Response of Ulcerated Perineal Hemangiomas of Infancy to Becaplermin Gel, a Recombinant Human Platelet-Derived Growth Factor

Brandie J. Metz, MD; Melissa C. Rubenstein; Moise L. Levy, MD; Denise W. Metry, MD

Background: Hemangiomas of infancy are the most common tumors of childhood, and ulceration is the most common complication. Many treatments have been used for hemangioma ulceration, although none are uniformly effective. A recent report described the successful use of 0.01% becaplermin gel, a recombinant human platelet-derived growth factor, for an ulcerated hemangioma refractory to standard care. We sought to further assess the responsiveness of hemangioma ulceration to 0.01% becaplermin gel and to compare its cost to that of conventional modalities.

Observations: We report a case series of 8 infants treated with becaplermin gel for ulcerated perineal hemangiomas of infancy. All infants were seen between January and June 2003 in the pediatric dermatology clinic at Texas Children's Hospital. Six female and 2 male infants were included. All of the hemangiomas were large (≥6 cm²), and of superficial or mixed superficial and deep morphology. Rapid ulcer healing occurred in all patients within 3 to 21 days (average, 10.25 days).

Conclusions: In this small series, 0.01% becaplermin gel was a safe and effective treatment for perineal hemangioma ulceration. The rapid healing achieved with 0.01% becaplermin gel allows a reduction in the risk of secondary infection, pain, and need for hospitalization, as well as in the costs that often accumulate from multiple follow-up visits and long-term therapy.

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A RECOMBINANT HUMAN platelet-derived growth factor-BB gel, 0.01% becaplermin gel (Regranex; Johnson & Johnson Wound Management Worldwide, a division of Ethicon, Somerville, NJ.), is approved in the United States for the treatment of lower extremity diabetic neuropathic ulcers and has also been reported to facilitate the healing of pressure ulcers.¹,²

Sugarman and colleagues³ reported the first case of 0.01% becaplermin gel used successfully for an ulcerated hemangioma of infancy (HOI) refractory to standard care that included meticulous wound care, topical antibiotics, and systemic corticosteroids. Although these authors did not experience HOI proliferation in their study, they were concerned about the potential of platelet-derived growth factor, a known angiogenesis stimulator, to induce HOI proliferation.

We conducted a retrospective chart review of 8 patients with ulcerated perineal HOI who were treated with 0.01% becaplermin gel in the pediatric dermatology clinic at Texas Children's Hospital between January and June 2003. Although 1 of the HOI was located on the hip, this lesion was included in our study because its location under the diaper predisposed it to the same physical factors as the perineum. Data from all 8 cases are summarized in Table 1. Our experience from cases 1 and 2 is described in detail below.

REPORT OF CASES

CASE 1

A Hispanic female infant with a mixed superficial and deep segmental HOI over the labia majora, gluteal cleft, and buttock initially presented to our service at the age of 6½ months with a small, superficial ulceration over her labia. Wound care was initiated with metronidazole gel and mupirocin cream applied twice daily and covered with a barrier paste. She returned 2 months later with 2 additional superficial perineal ulcerations (1.5 cm²). These ulcerations were injected with 1 mL of a 1:1 mixture of 20 mg/mL of triamcinolone and 6 mg/mL of betametha-

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sion, and wound care was continued. One week later she was hospitalized for worsening ulceration. Wound cultures grew Pseudomonas species. Despite treatment with intravenous antibiotics and continued wound care, the ulcers deepened to 3 cm (Figure 1A). Metronidazole gel plus barrier paste was continued at night but replaced in the morning with a thin layer of 0.01% becaplermin gel covered with barrier paste. An outpatient follow-up visit 19 days later showed complete healing of the ulcerations (Figure 1B).

CASE 2

A Hispanic female infant with a large, mixed superficial and deep segmental HOI on the buttocks and gluteal cleft presented with a 3-month history of multiple mixed ulcerations that had been unresponsive to treatment with wound care and topical, intrallesional, and systemic corticosteroids (Figure 2A). Treatment was initiated with a daily application of becaplermin gel followed by the application of a barrier paste. By her follow-up appointment 3 weeks later the ulcerations had completely healed (Figure 2B).

CASE SERIES

Six female and 2 male infants with ulcerated perineal HOI were included in our series (Table 1). All of the HOI were large (≥6 cm²) and of superficial or mixed superficial and deep morphology. In all 8 cases, rapid healing of the ulceration occurred within 3 to 21 days (average, 10.25 days with 0.01% becaplermin gel). The ulcerations had been refractory to conventional therapy in 5 of the 8 patients, while in the remaining 3 patients 0.01% becaplermin gel was the only medication used. We did not note HOI proliferation in any of our patients. In fact, in patient 1, in whom 0.01% becaplermin gel was inadvertently applied to ulcerated and nonulcerated HOI tissue, clinical findings consistent with invasion were evident (Figure 1B).

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Table 1. Ulcerated Hemangiomas Treated With 0.01% Becaplermin Gel

<table>
<thead>
<tr>
<th>Patient No./Age, mo</th>
<th>Location</th>
<th>Type/Stage/Size of Hemangioma</th>
<th>Ulceration Size/Depth/Bleeding</th>
<th>Duration of Ulceration</th>
<th>Previous Treatment</th>
<th>Treatment Regimen</th>
<th>Time to Healing, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/11.5</td>
<td>Labia, buttock</td>
<td>Mixed segmental/late proliferative/11 × 9 cm</td>
<td>3 × 3 cm/deep/Y</td>
<td>4 mo</td>
<td>Metronidazole, mupirocin, barrier paste,* intralesional steroids</td>
<td>0.01% becaplermin + barrier paste* once daily (AM), metronidazole + barrier paste* once daily (PM)</td>
<td>14</td>
</tr>
<tr>
<td>2/6.5</td>
<td>Buttocks, gluteal cleft</td>
<td>Mixed segmental/late proliferative/15 × 7 cm</td>
<td>Multiple/superficial and deep/Y</td>
<td>3 mo</td>
<td>Systemic steroids, intralesional steroids, topical steroids, wound care</td>
<td>0.01% becaplermin + barrier paste* once daily (AM)</td>
<td>21</td>
</tr>
<tr>
<td>3/3</td>
<td>Labia majora</td>
<td>Mixed segmental/early proliferative/3 × 2 cm</td>
<td>3 × 2 cm/deep/N</td>
<td>2 wk</td>
<td>None</td>
<td>0.01% becaplermin gel covered with moist gauze once daily</td>
<td>13</td>
</tr>
<tr>
<td>4/3</td>
<td>Buttock</td>
<td>Mixed segmental/early proliferative/4 × 3.5 cm</td>
<td>2 × 1 cm/superficial/N</td>
<td>2 wk</td>
<td>None</td>
<td>0.01% becaplermin + barrier paste* + occlusive dressing† once daily (AM)</td>
<td>10</td>
</tr>
<tr>
<td>5/10</td>
<td>Perineum</td>
<td>Superficial indeterminate/late proliferative/4 × 3 cm</td>
<td>Multiple 1-cm lesions/superficial/Y</td>
<td>3-5 days</td>
<td>Metronidazole, barrier paste*</td>
<td>0.01% becaplermin + barrier paste 3+ hydrocolloid dressing† once daily (AM); metronidazole + barrier paste + occlusive dressing† once daily (PM)</td>
<td>3</td>
</tr>
<tr>
<td>6/7</td>
<td>Perianal</td>
<td>Superficial indeterminate/late proliferative/4 × 2.5 cm</td>
<td>3 × 2 cm/superficially</td>
<td>1 mo</td>
<td>Neomycin-polymyxin β- bacitracin, barrier paste*</td>
<td>Metronidazole + barrier paste* once daily (AM); becaplermin + barrier paste* once daily (PM)</td>
<td>20</td>
</tr>
<tr>
<td>7/3.5</td>
<td>Gluteal cleft</td>
<td>Superficial segmental/early proliferative/paste* once daily/3 × 2.5 cm</td>
<td>&lt;1 cm/superficially</td>
<td>1 mo</td>
<td>None</td>
<td>Bepacidermin + barrier paste* once daily (AM); metronidazole + barrier paste* once daily (PM)</td>
<td>3</td>
</tr>
<tr>
<td>8/4</td>
<td>Right hip</td>
<td>Superficial indeterminate/early proliferative/4 × 2 cm</td>
<td>2.5 × 1 cm/deep/N</td>
<td>7 wk</td>
<td>Mupirocin, metronidazole, barrier paste,* hydrocolloidal dressing, systemic steroids, intralesional steroids</td>
<td>Bepacidermin gel twice weekly</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviations: N, no; Y, yes.
*The paste was zinc oxide-based.
†Tegaderm (3M Health Care, St Paul, Minn).
‡Duoderm (Convatec, Princeton, NJ).
Hemangiomas of infancy are the most common benign tumors of childhood and ulceration, the most common complication of HOI, occurs in 5% to 15% of cases. Ulceration generally develops during the proliferative phase of the HOI life cycle, and is more commonly seen with lesions showing segmental morphology, ie, with a plaque-like, linear, and/or geographic pattern over a specific cutaneous territory. The perineum is the most frequent site of HOI ulceration, probably because of recurrent friction, maceration, and repeated exposure to urine and feces. Whereas wound care is important in the management of perineal HOI ulceration, adherent dressings are often inefficient in this location. Rapid ulcer healing is desirable to reduce pain, bleeding, and the risk of infection.

None of the current modalities of HOI ulceration management are uniformly effective. While meticulous wound care is essential, topical antibiotics (most commonly mupirocin or metronidazole), topical, intralesional and/or systemic corticosteroids, and pulsed-dye laser may be used as adjunct therapy. Surgical excision may be required in the most refractory cases.

Platelet-derived growth factor, which promotes the recruitment and proliferation of cells involved in wound repair and enhances epithelialization, has been shown to promote angiogenesis. However, growth factors are known to have either stimulatory or inhibitory effects, depending on the tissue affected, because individual transduction molecules may be present in different amounts in different cell types. This may explain why 0.01% becaplermin induced ulcer healing, but not HOI proliferation, in our patients. Of interest is the significant involution observed at follow-up in patient 1, when it was discovered that 0.01% becaplermin had been inadvertently applied to the entire HOI surface rather than on the ulcerated areas only. It remains to be seen whether 0.01% becaplermin gel...
becaplermin has an effect, direct or indirect, on HOI in-
volution; and if so, whether this effect varies by lesion
morphology.

While the cost of 0.01% becaplermin gel may ini-
tially seem expensive, one must compare it with the cost
of alternative therapies. In our experience, multiple fol-
low-up visits and the long-term use of wound care agents,
in addition to other conventional agents, are often re-
quired to achieve healing. We calculated the average cost
of each topical medication when purchased from 4 sepa-
rate pharmacies in Houston (Table 2), and added the
standard costs of office visits, inpatient hospitalization,
intralasional corticosteroid injections, and pulsed-dye la-
sor therapy at our institution. The rapid healing in-
duced by 0.01% becaplermin gel not only reduced these
costs, but also the risk of secondary infection, pain, and
need for hospitalization, as 2 of our infants experienced
prior to receiving this medication.

In this small series, 0.01% becaplermin gel appears
to be safe and effective for the management of HOI ul-
ceration in the perineal location. A randomized con-
trolled trial of becaplermin gel for this indication, with
outcome measures to include time to healing, presence
or absence of HOI proliferation, cost, and quality of life,
is currently in development.

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meeting of the Society for Pediatric Dermatology; June, 2003;
Seattle, Wash.

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Table 2. Cost of Different Treatment Modalities
for Hemangioma Ulcerations

<table>
<thead>
<tr>
<th>Modality</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becaplermin gel (15 g)</td>
<td>519</td>
</tr>
<tr>
<td>Metronidazole gel (45 g)</td>
<td>69</td>
</tr>
<tr>
<td>Mupirocin ointment (22 g)</td>
<td>52</td>
</tr>
<tr>
<td>Barrier paste (4 oz)</td>
<td>3</td>
</tr>
<tr>
<td>Duoderm Extra Thin (4 × 4 in, 10 count)</td>
<td>49</td>
</tr>
<tr>
<td>Tegaderm (4 × 4 in, 10 count)</td>
<td>25</td>
</tr>
<tr>
<td>(Convatec, Princeton, NJ)</td>
<td></td>
</tr>
<tr>
<td>(3M Health Care, St Paul, Minn)</td>
<td></td>
</tr>
<tr>
<td>Office visit*</td>
<td>85</td>
</tr>
<tr>
<td>One-day hospitalization</td>
<td>1500-2000</td>
</tr>
<tr>
<td>Intralasional steroid injection</td>
<td>95</td>
</tr>
<tr>
<td>Pulsed-dye laser (per treatment)</td>
<td>251-787†</td>
</tr>
<tr>
<td>Surgical excision with repair</td>
<td>2100-2600†</td>
</tr>
</tbody>
</table>

*Level 3, established-patient visit.
†Cost varies with complexity of case and does not include general
anesthesia.

REFERENCES

human platelet-derived growth factor for the treatment of lower extremity dia-
2. Rees RS, Robson MC, Smiell JM, Perry BH. Becaplermin gel in the treatment of
pressure ulcers: a phase II randomized, double-blind, placebo-controlled study.
3. Sugarman JL, Mauro TM, Frieden IJ. Treatment of an ulcerated hemangioma with
5. Achauer BM, Chang CJ, Vander Kam VM. Management of hemangioma of in-
6. Chiller KG, Passaro D, Frieden IF. Hemangiomas of infancy: clinical character-
istics, morphologic subtypes, and their relationship to race, ethnicity, and sex.
7. Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical character-
593.
9. Heldin CH. Simultaneous induction of stimulatory and inhibitory signals by PDGF.