Topical application of capsaicin and flap survival

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SUMMARY. A study has been undertaken to investigate the relationship of capsaicin administration to flap survival. Skin flaps measuring 9 by 2 cm in size were raised on the dorsum of rats and covered with silicone gel sheet either containing or not containing capsaicin. Topical application of capsaicin transcutaneously resulted in a significant increase in the area of flap survival (P < 0.01).

We have described how some drugs such as prostaglandin E1 (PGF1) and heparin improve flap survival rate in experimental skin flaps.1-5 These drugs show similar effects on flap survival when administered systemically or topically.7 Many reports have evaluated the effects of systemic drugs on flap survival. For capsaicin, some reports describe little beneficial effect when capsaicin is systemically administered prior to flap elevation.6,7 We surmised the possibility that quite different effects would result if other means of administration were used and an experimental study using topically applied capsaicin was carried out.

Materials and methods

In our previous studies, we described a silicone gel drug delivery system (Dow Corning, K.K., Tokyo, Japan), containing Ofloxacin (OFLX, Daiichi Seiyaku, Tokyo, Japan).8 For this study, we prepared a silicone gel containing OFLX 0.02% and capsaicin (Sigma Chemical Company, St. Louis, USA) 0.025% (50 mg in 200 grams of silicone gel). Thirty female Hirosaki hairless rats, weighing from 250-350 grams, were randomly divided into three groups, A, B and C. All rats were anaesthetised with pentobarbital, 0.05 mg per gram body weight intraperitoneally. On the back of each rat, a caudally based skin flap, measuring 9 x 2 cm, was elevated and sutured back in place, as reported previously.1-5

In group A, no dressing was applied to the flap. In group B, immediately after the flap was sutured into position the whole flap was covered with silicone gel containing OFLX alone. In group C, the whole flap was covered with silicone gel containing OFLX and capsaicin. Group B was used to test whether silicone gel containing only OFLX had any influence on flap survival. After surgery, each rat was caged independently. On the sixth day after surgery, the silicone gel was removed and on the following day the area of flap survival was measured using a planimeter according to the method described previously.1-5 Wounds on the backs of rats gradually contract and so a week after surgery the area of the wounds have a tendency to become somewhat smaller than the initial area (18 cm²). The degree of contraction differs in each rat. We therefore evaluated the areas of flap survival (cm²) and flap survival rates (surviving flap area versus the total flap area taken as a percentage). The Mann–Whitney U test was employed to assess the differences in the mean area of flap survival and flap survival rate between each test group and the control group A.

Results

The areas of flap survival and the survival rates for the flaps in groups A, B and C are shown in Table 1. Compared with the areas of flap survival of groups A and B, group C showed a statistically significant increase in area of flap survival and survival rate (P < 0.01). No statistical difference was found between groups A and B for area of flap survival and survival rate (Tables 1 and 2).

Table 1 Area of flap survival and flap survival rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Area of flap survival (cm²)</th>
<th>Flap survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Interquartile range: 25th to 75th centile)</td>
<td>Median (Interquartile range: 25th to 75th centile)</td>
</tr>
<tr>
<td>Group A</td>
<td>8.1 (6.8–8.8)</td>
<td>52.0 (47.8–55.8)</td>
</tr>
<tr>
<td>Group B</td>
<td>8.2 (8.1–8.7)</td>
<td>50.4 (48.5–52.7)</td>
</tr>
<tr>
<td>Group C</td>
<td>10.2 (9.2–11.6)</td>
<td>66.0 (61.5–70.3)</td>
</tr>
</tbody>
</table>
Table 2 Comparison of groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Area of flap survival</th>
<th>Flap survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>A and B</td>
<td>$P = 0.5687$ (N.S.)</td>
<td>$P = 0.6775$ (N.S.)</td>
</tr>
<tr>
<td>A and C</td>
<td>$P = 0.0028$</td>
<td>$P = 0.0012$</td>
</tr>
<tr>
<td>B and C</td>
<td>$P = 0.0045$</td>
<td>$P = 0.0005$</td>
</tr>
</tbody>
</table>

Discussion

Capsaicin is a derivative of vanillyl amide, which is the major pungent ingredient found in the fruit of a variety of red peppers in the Capsicum genus and widely used as a specific de-activator of sensory afferent neurons. It causes vasodilatation and increases vascular flow. It also causes a depletion of sensory neuropeptides, including substance P, which has vasodilatory effects, and inhibits neurogenic inflammation induced by chemical irritants or by antidromic stimulation of sensory nerves. In an experimental study using rats, Kjartansson et al. reported that systemic pretreatment with capsaicin caused a dramatic decrease in flap survival area. Westin and Heden reported that sensory denervation with pretreatment using capsaicin does not influence the critical ischaemia time in rat island flaps. They discussed mainly the relationship of capsaicin pretreatment to vascular control by sensory nerves and concluded that the depletion of neuropeptides from sensory nerves does not have a negative effect on the tissue's ability to withstand prolonged complete ischaemia. In contrast, Chang et al. reported that systemic capsaicin pre-treatment combined with delayed surgical procedure increased flap survival.

Lippe et al. reported that capsaicin-sensitive afferent neurons play an inhibitory role in platelet aggregation. Furthermore, capsaicin itself has the effect of inhibiting platelet aggregation in rats. This effect of capsaicin can be observed if capsaicin is added after platelets have begun to aggregate at concentrations commonly used to activate sensory afferent neurons. We have previously described our experiments using rats, which showed that topical application of prostaglandin E1 and of heparin increased flap survival. We suspect that the mode of action of these drugs is not vasodilatation but platelet disaggregation. In the experiments described here, capsaicin was administered topically after flap elevation, so the effect on systemic sensory nerves caused by topical application of capsaicin on flaps can be disregarded. We conclude that the platelet disaggregation effects of capsaicin are its mode of action in the present experiments. Although further experiments are necessary, our present study suggests that one drug can result in completely different effects on flap survival, depending on the methods of administration, such as topical or systemic administration.

References


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