# The Transepidermal Absorption of Prostaglandin $E_1$ as a Topical Ointment: An Experimental Study of Application Over a Rat Skin Flap

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**Prostaglandin $E_1$ ($PGE_1$) ointment has been shown to improve the survival of skin grafts. However, the mechanism of the effects of $PGE_1$ through topical application is unknown. A rat skin flap model was used to determine whether $PGE_1$ 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 $PGE_1$ is absorbed through the skin.**

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In a previous report, we described the clinical effects of the continuous infusion of prostaglandin $E_1$ ($PGE_1$) 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 $PGE_1$ 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 $PGE_1$ 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, $PGE_1$ ointment is absorbed directly into the wound [3]. However, when applied over a graft or flap with intact epidermis, the absorption of $PGE_1$ has not been proven. In this study, $PGE_1$ absorption through the skin was demonstrated in an animal model.

## Materials and Methods

### Preparation of $PGE_1$ Ointment

The ointment was prepared by dissolving injectable 40 $\mu$g of $PGE_1$ in minimal volume of physiological saline solution. This solution was then blended with 10 g of polyethylenmineral 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 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, $PGE_1$ 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 $PGE_1$ 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 $PGE_1$ on the exterior of the flap would contami-

 

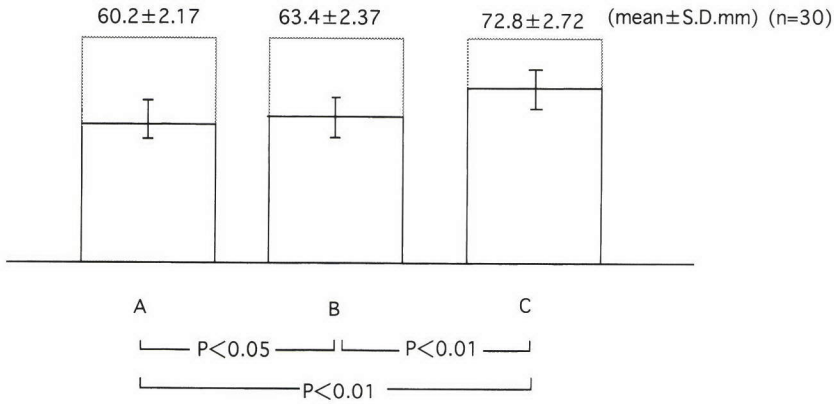


*Fig 1. The efficacy of topical $PGE_1$-containing ointment and occlusive dressing (ODT). $PGE_1$-containing ointment consisted of 40 μg $PGE_1$ in 10 g plastibase. Group A = control (no treatment); group B = plastibase + ODT; group C = $PGE_1$-containing ointment + ODT. The ointment was reapplied once a day, and survival length was assessed after 7 days. The survival length of group C was 12% greater than the survival length of group A.*

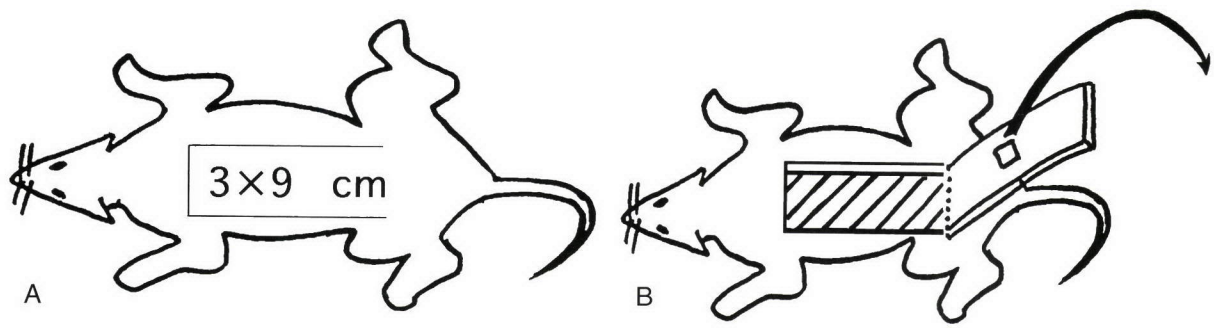


*Fig 2. (A) Caudally based flap is created on the back of each rat (3 × 9 cm). The flaps are then sutured as tightly as possible in their original position. (B) The flaps are harvested at 0, 12, 24, and 48 hours after the application of ointment. Five animals in each group are sacrificed at each time. From the center of the excised flap, an 8 × 8 × 1-mm sample of dermis is resected, frozen, and assayed for prostaglandin.*

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-

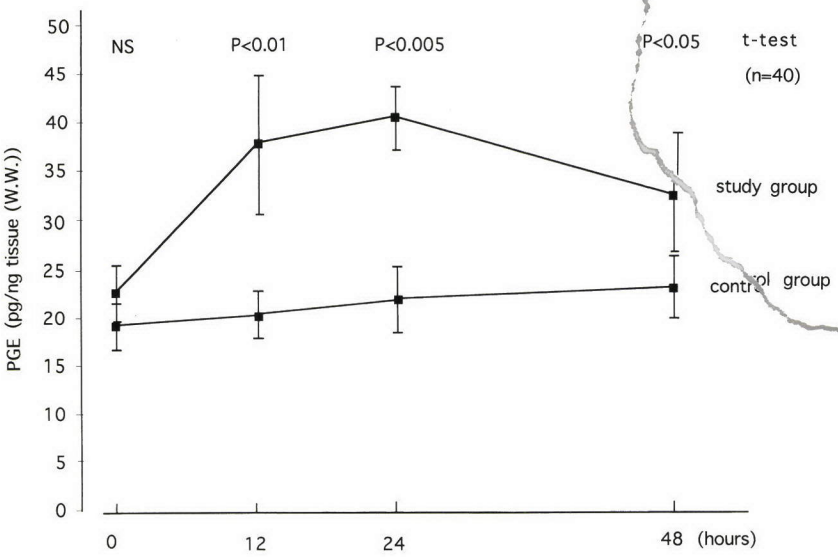


*Fig 3. Changes in prostaglandin (PGE) tissue content as a function of time. The PGE content increases in the control animals after flap creation. The PGE content in the study group is higher than that in the control group. W.W. = wet weight.*

stances 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 $PGE_1$ 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 $PGE_1$ administered in ointment form is absorbed through the skin. To prevent the $PGE_1$ ointment from seeping in from the wound edges, the sutures were tied tightly. Contamination by the $PGE_1$ 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 $PGE_1$ 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 $PGE_1$ absorption. It is indeed possible that some $PGE_1$ 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 $PGE_1$ absorption through the dermis and $PGE_1$ seepage around the wound edges. Because the PGE content in the study group peaked at 24 hours, the $PGE_1$ ointment should probably be applied once a day. We have previously shown that the effectiveness of $PGE_1$ 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 $PGE_1$ 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 $PGE_1$ 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 $PGE_1$ ointment on graft microcirculation and survival must be performed to establish the role of this treatment in plastic surgery.

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