

Is transdermal nitroglycerin application effective in preventing and healing flap ischaemia after modified radical mastectomy?

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Summary

Objective. We evaluated the efficacy of local nitroglycerin application in preventing and treating flap complications after modified radical mastectomy in a large patient cohort.

Patients and methods. Between 1993 and 2008, 6 426 patients undergoing surgery for stage II breast cancer were enrolled in this prospective study. Patients were randomised into treatment and control groups. In the treatment group a nitroglycerin preparation (Nitroderm) was applied to the flap area. Major complications, recovery periods, menopausal status, additional diseases (diabetes mellitus, hypertension, atherosclerotic heart disease) and adverse effects related to nitroglycerin use were recorded.

Results. The recovery rate without major complications was statistically significantly higher in the nitroglycerin-treated group than in the controls ($p < 0.001$).

Conclusion. Our results indicate that topical nitroglycerin reduces flap complications after breast surgery.

Surgical treatment of trauma, congenital malformations, burns and tumours often leaves wide and deep scars that can only be closed by skin flaps.¹ Flap complications are particularly common after breast surgery. Ensuring optimal survival of skin flaps after breast surgery avoids the prolonged hospitalisation, re-operation or infection that can result from even minor complications.²⁻⁴

Factors such as temperature, tissue perfusion pressure and neural stimulus can affect flap perfusion and complication rates.^{5,6} Many studies have therefore focused on continuous or intermittent vasodilator therapies to increase blood flow to ischaemic tissue.^{2,7,8} Topical nitroglycerin application has been widely used with this aim.⁹ Nitroglycerin dilates the veins and arteries, has a limited adverse effect profile and is easy to use.⁷

We evaluated the efficacy of local nitroglycerin application in preventing and treating flap complications after modified radical mastectomy in a large patient cohort.

Patients and methods

Between 1993 and 2008, 6 426 patients undergoing surgery for stage II breast cancer were enrolled in this prospective study. Modified radical mastectomy (MRM) was performed by the same team on all patients. Patients were randomised into treatment and control groups by a drawing method using a number table. Acute

circulation failure accompanied by clear hypotension, myocardial insufficiency related to obstruction, use of sildenafil, a recent history of myocardial infarction or acute cardiac insufficiency were criteria for exclusion from the study. All the patients who participated signed a detailed informed consent form.

In the treatment group, 8 hours after the operation, 50 mg of a nitroglycerin preparation (Nitroderm) was applied to the area 10 cm or less from the incision line for 8 hours, followed by a 16-hour break. Each new application was localised to a different region of the upper and lower flaps. Application was continued until the 5th postoperative day if the patient did not experience complications (Fig. 1). If a complication developed, application was continued until a decline was observed or a clear demarcation line had formed. Total flap necrosis with no signs of recovery was treated with debridement. Complications were classified into three groups: (i) ischaemia on the incision line (defined as ischaemia localised to the area immediately surrounding the incision); (ii) total flap ischaemia (defined as lack of perfusion covering more than two-thirds of the flap area); and (iii) total flap necrosis (defined as necrosis on more than two-thirds of the flap area). The transparent paper method was used to measure flap regions showing lack of perfusion.

Major complications, recovery periods, menopausal status, additional diseases (diabetes mellitus (DM), hypertension (HT), atherosclerotic heart disease (ASHD)) and adverse effects related to nitroglycerin use were recorded in the patients' files.

The results were evaluated with the Cox and Snell R-square, Nagelkerke R-square and chi-square tests for logistic regression analysis.

Results

Of the 6 426 patients, 3 174 (31.8% menopausal) were treated with local nitroglycerin application and 3 252 (68.2% menopausal) comprised the control group. Rates of DM and HT were statistically significantly lower in the nitroglycerin group than in the control group (DM 10.6% v. 12.7%; $p=0.008$, HT 13.5% v. 16.8%; $p<0.001$). The rate of ASHD did not differ significantly between groups (5.9% v. 4.9%; $p=0.075$).

The rate of recovery without a major complication was statistically significantly higher in patients treated with local nitroglycerin than in the control group ($p<0.001$) (Fig. 2).



Fig. 1. Superior flap necrosis and nitroglycerin application in a patient with diabetes mellitus.

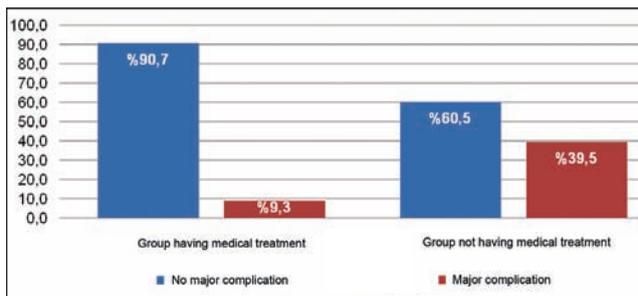


Fig. 2. Major complication rates in the study and control groups.

Major complications developed in 24.6% of total patients ($N=1 580$), in 9.3% of patients who received nitroglycerin treatment ($N=294$), and in 39.5% of the control group ($N=1 286$). Ischaemia on the incision line was observed in 18.8% of all patients, the rate being significantly lower in the nitroglycerin treatment group than in the control group (8.9% v. 28.3%; $p<0.001$). The rate of total flap ischaemia, observed in 5.4% of all patients, was also statistically significantly lower in the nitroglycerin treatment group than in the control group (0.3% v. 10.3%; $p<0.001$). Total flap necrosis was observed in 30 patients (0.5%), of whom only 1 was in the nitroglycerin treatment group and 29 were in the control group (0.3% v. 0.9%; $p<0.001$).

Of the patients who developed major complications, 43.3% recovered in 7 - 10 days, 32.2% in 11 - 18 days, and 22.5% in 19 - 21 days. In 2.0% of patients no recovery was observed and debridement was required. Recovery rates differed significantly between patients who did and did not receive nitroglycerin application ($p<0.001$), with 75.9% of the patients in the nitroglycerin treatment group who developed a complication recovering in 7 - 10 days and only 1 patient requiring debridement, while in the control group 35.5% recovered in 7 - 10 days, 35.4% in 10 - 18 days, 26.7% in 18 - 21 days, and 29 required debridement.

The rate of major complications was statistically significantly higher among postmenopausal patients than premenopausal patients (81.5% v. 18.5%; $p<0.001$). Rates of ischaemia on the incision line (premenopausal 13.8%, postmenopausal 20.8%) and total flap ischaemia (premenopausal 1.0%, postmenopausal 7.2%) were both significantly higher among postmenopausal women ($p<0.001$). The rate of total flap necrosis did not differ significantly between the two groups ($p=0.399$).

The rate of major complications among patients with DM was significantly higher than that among patients without (41.0% v. 22.4%; $p<0.001$), as were rates of total flap ischaemia and total flap necrosis ($p<0.001$) but not incision line ischaemia. The rate of major complications among patients with HT was also significantly higher than among patients without (31.4% v. 23.4%; $p<0.001$), and again there were significantly higher rates of ischaemia on the incision line and total flap ischaemia ($p<0.001$) but no significant difference in the rate of total flap necrosis ($p=0.195$). ASHD was associated with a statistically higher risk of major complications (38.2% v. 23.8% of patients; $p<0.001$), total flap ischaemia ($p<0.001$) and total flap necrosis ($p<0.001$), but not with a higher rate of incision line ischaemia ($p=0.313$).

After controlling for the statistically significant negative effects of postmenopausal status and other diseases, patients treated with nitroglycerin were 6 - 7-fold less likely than the control group to develop a major complication.

The only observed adverse effect of nitroglycerin was headache, observed in 346 of the patients treated with nitroglycerin (10.8%) and 381 of the patients in the control group (11.7%).

Discussion

In recent years many agents, including sympatholytics, vasodilators, calcium channel blockers, prostaglandin inhibitors, anticoagulants and glucocorticoids, have been evaluated for their potential to prevent or reverse flap necrosis. Only some have been found effective, and others are difficult to implement in wide-scale clinical practice. An ideal agent is not yet available.⁹⁻¹¹

The mechanisms underlying flap ischaemia and necrosis are not yet fully understood. Adrenergic vasoconstriction resulting from the surgery is thought to be a major factor causing lack of circulation to the flap.¹⁰ Some researchers have postulated that flap ischaemia depends only on venous insufficiency, others that it is secondary to pure arterial insufficiency, and others that both venous and arterial vasoconstriction are involved.¹¹ It has also been proposed that microvascular platelet aggregation plays a role through increased levels of the vasoconstrictor thromboxane A₂, which is thought to increase rapidly after surgical intervention.¹⁰ Vasodilators have been a natural target of studies of prevention and treatment of flap ischaemia.

In addition to being highly efficient in preventing ischaemia and necrosis, the ideal agent should be easily applicable, reliable, cost effective, and used only after operation. Nitroglycerin meets most of these criteria, and apart from being a potent vasodilator has effects leading to prevention of platelet aggregation that have been examined in mouse, pig and primate models. Although its mechanism of action is not fully understood, it is considered a valuable agent for preventing and treating flap complications.^{2,12,13} In our patients we found that it resulted in a significant decrease in the frequency of complications and a shorter period of recovery.

Several studies have suggested that nitroglycerin ointment is not beneficial. Dunn *et al.* reported that topical nitroglycerin ointment did not increase the survival of skin flaps, but their experimental design involved only a single application of nitroglycerin, which may not be sufficient.¹⁴ The number of treated patients and the complication rate may also have limited the scope of the study.

The most frequent adverse effect of nitroglycerin is headache, thought to be related to vasodilatation of cerebral vessels. In our study this was the only adverse effect observed, and it could be controlled without dose reduction by non-steroidal anti-inflammatory drugs. Other adverse effects such as anxiety, facial

rash, postural hypotension, weakness and tachycardia have been reported^{11,12,15} but were not observed in our cohort, possibly because patients with cardiac risk factors were excluded to prevent their occurrence.

Conclusion

Our findings indicate that topical nitroglycerin prevents tissue ischaemia and necrosis effectively and assists in the prevention of and recovery from complications after MRM. It is also well tolerated, cost effective, safe and easy to use.

REFERENCES

- Zhang J, Lipa J, Black C, *et al.* Pharmacological characterization of vasomotor activity of human musculocutaneous perforation artery and vein. *J Appl Physiol* 2000; 89: 2268-2275.
- Nichter L, Sobieski M, Edgerton M. Efficacy of topical nitroglycerine for random-pattern skin-flap salvage. *Plast Reconstr Surg* 1985; 75(6): 847-852.
- Gribbe Ö, Samuelson UE, Wiklund NP. Effect of nitric oxide synthase inhibition on blood flow and survival in experimental skin flap. *J Plast Reconstr Aesthet Surg* 2007; 60: 287-293.
- Kane AJ, Barker JE, Mitchell GM. Inducible nitric oxide synthase (NOS) activity promotes ischemic skin flap survival. *Br J Pharmacol* 2001; 132: 1631-1638.
- Waters LM, Pearl RM, Macualay RM. A comparative analysis of the ability of five classes of pharmacological agents to augment skin flap survival in various models and species: an attempt to standardize skin flap research. *Ann Plast Surg* 1989; 23(2): 117-122.
- Özyazgan I, Özköse M, Baçkol G. Nitric oxide in flow-through venous flaps and effects of L-arginine and nitro L-arginine methyl ester (L-NAME) on nitric oxide and flap survival in rabbits. *Ann Plast Surg* 2007; 59: 550-557.
- Gatti JE, Brousseau DA, Silverman DG, LaRossa D. Intravenous nitroglycerine as a means of improving ischemic tissue hemodynamics and survival. *Ann Plast Surg* 1986; 16(6): 521-526.
- Rogers RA, Riviere JE. Pharmacologic modulation of the cutaneous vasculature in the isolated perfused porcine skin flap. *J Pharm Sci* 1994; 83(12): 1682-1689.
- Price MA, Pearl RM. Multiagent pharmacotherapy to enhance skin flap survival: lack of additive effect of nitroglycerine and allopurinol. *Ann Plast Surg* 1994; 33: 52-56.
- Davis RE, Wachholz JH, Jassir D, Perlyn CA, Agrama MH. Comparison of topical anti-ischemic agents in the salvage of failing random pattern skin flaps in rats. *Arch Facial Plast Surg* 1999; 1: 27-32.
- Rorich RJ, Chery GW, Spira M. Enhancement of skin flap survival using nitroglycerin ointment. *Plast Reconstr Surg* 1984; 73(6): 943-948.
- Scheuer S, Hanna MK. Effect of nitroglycerin ointment on penile skin flap survival in hypospadias repair. *Urology* 1986; 27(5): 87-95.
- Fan Z, He J. Preventing necrosis of the skin flaps with nitroglycerin after radical resection for breast cancer. *J Surg Oncol* 1993; 53: 210.
- Dunn LC, Brodland DG, Griego RD, *et al.* A single postoperative application of nitroglycerin ointment does not increase survival of cutaneous flaps and grafts. *Dermatol Surg* 2000; 26: 425-427.
- Scholefield JH, Bock JU, Marla B, *et al.* A dose finding study with 0.1%, 0.2% and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures. *Gut* 2003; 52: 264-269.