Abdominoperineal resection (APR) is currently the operative procedure of choice for patients with anorectal complications of inflammatory bowel disease (IBD) where a restorative proctocolectomy is either undesirable or impossible to perform. The challenge in these patients is poor perineal wound healing. A retrospective chart review was conducted of 118 patients (average age 44 years, range 28–73) with intractable IBD who underwent APR to evaluate perineal wound healing outcomes. Forty-four (44) had Crohn’s disease (CD) and 74 had ulcerative colitis (UC). Three months after surgery, the wounds of 10 patients (six with CD and four with UC) remained unhealed with a standard protocol of sterile gauze dressings, sitz baths, and irrigation as needed. In these patients, daily topical application of a small amount of platelet-derived growth factor (rhPDGF) was added to the regimen of care. Six of the 10 unhealed wounds healed following rhPDGF application (average 80 days). The four patients whose wounds did not heal after 6 to 12 months had CD and underwent surgical revision followed by topical rhPDGF application. These wounds healed after an average of 107 days. The results of this case series confirm that delayed perineal wound healing is common following APR, especially in patients with CD, and may confirm previously reported observations that the effects of rhPDGF are most encouraging in small area defects that can be filled. Studies to evaluate the safety, efficacy, and effectiveness of this treatment modality are warranted.

Key Words: rhPDGF, abdominoperineal resection, perineum, wound closure, perineal wound healing


Potential Conflicts of Interest: none disclosed
PLATELET-DERIVED GROWTH FACTOR IN PERINEAL WOUND HEALING

Methods

A retrospective record review of all patients who underwent APR between January 1996 and May 2007 for treatment of IBD by a single surgeon at The Mount Sinai Hospital (New York, NY) was conducted. Data abstraction and review were performed by two reviewers. Data were entered into an Excel spreadsheet and data analysis was performed using SPSS® (Chicago, IL). Mean and median of age, duration of disease, and time to wound healing were calculated. Gender, type of IBD, procedure, and surgical interventions related to the perineal wound were recorded. Duration of rhPDGF application also was recorded. Numerical data were analyzed using Student’s t-test and categorical data were compared using chi-square. Statistical significance was defined as \( P < 0.05 \).

Surgical procedures. Records showed that all operations were performed using simultaneous abdominal and perineal teams. The perineal rectal dissection was performed in the inter-sphincteric plane using electrocautery. After the rectum was removed, the residual levator muscles were re-approximated with interrupted absorbable sutures. The ischiorectal fat and residual external sphincter muscles also were re-approximated in layers with absorbable sutures and the skin then was closed primarily with interrupted absorbable sutures. Closed suction pelvic drains were placed in the pelvis from above; perineal drains were not used.

In the postoperative period, perineal wounds initially were treated daily with dry sterile gauze dressings. Perineal wounds that had drainage were treated daily with saline irrigation or sitz baths and wet-to-dry dressings. Conservative treatment with wound care was continued for at least 3 months. If the wound remained unhealed after 3 months, daily topical application of growth factor becaplermin gel 0.01%, 100 μg/g (Regranex®, Systagenix Wound Management, Quincy, MA) was prescribed and wound irrigation was discontinued. The growth factor treatment was applied daily into the open perineal wound by the patient according to the product package insert directions. A thin layer (1 mm to 2 mm) of ointment was applied using a finger or a cotton applicator; the wound then was covered with a dry gauze dressing. Patients were allowed to shower as needed.

Written informed consent was not obtained because rhPDGF is FDA approved for use on diabetic ulcers and was used in this series as an offlabel adjunct to conservative wound care for patients with delayed healing of the perineal wound. Operative revisions were performed as needed if wounds remained unhealed 6 to 12 months after surgery.

Results

The records of 118 patients who underwent APR were reviewed. Of those, 44 had Crohn’s disease (CD) and 74 had ulcerative colitis (UC). None of the patients had anal or rectal cancer and none had received radiation to the pelvis or perineum. In all patients with UC, the indication for surgery was intractability. The indication for surgery in all patients in the CD group was intractability with severe perianal disease.

In the CD group, six out of 44 patients (14%) had unhealed wounds after 3 months; four out of 74 wounds in patients (5%) in the UC group did not heal during that time period \( P < 0.05 \); in total, six men and four women, average age 44 years (range 28–73) (see Table 1). Of these patients, six out of 10 healed following the addition of rhPDGF to their treatment regimen. Median time from APR to rhPDGF addition was 89 days (range 42–171 days) and the median time from rhPDGF addition to complete wound healing was 80 days (range 42–147) (see Figure 1). No adverse events related to rhPDGF occurred. The remaining four patients in this series with delayed perineal wound healing required operative interventions: one gracilis myocutaneous flap and three perineal wound revisions. All four patients requiring surgical revision had CD. After revision of the perineal wound, rhPDGF was applied and the wounds healed after a median of 107 days (range 98–118 days).

Discussion

Traditional management of perineal wounds following APR consists of the application of damp-to-dry gauze dressings. Alternative methods, such as the use of negative pressure wound therapy (NPWT), have been tried but anatomic challenges involving the perineal wound often compromise the tight seal required for this therapy. Wound failure after 6 months usually requires surgical intervention and placement of a well-vascularized, nonirradiated tissue flap to a large defect, or skin grafting to clean granulating wounds.

Key Points

- Perineal wound healing following abdominoperineal resection (APR) can be delayed, especially in patients with inflammatory bowel disease (IBD).
- Evidence-based protocols of care are not available and most wounds are managed conservatively with gauze dressings, sitz baths, and irrigation.
- Of the 10 wounds in this case series that remained unhealed 3 months, six healed when topical growth factor treatment was included in the protocol of care.
- Study data to help clinicians provide optimal care for patients with these high-risk wounds are needed.
and precarious vascularity are not uncommon with the application of flaps and may lead to healing failure.

In the last decade, the use of advanced wound treatment modalities including tissue-engineered products, hyperbaric oxygen, NPWT, electrical stimulation, and recombinant growth factors has been explored.

Growth factors are the engines, or modulating factors, that drive wound healing. Known endogenous sources of PDGF include the alpha granules of platelets, vascular endothelial cells, smooth muscle cells, fibroblasts, neutrophils, and epithelial cells. In 1998, the FDA approved rhPDGF, a recombinant protein produced in the yeast Saccharomyces cerevisiae, for topical treatment of nonischemic diabetic neuropathic ulcers. It is currently the only growth factor approved for clinical use. In a review of the current literature, PDGF has been found to stimulate the production of glycosaminoglycans, proteoglycans, and collagenase; it acts as a vasoconstrictor and induces replication of fibroblasts and smooth muscle cells. Over the first several days after an injury, its release from platelets and endothelial cells allows for directed and sequential migration of neutrophils, macrophages, and fibroblasts into and around damaged tissues. In a 1993 study evaluating the molecular properties of five families of peptide growth factors, it was noted that stimulation by PDGF of the newly arrived cells at the wound site results in endogenous production of the growth factor and provisional extracellular matrix (ECM) synthesis, fibroblast proliferation, and eventually collagen production. This stimulation continues for 2 to 3 weeks, after which PDGF contributes to wound remodeling by helping orchestrate active collagen turnover and cross-linking.

The failure of perineal wounds to readily heal after APR for IBD has stimulated considerable discussion and served as an impetus for the development of a number of operative approaches to deal with the problem. It is not unusual for the perineal wound to take many months to heal completely. In a 2005 retrospective case series of 160 patients who underwent APR, 35% had major wound complications; when analyzed for persons without previous pelvic irradiation, the complication rate was 19%. A retrospective series of 112 patients undergoing proctectomy for Crohn’s colitis found that early healing (within 12 weeks) of perineal wounds occurred in only 63% of the patients. Healing was delayed by more than 1 year in 21 patients (19%) and in 10 patients (9%) the perineal wounds never healed. Watts et al reported that 24.7% of 93 patients who underwent proctectomy for UC had an unhealed perineal wound for more than 6 months after surgery. Manjoney et al have reported similar discouraging statistics. Many authors consider IBD to be a poor prognostic indicator for healing.

In a literature review of nine studies with 1,315 patients, Del Pino and Abcarian examined the cause, prevention, and management of the most common perineal complications and their failure to heal secondary to abdominoperineal resections. In a series of patients with adenocarcinoma, perineal wound complications (16.5%) ranked second to urologic problems (21%) in overall frequency. Patients with IBD demonstrated an even higher incidence of delayed perineal wound healing than patients with UC (14% versus 5%, P <0.05). Furthermore, all patients requiring operative intervention of the perineal wound after 6 months had CD. This difference may be due to chronic perineal pathology in patients with CD.

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use has been reported by others.36,41 Increased incidence of poor perineal wound healing with steroid due to the small number of patients in their series.28,48 An in-ention. Although a history of corticosteroid use did not ad-

Table 1. Summary of patient baseline characteristics, procedure, and interventions

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ gender</th>
<th>Disease, duration, and indication for APR</th>
<th>Procedure</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63/M</td>
<td>Ulcerative colitis x 14 years Fistulae, refractory pouchitis</td>
<td>APR j-pouch</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>38/F</td>
<td>Crohn’s x 15 years Fistulae, stricture</td>
<td>TPC-I</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>45/M</td>
<td>Ulcerative colitis x 7 years Fistulae, refractory pouchitis</td>
<td>APR j-pouch</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>38/F</td>
<td>Crohn’s x 17 years Fistulae</td>
<td>APR</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>42/M</td>
<td>Ulcerative colitis x 9 years Rectal stricture</td>
<td>APR</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>41/F</td>
<td>Ulcerative colitis x 24 years Refractory pouchitis</td>
<td>APR j-pouch</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>34/F</td>
<td>Crohn’s x 9 years Fistulae</td>
<td>TPC-I</td>
<td>Wound revision POD 980</td>
</tr>
<tr>
<td>8</td>
<td>35/M</td>
<td>Crohn’s x 3 years Medically refractory disease</td>
<td>APR</td>
<td>Gracilis flap POD 772</td>
</tr>
<tr>
<td>9</td>
<td>73/M</td>
<td>Crohn’s x 30 years Medically refractory disease</td>
<td>TPC-I</td>
<td>Wound revision POD 826</td>
</tr>
<tr>
<td>10</td>
<td>28/M</td>
<td>Crohn’s x 19 years Fistulae, abscesses</td>
<td>TPC-I</td>
<td>Wound revision POD 504</td>
</tr>
</tbody>
</table>

M = male; F = female; TPC-I = total proctocolectomy ileostomy; APR = abdominoperineal resection; POD = post-operative day

with IBD (50% versus 35%). It also was noted that patients with Crohn’s colitis fared worse — 30% experienced a delay in wound healing longer than 3 months and 10% developed perineal sinuses.47 Factors not found to be associated with perineal wound problems were age and gender.32

Jalan et al48 retrospectively reviewed outcomes of 115 patients with UC and found poor healing was significantly associated with the use of open packing, female gender, and surgery during the first attack of UC, as well as the presence of perineal sepsis; 55% of the patients needed longer than 6 months to heal and 20% never healed. Factors that did not have any detrimental effect included patient age, severity of colitis, prolonged disease, and the extent of colonic involvement. Although a history of corticosteroid use did not adversely affect outcome in this study, this finding may have been due to the small number of patients in their series.29,48 An increased incidence of poor perineal wound healing with steroid use has been reported by others.36,41

Growth factors control many of the key cellular activities involved in the normal tissue repair process. The underlying rationale for growth factor therapy is based on the theory that in problematic and chronic wounds, the production of one or many growth factors is suboptimal. Hypothesizing a positive effect on wound healing, investigators have examined the benefits of exogenous growth factor application for wound healing by adding more of a growth factor that is lacking or by giving the surrounding tissue the ability to upregulate its own growth factor production.21,37

A meta-analysis4 of five randomized trials of nonhealing lower extremity ulcers in patients with diabetes found an increased incidence of ulcer healing using growth factors compared with placebo (50% versus 36%, P < 0.007) and a decreased time to healing (14 weeks versus 20 weeks, P = 0.01) in isolated cases, a variety of non-diabetic chronic wounds have healed after rhPDGF application, including a Mohs surgery site, a skin donor site, defects from acute fingertip trauma,8 periodontal osseous defects,9 ulcers secondary to lymphedema, recurrent burn contractures,10 pyoderma gangrenosum,11,12 and three separate cases of successful treatment of ulcers in irradiated wounds.2,13,14 A prospective randomized trial5 comparing rhPDGF with a topical antibiotic applied daily after 4-mm punch biopsy in healthy volunteers showed a faster rate of healing with PDGF (71% of wounds healed by postoperative day 10 with rhPDGF compared to 28% with the antibiotic, P = 0.0005). Results of a prospective randomized trial7 of rhPDGF compared to surgilube after postoperative abdominal wound separation (N= 21) demonstrated a 35% reduction in healing time in the growth factor group (P = 0.05). Encouraging results from a case series9 of eight infants with ulcerated hemangiomas in which rhPDGF was applied to perineal sites also have been reported. The majority of wounds had been refractory to conventional therapy but all wounds healed within 21 days of growth factor treatment and no tumor growth was observed despite concerns of applying an angiogenic growth factor to a hemangioma.

Not all studies have shown improvement of ulcer healing with rhPDGF; this has led to concerns over true treatment efficacy. The studies in which rhPDGF performs best seem to be those in which small areas can be filled — eg, pharyngocutaneous fistulae, 4-mm punch biopsy sites, and periodontal defects, and in studies where differences in the degree of healing were maximal early in the research (3 months).15 This is consistent with PDGF’s biological role early in wound healing, acting as a mitogen for mesenchymal cells, and may explain the positive results of this case series, where small but persistent perineal sinuses closed during exposure to rhPDGF.

Although manipulating the healing process through wound supplementation with agents that are natural contributors to the healing process is an appealing concept, it...
has thus far been too costly to carry out the experimental studies required for FDA approval. Also, although the cost of rhPDGF is high (~$640 per 15-g vial) and the overall cost effectiveness has not been addressed in this context, computer modeling techniques and European center data suggest that adding rhPDGF to standard wound care for diabetic neuropathic ulcers may reduce overall cost of care.

**Clinical and Study Limitations**

As with any growth factor, PDGF application is contraindicated at known sites of neoplasms because in vitro PDGF is a mitogen and stimulates angiogenesis. Three phenomena are particularly concerning for poor oncological outcome with application: APR is associated with approximately twice the risk of recurrence compared to low anterior resection for rectal cancer, rare cutaneous metastasis has been reported after APR, and blockade (not stimulation) of the PDGF receptor improves local chemotherapy delivery in a mouse model. In June 2008, the FDA announced the addition of a boxed warning to the becaplermin label to address the increased risk of cancer mortality in patients who use three or more tubes of the product. The retrospective study that prompted FDA action compared cancer incidence and mortality among 1,622 patients exposed to becaplermin with 2,809 otherwise similar patients who were not exposed. Among the exposed patients, no significant increase in the incidence of cancer was noted but a five-fold increased risk of cancer mortality was noted in patients exposed to at least three tubes of becaplermin. The adjusted rate ratio for overall cancer incidence among becaplermin-treated patients was 1.2 (95% confidence interval [CI], 0.7 – 1.9), and the corresponding death rate ratio was 1.8 (95% CI, 0.7 – 4.9). For patients who had been exposed to three or more tubes of the gel, the adjusted mortality rate ratio was 5.2 (95% CI, 1.6 – 17.6), with an actual incidence rate of 3.9 cancer deaths per 1,000 person-years of treatment. For this reason, the authors of the current study did not use becaplermin in patients undergoing APR for cancer.

The limitations of this case series are those inherent to retrospective studies and the absence of a control arm. Although the observed results are encouraging, the safety, efficacy, and effectiveness of rhPDGF in the care of perineal wounds remains to be established.

**Conclusion**

Delayed healing of the perineal wound in patients with IBD undergoing APR remains a difficult problem and care must be individualized. The results of this study are promising — 60% of perineal wounds with delayed healing closed with the addition of topical growth factor. The results observed in the current case series suggest that topical rhPDGF may facilitate wound healing in patients who do not have a malignancy and whose perineal wound does not respond to standard care.

**References**