Prostaglandin E₁ (PGE₁) ointment has been shown to improve the survival of skin grafts. However, the mechanism of the effects of PGE₁ through topical application is unknown. A rat skin flap model was used to determine whether PGE₁ is absorbed through the intact skin. The prostaglandin concentrations in the flaps in the study group were greater than those in the controls. It is suggested that PGE₁ is absorbed through the skin.


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In a previous report, we described the clinical effects of the continuous infusion of prostaglandin E₁ (PGE₁) into flap feeding arteries on the prevention of flap necrosis and the improvement of local microcirculation and flap survival [1]. Basic research and clinical studies of PGE₁ ointment have been concluded in our laboratory. This work has resolved in the discovery that the concurrent use of occlusive dressing therapy augments the effectiveness of PGE₁ ointment. As a result, flap survival was augmented by about 12% in the treated group [Fig 1] [2].

When applied over areas of ulceration or tissue loss, PGE₁ ointment is absorbed directly into the wound [3]. However, when applied over a graft or flap with intact epidermis, the absorption of PGE₁ has not been proven. In this study, PGE₁ absorption through the skin was demonstrated in an animal model.

Materials and Methods

Preparation of PGE₁ Ointment
The ointment was prepared by dissolving injectable 40 μg of PGE₁ in minimal volume of physiological saline solution. This solution was then blended with 10 g of polyethylene mineral oilgel (plastibase). The ointment was used within 1 hour of preparation. A new batch was prepared each time the ointment was applied.

Experimental and Control Group Animals
The experiment was performed using 40 male Wistar rats weighing approximately 400 g. On the back of each rat, a 3 × 9-cm flap was raised with a caudal base (Fig 2A). The flaps were created by dissecting beneath the panniculus carnosus and sutured back to its original position, creating a tight seal at the skin edge. The rats were divided into a study and control group. In the study group, PGE₁ ointment was applied evenly to the entire surface of the flap and covered by an occlusive dressing using a polyurethane sheet. The flap in the control group was covered with plastibase and an occlusive dressing. The flaps (five at each time in each group) were harvested at 0, 12, 24, and 48 hours after the application of ointment.

Measurement of PGE₁ Content in Tissue
Immediately after harvesting the flaps, an 8 × 8 × 1-mm section of dermis was removed and tested (see Fig 2B). To avoid the possibility that the PGE₁ on the exterior of the flap would contami-
nate the specimen, the surface layer was excised and the inner layer was assayed. The tissue samples were frozen in liquid nitrogen. Ethanol was added, and the sample was homogenized and centrifuged. Total prostaglandin E (PGE) content in the supernatant was quantified using a commercially available radioimmunoassay. One operator performed all of the flap procedures under the same conditions. Extreme precautions were taken when harvesting the treated flaps to ensure that surface PGE$_1$ did not contaminate the inner layers of tissue. The significance of difference was assessed with t-tests.

**Results**

The PGE content in the control flaps increased with from 19.40 ± 2.44 (mean ± SD) pg/ng tissue (wet weight [ww]) to 22.85 ± 3.26 (mean ± SD) pg/ng tissue (ww) (Fig 3). This increase in PGE content was consistent with the physiologic response to the creation of the flap. The PGE content in the study group increased from 22.64 ± 3.04 (mean ± SD) pg/ng tissue (ww) to a peak of 40.72 ± 3.27 (mean ± SD) pg/ng tissue (ww) at 24 hours. At 48 hours, the PGE content was still greater in the study group compared with the controls. The PGE content in the study group was higher than that in the controls at 12, 24, and 48 hours after the application of ointment. The differences at each point were statistically significant with the t-test. These data suggest that PGE$_1$ is absorbed into the flap through the skin.

**Discussion**

Prostaglandin E$_1$ has been studied along with other materials in an effort to improve flap survival [4–6]. Unfortunately, most of these sub-
stanes have required systemic administration. Because systemically administered drugs are often associated with some side effects, a locally delivered agent may be better tolerated. We have conducted a series of experiments to determine the efficacy of locally administered PGE₁ by continuous arterial infusion [1] and have studied the effects of occlusive dressings on drug effectiveness [2]. Furthermore, moist environment itself augmented the survival length of the skin flap [7]. It is easy to understand that the topically administered drugs show their effectiveness on the ulcers because they can be absorbed directly through the wound surface. However, when the skin grafts or flaps need to be rescued by some drug, it is necessary for the drug to be absorbed through the intact skin. The purpose of the current experiment was to determine whether PGE₁ administered in ointment form is absorbed through the skin. To prevent the PGE₁ ointment from seeping in from the wound edges, the sutures were tied tightly. Contamination by the PGE₁ ointment was avoided during the harvest of the specimen by excision of the superficial layers of the skin. The assays were performed on samples from the dermal layers. Because radioimmunoassay kits for PGE₁ itself are not available, total prostaglandin content was measured. By the results, the clear increase in prostaglandin content in the study group compared with the control group was believed to reflect PGE₁ absorption. It is indeed possible that some PGE₁ gained access to the specimen via the wound edges. However, because the same procedures are used in clinical practice, it may not be necessary to make the distinction between PGE₁ absorption through the dermis and PGE₁ seepage around the wound edges. Because the PGE content in the study group peaked at 24 hours, the PGE₁ ointment should probably be applied once a day. We have previously shown that the effectiveness of PGE₁ ointment is increased by a moist environment [2]. Thus, lower concentration preparations may be used to achieve the same effect. This method is more cost effective than applying a high-concentration ointment with a gauze dressing. Grafts and flaps are the most commonly used techniques in plastic and reconstructive surgery. Thus, any method that may improve graft survival may have widespread application. Although PGE₁ may be administered by intravenous infusion [5], enormous doses must be delivered to achieve an adequate local concentration. This is associated with major systemic effects. Local arterial injections yield immediate and substantial effects, but the treatment requires technical expertise and the patient's cooperation. In contrast, the application of PGE₁ ointment with an occlusive dressing is simple and relatively inexpensive. The potential clinical applications of this technique are numerous. Further studies of the specific effects of PGE₁ ointment on graft microcirculation and survival must be performed to establish the role of this treatment in plastic surgery.
References