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The relationship between time of application of Prostaglandin E1 and improved flap survival

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SUMMARY. **Using 60 Hirosaki hairless rats, the relationship between the time of starting topical administration of Prostaglandin E1 using silicone gel and flap survival rate is described. Compared to control groups, beginning the administration of PGE1 at 0 ($P < 0.01$) and 3 h ($P < 0.05$) after flap elevation resulted in an increased flap survival area (Student's t-test). However, in groups in which PGE1 administration was begun at 6, 9 and 12 h after flap elevation, no statistically significant differences could be detected.**

We have previously reported on the effectiveness of the topical application of Prostaglandin E1 (PGE1) in improving experimental flap survival area.[1-2] This paper reports further on the relationship between time of application of PGE1 and flap survival rate.

Materials and methods

In our previous studies,[1] we described a silicone gel drug delivery system (Dow Corning, K.K., Tokyo, Japan) containing Ofloxacin (OFLX, Daiichi Seiyaku, Tokyo, Japan) for flap coverage. For this study, we prepared a silicone gel containing 0.02% OFLX and 10^{-5}% of PGE1 (Ono Pharmaceutical, Osaka, Japan) on a sheet measuring 12 × 15 cm. Sixty female Hirosaki hairless rats, weighing from 250–350 g, were divided into six groups from A to F. On the back of each rat, a skin flap, measuring 9 × 2 cm, and caudally based, was elevated and sutured back in place, in the same manner as reported previously.[1] In group A, immediately after the flap was sutured into position, it was covered with silicone gel, over an area measuring 4 × 14 cm and containing only OFLX, and this served as a control. In groups B to F, immediately after the flap was sutured into position it was covered with silicone gel containing OFLX and PGE1. In groups B to F, when silicone gel was applied on the flap, a water impermeable thin plastic film was applied between the flap and the silicone gel, to prevent the contained drug from reaching into the rat skin. In group B, the plastic film only was removed immediately after the silicone gel was applied on the flap. In group C, the plastic film was removed 3 h after flap elevation. Additionally, in groups D, E, and F, the plastic film was removed at 6, 9 and 12 h after flap elevation.

On the seventh day after the flap elevation, the silicone gel was removed, and on the following day, the surviving flap area was evaluated and measured using a planimeter according to the method of Roth *et al.*[2] Student's t-test was employed to assess the differences in the mean flap surviving area and flap survival rate between each test group and the control group A.

Results

The surviving area and survival rate of the flaps in Groups A to F were listed in Table 1 and Figure 1. Compared with the surviving area of group A, groups B ($p < 0.01$, Student's t-test) and C ($p < 0.05$, t-test) showed a statistically significant increased surviving area. There were no significant differences between groups A, D, E and F in either the surviving area or in the survival rate.

Discussion

In the distal portion of a flap which is too large for its supporting blood supply, blood flow is inadequate during the first 12 h after raising, and irreversible ischaemia will result in flap necrosis.[3] We postulated that beneficial effects of PGE1 and heparin would not be apparent if administration of the drug is too late after flap elevation. We also think that it is clinically important to know during what maximal period of time drug administration can effectively prevent flap necrosis. The tolerance time is influenced by many

Table 1 Flap surviving area and survival rate in each test group

	Surviving area (cm^2)	*Survival rate* (%)
Group A	9.1±1.5	50.3±7.5
Group B	12.5±1.8	64.5±4.7
Group C	11.0±0.5	62.4±4.4
Group D	9.7±1.6	56.4±7.1
Group E	9.1±1.4	51.3±6.8
Group F	8.5±1.4	48.5±8.2

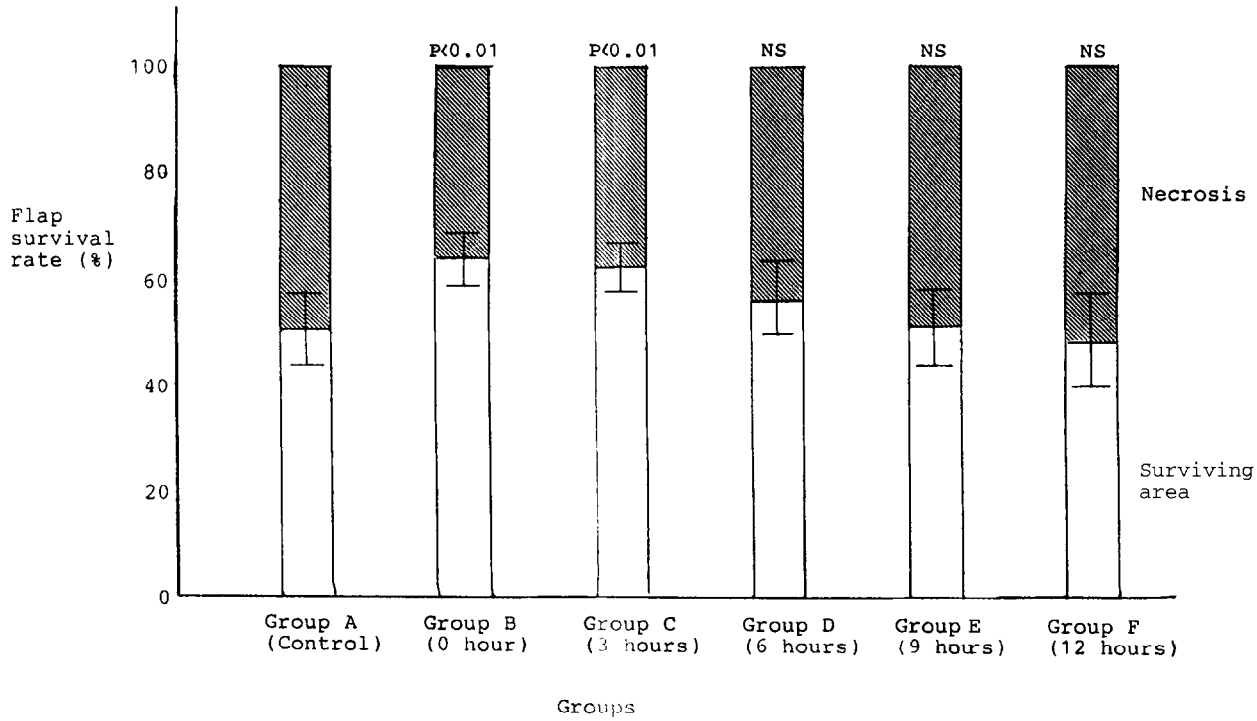

Fig. 1

Figure 1—Flap survival rate in each of the groups.

factors in the same species of animals, such as blood viscosity, anaemia, fibrinolysis, and protein deposition.[3] Kerrigan and Daniel reported that rat skin is able to tolerate 6–9 h of ischaemia, rabbits 8 h, pigs 8–13 h, and amputated digits 6–8 h.[4] They also suggested that pharmacological methods to increase flow should be started before the no reflow phenomenon is established.[4] Campbell *et al.*[5] reported that ischaemic necrosis of the flap of the rat occurs at between 8 and 12 h, and any attempt to resuscitate flaps would be more effective if instituted before 8 h of ischaemia.

From our experiences, although PGE1 administration using silicone gel up to 3 h after flap elevation improved flap survival of the rat, administration beyond 6 h after flap elevation did not result in any improvement. We believe that this is because topically applied PGE1 using silicone gel seems to take some time to reach the microvasculature of the flap through the skin.

These results indicate that when applying silicone gel containing PGE1 to achieve survival in a poorly vascularised flap, it should be applied within a few hours after performing the flap elevation. Although there have been many reports which describe various kinds of drugs as being beneficial in improving the flap survival rate in experimental studies, some of them are unlikely to be successful in the treatment of the failing flap in clinical practice.[3] We suspect that such an unsuccessful result would depend on the time when administration of the drug was begun. Our present result could be one of the guidelines to determine the time when topical application of PGE1 should be initiated to treat a failing flap.

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