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A study of topical and systemic Prostaglandin E1 and survival of experimental skin flaps

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SUMMARY. **A study has been undertaken to investigate Prostaglandin E1 administration procedure for improving flap survival. Whether the drug was administered continuously or transcutaneously using a silicone gel drug delivery system; or was topically injected into the critical zone of the flap; or was intraperitoneally administered intermittently over an hour after surgery a statistically significant improvement of flap survival occurred ($P < 0.01$, Student's *t*-test).**

However, no improvement of flap survival was seen when the drug was administered only once intraperitoneally immediately after flap elevation, although administered doses of the drug in those rats was equal to the doses in the rats which received intermittent administration of the drug intraperitoneally over an hour after surgery.

We have previously reported that topical and continuous application of Prostaglandin E1 (PGE1) using a silicone gel drug delivery system has been found effective in improving the flap survival rate in experimental rat models.[1-3] Pursuing this research further, we have now investigated whether different methods to administer PGE1 other than the silicone gel drug delivery system might result in improvement of the flap survival.

Materials and methods

Silicone gel was obtained from Dow Corning K.K., Tokyo, Japan, Prostaglandin E1 from Ono Pharmacy Co., Osaka, Japan, and Ofloxacin from Daiichi Seiyaku, Tokyo, Japan. Ninety female Hirosaki hairless rats, weighing from 250–350 g each, were used for this study. Nine groups of rats, consisting of 10 rats to a group, were formed and designated as Groups A through I. Groups A to E were used for the first study, Groups F to H for the second study, and Group I for the third study.

First study

Using the procedure that has been previously described,[1-3] on the back of each rat in Groups A through E, a caudally based skin flap that included the panniculus carnosus, 9×2 cm, was elevated and immediately sutured *in situ*. On completion of this surgery, each rat was independently caged. Group A rats were the control group, and received no drug administrations. As for Group B rats, immediately after the flap was sutured, a silicone gel sheet containing 0.02% OFLX and 10^{-5}% PGE1, 14×4 cm in size, which was a little larger than the flap on all sides, was sutured on the back of the rats, a procedure that has been previously described.[1-3] Group C rats received one administration of a 1 ml 2×10^{-5}% PGE1 solution (0.2 microgram of PGE1 in 1 ml of saline water) that was topically applied immediately after flap suturing beneath the entire flap. Although the applied PGE1 solution leaked from the wound, no steps were taken to prevent this leakage. Group D rats received 0.3 ml of a 2×10^{-5}% PGE1 solution at the same concentration as Group C that was injected into the subcutis of the flap 5 cm from the flap tip, the region considered the critical zone where necrosis occurs if PGE1 is not applied. Previous experiments[1,2] have identified this critical zone. Group E rats received one administration of a 1 ml 2×10^{-5}% PGE1 solution that was injected intraperitoneally immediately after flap suturing.

Second study

For this study, a flap just like that in the first study and a 2×10^{-5}% PGE1 solution was used. Group F rats received 1 ml of a saline solution without PGE1 intraperitoneally immediately after flap elevation and served as the controls. Group G rats were given a 1 ml PGE1 solution intraperitoneally immediately after flap elevation, and at 15 min and 30 min after flap elevation (total 0.6 microgram of PGE1). Group H rats were given 1 ml intraperitoneal dose of the PGE1 solution immediately after flap elevation, and at 15, 30, 45, and 60 min after flap elevation (total 1 microgram of PGE1).

Third study

Based on the results of the second study, the Group I rats received only a 1 ml intraperitoneal injection of a 10^{-4}% PGE1 solution (1 microgram of PGE1) immediately after flap elevation.

On the 7th day after surgery, following a procedure previously described,[1,2] the rats were anaesthetised

and the area of the flap that had survived and the flap survival rates were evaluated.

Results

The area of the flap that had survived and survival rate of each rat group are listed in Table 1. With regard to the area of the flap that had survived and the percentage of flap survival, compared with the results seen in our Group A control rats, a statistically significant difference was only seen in rat Groups B, D and H ($P < 0.01$, Student's t-test). Further, compared to the results seen in Group F, a statistically significant difference was also seen in these same B, D, and H rat groups ($P < 0.01$, Student's t-test, Table 1, Figs 1, 2).

Table 1 The flap surviving area and flap survival rate based on various administration of PGE1

Group ($n = 10$)	*Surviving area* ($cm^2 \pm S.D.$)	*Survival rate* ($\% \pm S.D.$)
A	10.1 ± 1.2	56.3 ± 6.5
B	12.4 ± 1.0*	69.1 ± 5.6*
C	10.2 ± 0.5	56.7 ± 3.0
D	11.7 ± 1.1*	64.7 ± 6.2*
E	10.3 ± 1.1	57.2 ± 6.4
F	9.9 ± 1.4	54.8 ± 7.8
G	10.9 ± 1.7	60.7 ± 9.4
H	12.6 ± 0.9*	70.2 ± 5.2*
I	10.2 ± 0.7	56.6 ± 3.8

* $P < 0.01$ (Student's t-test) compared to the control groups (Group A and Group F).

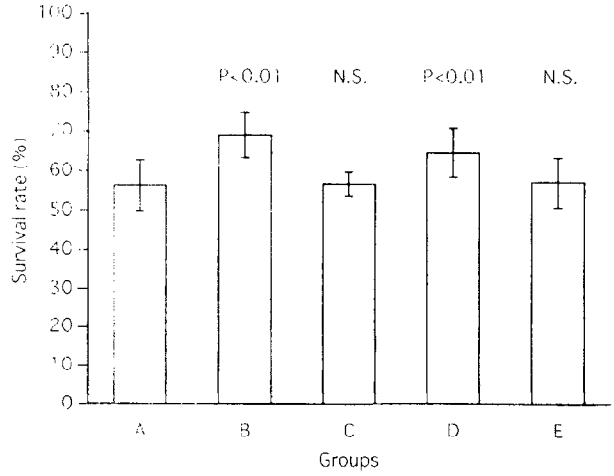

Fig. 1

Figure 1 Flap survival rate of Groups A–E rats (n = 10).

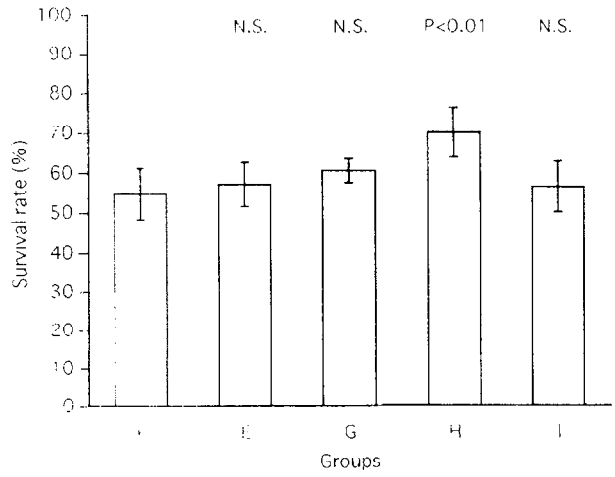

Fig. 2

Figure 2 Flap survival rate of Groups E–I rats (n = 10).

Discussion

There have been many reports that PGE1 and Prostaglandin I2 (PGI2), administered topically or systemically, improve flap survival in animal models and in clinical practice.[1–11] It has also been reported that administered Prostaglandins have an extremely short half-life,[11] and that the major portion of the systemically administered PGE1 is quickly metabolised in the lung.[8] In the first study, no improvement in flap survival occurred in Groups C and E. It thus can be speculated that in Group E rats, the intraperitoneally administered PGE1 was metabolised promptly, and that in Group C rats, most of the administered PGE1 leaked from the wound soon after it was administered. However, in Group B rats, PGE1 administration was continuous. In Group D rats, 3 h after the injection of the PGE1 solution, a weal presented on the injected site of the flap, so that it seemed that topically injected PGE1 would be retained in the critical zone at least 3 h after surgery. These findings lead us to conclude that if PGE1 is used to save a failing flap, either the PGE1 should be continuously administered to the critical zone, or the PGE1 should present in the tissue of the critical zone of the flap for some period of time after surgery.

As for the second study, although the PGE1 solution administered was the same concentration used for Group E, G and H rats, only in Group H rats did flap survival occur. For Group H rats, a total 1 microgram of PGE1 was administered, the same dose administered for Group I rats. However, in the third study, Group I rats showed no improvement in flap survival. The difference in the medication protocol between the Group H and I rats was that the PGE1 dose for the Group I rats was administered once immediately after surgery, whereas in Group H rats the PGE1 dose was given intermittently over a period of 60 min after surgery.

In clinical practice, an intravenous PGE1 is frequently given to improve the survival of flaps that appear to be failing.[9] Suzuki *et al.* reported the clinical effects of intravenous PGE1 administration in salvaging failing flaps, and indicated that this treatment was effective in 41 of 50 cases.[9] However, they did not refer to the beginning time and duration of time of intravenous administration of PGE1. Many reports have indicated that a PGE1 or PGI2 administration after experimental and clinical surgery improves the chances of flap survival.[1,8–10,11] In those reports, the PGE1 was either intermittently or continuously administered for several hours or for some days after surgery.[1,4,7,10]

Intraperitoneally administered PGE1 travels to the flap by the blood stream. Based on our findings, when

PGE1 is systemically administered to improve flap survival in an animal model, it should be administered not as a one-shot injection but administered continuously over a period of about 1 h. We suspect that in clinical practice, intravenous PGE1 should be administered continuously over some period of time, at least 1 h. Further, based on our previous research, the PGE1 administration should be initiated within a few hours after flap elevation.[3]

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