallatah, MD, and Bader K Tayara, MD, managed the analyses of the study. Hassan Yami, MD, and Mahmoud Abdelmoeti, MD, managed the literature searches. All authors read and approved the final manuscript.

Acknowledgement

All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript

Consent

This study is approved by the King Fahd Military Medical Complex research committee, and informed consent was given. The protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

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