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Prevention of Wound Edge Necrosis by Local Application of Dimethylsulfoxide

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Key words. Dimethylsulfoxide ; tissue transfer ; skin flap ; flap necrosis.

Abstract. *Background :* Surgical flap necrosis is one of the most common problems after procedures such as mastectomies and regional lymph node dissections. In this prospective randomized study, the effect of topical dimethylsulfoxide (DMSO) on skin flap viability was analyzed.
Material and methods : Sixty-six consecutive patients with breast cancer who had skin flaps created during mastectomy were randomized into two groups. Topical DMSO was applied on surgical flaps of the patients in Group-1, topical saline was applied for those in Group-2. Necrotic flap edges were recorded during the follow-up period for each patient, then excised and weighted in a blind manner.
Results : The mean weight of flap edge necrosis was 23.48 ± 9.5 (mean ± sem) µg in DMSO group and 126,27 ± 44.8 µg in control group (p = 0.03). The hospitalization period was 9.6 ± 0.5 days and 11.8 ± 0.8 days in DMSO group and control group respectively (p = 0.02). There were no side effects due to DMSO.
Conclusion : The application of DMSO reduced skin flap necrosis and improved outcome of surgical flaps.

Introduction

Surgical flap necrosis is one of the most common problems after mastectomies (1-3).

Causes of flap necrosis have been previously investigated but still remain undefined. Vasoconstriction as a result of mechanical manipulation, temperature change, catecholamine action cause a significant decrease in perfusion, especially in the edges of the skin flaps. Furthermore oxygen derived free radicals generated at reperfusion mediate a significant degree of the tissue damage (4, 5).

A variety of pharmacological agents and different manipulative procedures such as vasodilators, prostaglandins, antiadrenergic agents, anti-inflammatories, free radical scavengers and alterations of temperature have been tested to decrease or eliminate the areas of necrosis (4-8).

A small number of studies investigated Dimethylsulfoxide (DMSO) and its effect on skin flaps. In 1966 Adamson *et al.* reported a greatly enhanced flap survival in rat skin flaps subjected to various degrees of ischaemia (8-11). Further studies using rat models with both DMSO topical and intraperitoneal administration showed reduction of necrosis in skin flaps. Recently, Luby *et al.* reported that topical use of DMSO improves surgical flap viability and this study is the unique investigation on human (12).

In the presented prospective randomized study, the effect of topical DMSO on skin flap viability was analysed.

Material and methods

Sixty-six consecutive patients with breast cancer who had skin flaps created during mastectomy were randomized to the treatment group with DMSO or control group. A signed informed consent was obtained from each patient.

Patients who had conditions which could affect vascular system such as, vasculitis, systemic lupus erythematosus, diabetes mellitus, collagen vascular disease or steroid use, were not included in the study. Also, patients included in this study did not receive preoperative radiation, cytotoxic chemotherapy or immunotherapy for treatment of the primary neoplasm and did not receive antihistaminic agents which may antagonize the effects of DMSO.

For mastectomy, transverse elliptical incisions were used. Skin flaps were dissected in the plane of subcutaneous fascia between subcutaneous fat and breast tissue. The superior and inferior flaps were reapproximated without tension.

All procedures were performed by the same surgical team.

Topical DMSO solution composed of 60% DMSO, 10% urea and 30% distilled water was applied to the treatment group. The solution was sprayed to the entire flap area immediately after the wound was sutured and then every 2 hours for the first 48 hours and finally every 4 hours between postoperative days 3 to 7. Normal saline was applied in the same manner for the control group. Skin flaps were evaluated on each postoperative

Table I

Charasteristics of the patients

Features	Group-1	Group-2	p-value
Number of patients	33	33	
Mean age	51.8 ± 1.6	51.4 ± 1.8	0.8*
Number of smokers	5	5	1.0**
Mean number of cigarettes per day (in smokers)	20.6 ± 3.8	18.6 ± 2.0	0.6*
Mean period of surgery (hours)	3.1 ± 0.8	3.1 ± 0.9	0.4*
Mean level of haemoglobin	12.7 ± 0.1	13.5 ± 1.9	0.2*
Mean systolic BP (mm Hg)	135.8 ± 1.9	135.9 ± 1.9	0.9*
Mean diastolic BP (mm Hg)	80.2 ± 0.7	81.9 ± 0.8	0.1*
Mean days of lymphatic drainage	7.3 ± 0.4	6.9 ± 0.4	0.3*

Group-1 : Treatment group with DMSO
Group-2 : Control group with saline
Mean values were given with their standard error (= SEM)
* Student's t test
** Chi-squared test.

day by a senior surgical resident who was not in the operating team and was not directly involved in the clinical care. The observer was unbiased. When necrosis occurred, the non vital skin was left until the demarcation border was clearly occurred and then debridement was performed. Further, the weight of the necrotic area was obtained in micrograms. This procedure was performed in a blind manner by the same observer. Student's t test and chi-squared test were used for the statistical significance of differences in the data, using SPSS software package.

Results

Of the 66 patients, 33 were randomized to treatment group with DMSO (Group-1) and 33 were randomized to control group (Group-2).

There were no significant differences between the groups with respect to age, type and period of surgery, incidence of smoking, level of blood haemoglobin, mean systolic and diastolic blood pressure and lymphatic drainage (Table I).

While the mean weight of necrotic tissue in flap edges was 23.48 (± 9.5) μg in Group-1, it was 126.27 (± 44.8) μg in Group-2 (p = 0.03) (Fig. 1). The mean hospitalization period for Group-1 and Group-2 patients were 9.6(± 0.5) and 11.8 (± 0.8) days, respectively and this difference was also statistically significant (p = 0.02). The mean weights of necrosis for all patients in smokers (10 patients) and non smokers (56 patients) were 104.2 ± 0.9 μg and 69.6 ± 0.2 μg respectively, but this was not statistically significant (p = 0.6). The weights of necrotic tissue in flap edges of both treatment and control groups according to smoking are seen in Table II. No side effect related to DMSO except from the garlic-like taste and breath odour of patients in Group-1 was seen.

Discussion

DMSO is a relatively simple, naturally occurring compound whose metabolites both the sulfide and sulfone are normally found in human (13). Many studies with animals demonstrated that the chemical has several pharmacological actions such as membrane penetrant, anti-inflammatory, local analgesic, bacteriostatic, diuretic, cholinesterase inhibitory, vasodilatory and collagen solvent (13, 14). A small number of studies have looked at DMSO and its effect on skin flaps.

In 1966 Adamson, published a report on the effects of local DMSO treatment of pedicle flaps in rats. They observed a marked improvement of the circulation after local treatment with 70 % solution of DMSO. In addition they proposed that DMSO caused vasodilation via a histamine-like effect that could be blocked by antihistaminic agents (9). Haller *et al.* studied the effect of systemic DMSO on skin flap blood perfusion in a rat model and reported a significant increase in blood perfusion with intraperitoneal administration of DMSO (8). In another study Carpenter *et al.* reported that DMSO increased the survival of primarily ischaemic island skin flaps and prevented ischaemia reperfusion injury (15).

In a recent prospective study Luby *et al.* reported that the topical administration of 60% DMSO significantly reduced flap ischaemia in human (12). Similar to the results of Luby *et al.*, our study showed that the topical application of DMSO reduced skin flap necrosis and improved outcome of surgical flaps. The mean weight of necrotic tissue was 126.27 μg in the control group and were reduced to 23.48 μg in DMSO group. In our series,

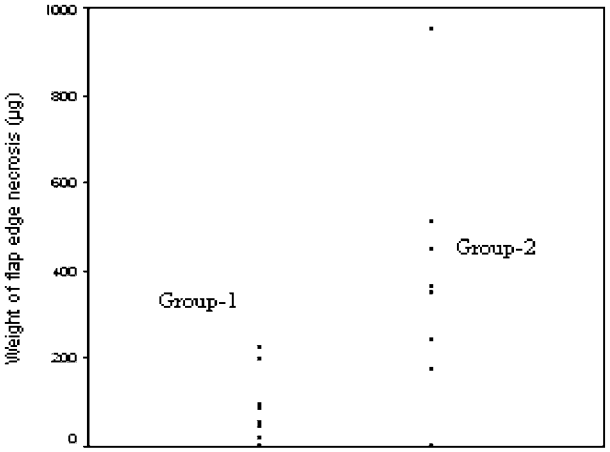

Fig. 1
Weight of necrotic flap edges in both groups measured in micrograms (p = 0.03).

a shorter duration of hospitalization was also noted among the Group-1 patients.

The mechanism of action of DMSO is not fully understood. It causes histamine release by mast cells and this effect is probably responsible for the vasodilation (14-16). It is a free radical scavenger and thus may reduce oxidative stress after ischaemia (15-17). DMSO has local anesthetic effects and thus would improve ischaemic injury by effects on cell excitation (17). It also significantly inhibits platelet aggregation and increases prostaglandin E1 which causes vasodilation (12, 16).

When used topically DMSO is a safe and well-tolerated drug. The most noticeable side effect is a garlic like taste and odour of the breath that occurs within a few minutes after administration (13). The other side effects include erythema, oedema and pruritis that may be caused by the release of histamine (13, 16). In the presented study, the patients have complained about the garlic-like taste and odour of the breath and no other complication was seen.

Smoking, wound closure under tension and ultrasuperficial dissection of skin flaps are important risk factors for wound healing and flap necrosis (1, 3, 6, 18-23). In this series in order to prevent necrosis care was taken to suture the wound edges without tension.

Smoking has well-documented adverse effects on wound healing, oxygen delivery and blood flow in tissue (18). Nicotine and carbon monoxide are the most potent toxins present in tobacco smoke that adversely affects tissue oxygenation and impair wound healing. Nicotine indirectly inhibits capillary blood flow by systemically releasing catecholamines. When released, catecholamines act directly on α_1 adrenergic receptors of smooth muscle cells to cause vasoconstriction. Carbon monoxide competitively inhibits the binding of oxygen, causing the oxyhaemoglobin dissociation curve to shift to the left and decreasing the oxygen availability to tissues (18-20). In a recent study Sørensen *et al.* reported that both light and heavy smoking were predictive for skin flap necrosis (21). In this series, although an increase flap edge necrosis was seen in smokers for both groups, this was not statistically significant.

Ultrasuperficial dissection of skin flaps is another cause of flap necrosis. The surgeon must be aware of the necessity for flap elevation with consistent thickness to avoid creating devascularized subcutaneous tissue (1, 3). In our series skin flaps were dissected in the plane of subcutaneous fascia between subcutaneous fat and breast tissue. All procedures were performed by the same surgical team in order to standardize the flap thickness.

In conclusion, the present study showed that the topical application of DMSO reduced skin flap necrosis and improved outcome of surgical flaps. With its safety and good tolerance, it may easily be applied after mastectomy to reduce skin flap necrosis.

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Table II

Weights of flap edge necrosis for treatment and control groups according to smoking

	Mean (± sem) weight of necrosis (µg)				
	n	All patients	Group-1	Group-2	p-value*
Smokers	10	104.2 ± 0.9	24.4 ± 0.2	190.0 ± 1.9	0.04
Non smokers	56	69.6 ± 0.2	18.4 ± 0.1	114.9 ± 0.4	0.04
p-value*		0.6	0.8	0.6	

Group-1 : Treatment group with DMSO
Group-2 : Control group with saline
* Student's t test for independent samples.

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