

A STUDY OF THE TREATMENT TIME NECESSARY FOR THE VASODILATOR DRUG ISOXSUPRINE TO PREVENT NECROSIS IN A SKIN FLAP

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Isoxsuprine has been shown to prevent necrosis and increase survival of skin flaps in the rat, muscle flaps in the rabbit and myocutaneous flaps in the pig (Finseth and Adelberg, 1978; Finseth and Adelberg, 1979; Finseth *et al.*, 1979; Finseth and Zimmermann, 1979). It is a long acting vasodilator drug from beta-adrenergic receptor stimulation and possibly has a direct relaxation effect on vascular smooth muscle. In all these experiments, isoxsuprine was given for two weeks prior to raising the flaps. This arbitrary selection of a two week period was based on the assumption that increased flap survival required sustained vasodilation over some definite time period and that this was the basic microcirculatory mechanism responsible for the "delay phenomenon" (Finseth and Adelberg, 1978, 1979). This experiment was designed to determine the time period necessary to obtain the maximum effect of isoxsuprine in preventing flap necrosis.

METHODS AND MATERIALS

The experimental model is the neurovascular island skin flap consisting of the entire abdominal wall of the rat based only on one groin (superficial epigastric) neurovascular bundle (Finseth and Cutting, 1978). The contralateral half of the flap across the midline from the neurovascular supply is essentially a random pattern flap attached to the axial pattern ipsilateral half. When this flap is raised in the untreated animal, a consistent pattern of flap necrosis and survival occurs.

Each experimental group consisted of seven Long-Evans rats weighing between 300 and 400 grams. Anaesthesia was provided by intraperitoneal nembutal (30 mg/kg solution) with 8 mg/kg increments as required. The abdominal wall skin was closely and widely clipped. The rats were mounted on a plexiglass board with the limbs stretched out with elastic bands.

Each flap measured 9 cm from xiphoid to pubis and 9 cm across the midabdomen. The upper margin followed the lower rib cage border and the lower margins followed the upper thigh skin crease. The circumferential wound was accurately closed with cotton sutures with attention to "cross-hatching" marks made before cutting the skin (Fig. 2A). At the end of the operation a collar made of X-ray film was placed around the rat's neck. Failure to place such a collar in previous experiments had led to a high incidence of autocannibalism of the flap. The rats were kept in separate cages.

After 7 days the surviving area of each flap was measured.

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EXPERIMENTAL DESIGN

Isoxsuprine 1 mg/kg was given daily intraperitoneally to four groups of seven rats each for 7, 9, 11 or 13 days respectively, prior to elevation of the abdominal wall flap, and continued for 7 days postoperatively. The two control groups consisted of rats whose flaps were raised without any preoperative treatment with isoxsuprine. One control group had postoperative isoxsuprine 1 mg/kg/day postoperatively for 7 days; the other did not receive any postoperative medication.

RESULTS

The results are indicated in Table I and Figure 1. Representative examples of flaps from each preoperative treatment time period are presented in Figure 2B.

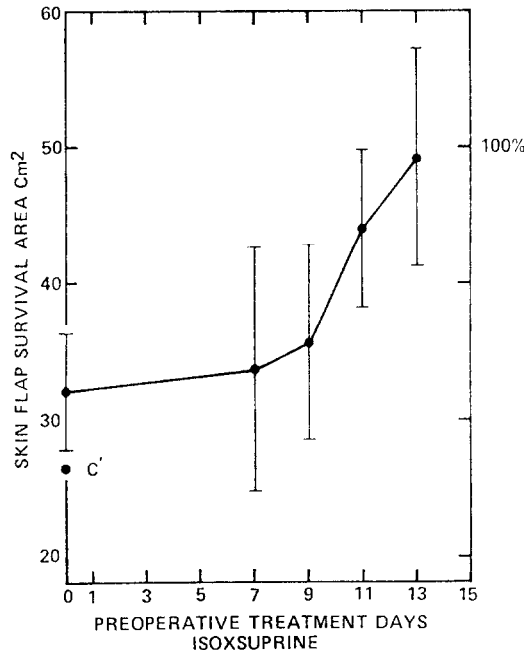


FIG. 1. The data. The line connects the mean values for varying preoperative treatment times with isoxsuprine, and with continued postoperative treatment. C¹ is the value obtained with neither preoperative or postoperative treatment.

To achieve its full effect it appears that isoxsuprine must be given for at least 13 days preoperatively. From the 7th to the 13th day the effect of increased flap survival appears to be cumulative. Postoperative treatment with isoxsuprine without any presurgical treatment does yield some increased flap survival as compared to those controls without postoperative medication.

We can only speculate at this time about the events and developments occurring in the microcirculation under the constant impact of sustained vasodilation (pharmacologically induced vascular smooth muscle relaxation) during the obligatory two-week period necessary to obtain the full physiologic effect of increased nutritional (capillary) blood flow following the acute ischaemic stimulus of raising a flap.

TABLE I

To show the surface area of abdominal flap surviving after preoperative treatment with isoxsuprine

Experimental Group preoperative treatment time (days)	n	Mean cm ²	Standard deviation
Control, no postoperative treatment	7	26.5	7.0
Control, with postoperative treatment	7	31.8	4.3
7 days postoperative treatment	7	33.7	9.0
9 days postoperative treatment	7	35.7	7.2
11 days postoperative treatment	7	44.0	5.8
13 days postoperative treatment	8	49.2	8.0

Why does it take one week for the pretreatment effect to be observed? Why is the pretreatment effect cumulative from one to two weeks? Perhaps there are anatomical changes and a reorganization of the microcirculation that are occurring to account for this ability of tissue to withstand an acute ischaemic stimulus or injury as happens when we raise a flap. Further study along these lines is necessary to enable us, as surgeons, to prevent the serious complication of flap necrosis.



FIG. 2A. Experimental model flap immediately after resuture in its bed.

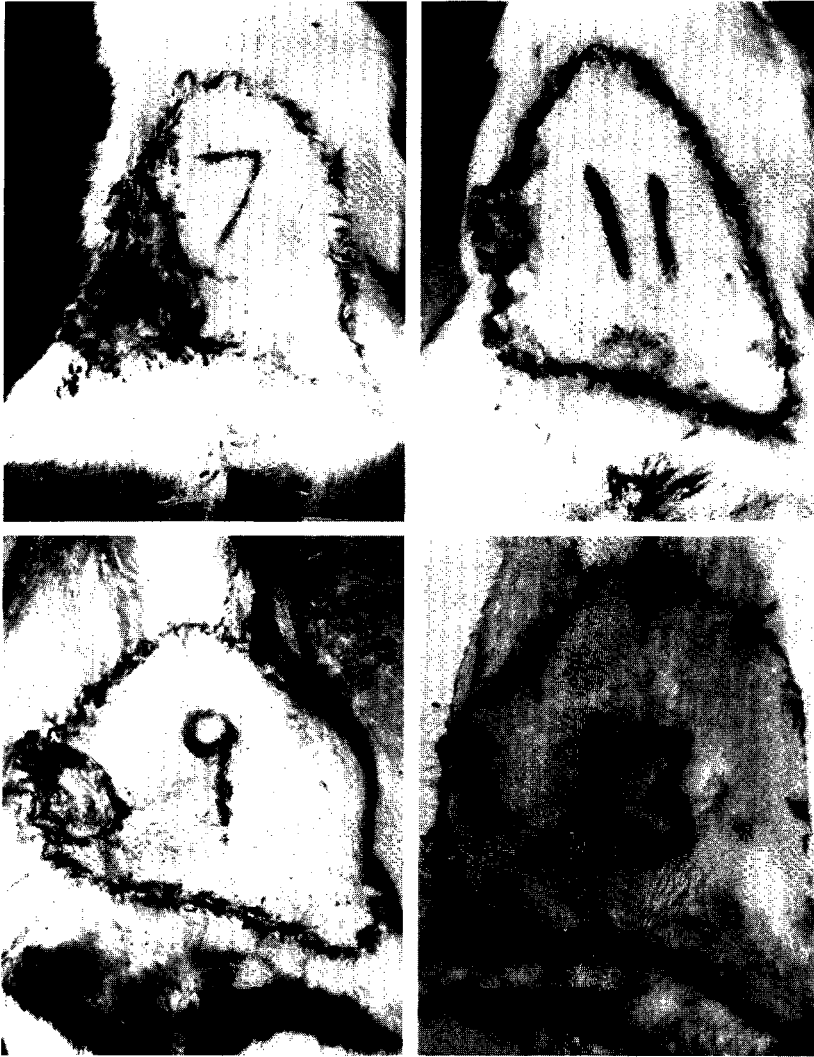


FIG. 2B. Representative flaps from the experimental groups. The numbers represent preoperative treatment days with isoxsuprine.

CONCLUSION

These results show that administration of isoxsuprine at least 13 days prior to flap elevation and continuance at least 7 days postoperatively does lead to complete survival of the abdominal neurovascular island skin flap in the rat.

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