Effects of Nitroglycerin Ointment on Mastectomy Flap Necrosis in Immediate Breast Reconstruction: A Randomized Controlled Trial

by

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Abstract

Background: Mastectomy flap necrosis is a common complication of immediate breast reconstruction that impacts recovery time and reconstructive success. Nitroglycerin ointment is a topical vasodilator that has shown to improve skin flap survival in animal models. The objective of this study was to evaluate if the application of nitroglycerin ointment to the breast skin after mastectomy and immediate reconstruction causes a decrease in the rate of mastectomy flap necrosis compared to placebo.

Methods: This study was conducted as a randomized controlled trial and included patients aged 21 to 69 years undergoing mastectomy and immediate breast reconstruction at the University of British Columbia affiliated hospitals (Vancouver, Canada). Patients with a medical history that precluded the administration of nitroglycerin were excluded from the study. The target sample size was 400 patients. Nitroglycerin ointment (45mg) or a placebo was applied to the mastectomy skin at the time of surgical dressing.

Results: The trial was stopped at the first interim analysis after 165 patients had been randomized (85 treatment vs. 80 placebo). Mastectomy flap necrosis developed in 27 patients (33.8%) receiving placebo and in 13 patients (15.3%) receiving nitroglycerin ointment; between-group difference = 18.5% (p=0.006, 95% CI: 5.3% to 31.0%). Postoperative complications were similar in both groups (nitroglycerin: 22.4% (19/85) vs. placebo: 28.8%, (23/80)).
**Conclusion:** In patients undergoing mastectomy and immediate reconstruction, there was a marked reduction in mastectomy flap necrosis in patients who received nitroglycerin ointment. Nitroglycerin ointment application is a simple, safe and effective way to help prevent mastectomy flap necrosis.
Preface

All of the work presented henceforth was conducted at University of British Columbia affiliated hospitals and faculty medical offices. The trial was approved by both Health Canada [file #: 9427-U0146-98C] and by the University of British Columbia’s Clinical Research Ethics Board [certificate # H12-01161]. The Clinical Trial Registration number is NCT01608880 and the URL for the trial registry is http://clinicaltrials.gov/.

Author contributions

Dr Perry Gdalevitch: Lead investigator, responsible for the original concept and study design, ethics approval, Health Canada approval, preparation of data case report forms and consent forms, overseeing patient recruitment, recruiting patients, data collection/entry, interim report preparation, overseeing statistical analysis and writing/editing of manuscript including figures and tables.

Dr Nancy Van Laeken: Recruited patients and completed case report forms.

Seokjae Bahng: Participated in data entry from data sheets and patient charts.

Dr Esta Bovill: Recruited patients and completed case report forms.

Dr Adelyn Ho: Participated in study design, ethics protocol preparation and patient recruitment.

Dr Peter Lennox: Recruited patients and completed case report forms.

Dr Penelope Brasher: Involved in initial study design and performed sample size calculation, interim analysis and final statistical analyses, contributed to the writing of the manuscript and editing the final manuscript.
Dr Sheina Macadam: Contributed to study design, ethics approval, Health Canada approval, patient recruitment, data review, statistical analysis, interim report and editing of manuscript. Member of thesis committee.

**Publication**

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A very heartfelt thanks to the Educational Foundation of the Canadian Society of Plastic Surgeons for their financial support (10,000$) of this project.

Finally, I am deeply indebted to my family for their continued support, love and encouragement. To my parents, for making me believe that I can do whatever I set my mind to. To my sister, for inspiring me daily with your brilliance and courage. To my husband, for your incredible patience, boundless encouragement, unwavering faith and unconditional love. Last but not least, to my beautiful children of whom I am constantly in awe.
Dedication

To Daniel
1 Introduction

1.1 Background

The blood supply to the breast skin comes from the underlying breast gland and from the dermal and sub-dermal plexuses of the skin. During mastectomy, the blood supply to the skin is compromised which may lead to areas of superficial or full thickness mastectomy flap necrosis (Figure 1). These areas become obvious in the first post-operative week and can lead to prolonged recovery, delay in adjuvant treatments and an unsatisfactory reconstructive outcome.

Mastectomy flap necrosis is a frequent complication occurring in 18-30% of patients undergoing mastectomy and immediate reconstruction. The incidence of this complication has increased as the rate of nipple-sparing mastectomies and direct-to-implant reconstructions have increased. Other risk factors for developing this complication are well described and include: increasing age (>65 years old), obesity (BMI >30), large breast size (mastectomy weight >800 grams), wise-pattern incision, previous radiation and active smoking.

Prevention of mastectomy flap necrosis is dependent on the surgeon’s intra-operative clinical judgment as he/she evaluates mastectomy skin that needs to be excised. Recently, laser assisted indocyanine green dye angiography (SPY Elite) is an intraoperative tool which may help determine areas of decreased perfusion thereby allowing the surgeon to excise these more accurately. Although SPY elite has been shown to be highly sensitive and specific, it is an expensive tool not readily available outside of large centers.
recent cost analysis showed that the use of SPY for prevention of mastectomy flap necrosis is only cost effective if used in high-risk patients (BMI>30, smokers, mastectomy weight >800grams). An ideal preventative measure for mastectomy flap necrosis would be simple, cheap and easy to administer.

Nitroglycerin ointment is a potent topical vasodilator that increases local blood flow to the skin by dilating both arteries and veins. It has been shown to enhance skin flap survival in an animal model following frequent application of 2% nitroglycerin ointment. First described for the management of angina pectoris, nitroglycerin ointment is currently being used to aid in the healing of anal fissures, pressure sores and peripheral tissue ischemia in neonates. In 1993, Fan et al. prospectively evaluated the effect of a single dose of post-operative nitroglycerin ointment (1ml, 5mg) on the skin flaps of patients undergoing radical mastectomy (without reconstruction) and found that nitroglycerin application significantly reduced the mastectomy flap necrosis rate from 60% (24/40 control) to 19% (8/42 nitroglycerin treated) without any side effects. In 2010, in a large randomized trial (>6000 patients), Kutun et al. evaluated the effectiveness of a nitroglycerin transdermal patch (Nitroderm, 50mg, 8hours/day for 5 days) on the skin flaps of patients undergoing modified radical mastectomy without reconstruction and found a significant reduction (39.5% versus 9.3%) in mastectomy flap necrosis with minimal side effects (headache in 10% of patients, similar to control group). Despite this evidence, nitroglycerin ointment is not currently being used to prevent mastectomy flap necrosis and there are no studies evaluating the effect of nitroglycerin ointment on mastectomy flap necrosis rates in patients undergoing...
mastectomy with immediate reconstruction.

1.2 Study Objective

The primary objective of this study was to evaluate if a single post-operative application of nitroglycerin ointment (Nitro-Bid 2%, 45mg) decreases the rate of mastectomy flap necrosis in patients undergoing mastectomy with immediate breast reconstruction compared to patients receiving placebo. Secondary objectives included evaluating the effect of nitroglycerin ointment on the treatment received for mastectomy flap necrosis (dressings and/or debridement and closure) as well as on early complications such as seroma, hematoma, infection, explantation and capsular contracture.
2 Methods

2.1 Patient Trial Eligibility

The study was undertaken with the approval of the University of British Columbia Clinical Research Ethics Board (September 20th, 2012). Permission for the off label use of Nitro-Bid (nitroglycerin ointment 2%) was approved by Health Canada’s Therapeutic Products Directorate (August 29th, 2012). Starting in December 2012, all patients between the age of 21 and 69 that underwent skin-sparing or nipple-sparing mastectomy followed by immediate breast reconstruction at three university-affiliated centers were reviewed for study eligibility. Patients were recruited by participating surgeons (or their designate) and informed consent was obtained in the office or in the pre-operative care unit on the morning of surgery. Patients with a medical history that precluded the administration of nitroglycerin were excluded from the study (history of cardiac insufficiency, hypotension, sensitivity to nitrites, severe liver impairment, glaucoma, hyperthyroidism, recent head trauma, severe anemia; or taking the following medications: alteplase, aspirin, beta-blocker, calcium channel blocker, diuretics or thiazides).25

2.2 Sample Size Calculation

We reviewed the mastectomy flap necrosis rate at our institution for the years 2008 to 2011, which varied from 10.5% to 38.3%. Assuming a 20% rate for the placebo group, and considering a clinically significant rate reduction of 50%, a sample size of 200 patients per arm for a total of 400 patients was calculated (α=0.05, 2-sided; β=0.20). A single interim efficacy analysis was planned after 50% of patients had been accrued. A Peto-Haybittle stopping boundary (P < 0.001) was to be employed.
2.3 Data Collection

Pre-operative, operative and post-operative case report forms (CRF) were created for the purpose of prospective data collection and were completed by the surgeon. The following information was collected on the pre-operative CRF (Appendix A): date of birth, body mass index, smoking status, pathology, history of biopsy or lumpectomy, radiation exposure, chemotherapy exposure, hormonal treatment, medical comorbidities; breast measurements including bra size, breast ptosis and previous scars.

The following information was collected on the operative CRF (Appendix B): dates and details of the surgical interventions including general surgeon, plastic surgeon, use of local anesthetic, type of mastectomy, laterality, size of mastectomy specimen, lymph node sampling, type/size of alloplastic device, acellular dermal matrix size and thickness, autologous flap details, mastectomy incision as well as a mastectomy flap thickness score.

The following information was collected on the post-operative CRF at every post operative visit (Appendix C): timing of drain removal; early complications such as infection, seroma, hematoma; the presence and details of mastectomy flap necrosis (superficial or full thickness; location and size; treatment); need for post-operative chemotherapy, radiation or hormonal treatment. Mastectomy flap necrosis was defined as any delay in wound healing and further classified as marginal (1-2mm along the incision) or flap necrosis (incisional further than 2mm and all other breast skin areas). Surgeons
were asked to classify the necrosis as superficial (epidermolysis) or full thickness (into the dermis). Breast diagrams were provided for surgeons to note the area and size of necrosis.

### 2.4 Randomization and Ointment Application

A senior statistician at the Clinical Centre of Epidemiology and Evaluation at the University of British Columbia created the randomization sequence using the Stata 11.0 software package, (StataCorp LP, College Station, Texas). The randomization was stratified by staff surgeon and permuted blocks of varying size were employed. The randomization list was provided to a research coordinator who was not involved in patient recruitment or treatment. No other person had access to the randomization list. Nitroglycerin ointment (Nitro-Bid 2%) was used in its original 60 grams packaging to avoid issues related to contamination, impurities and stability as required by Health Canada. The placebo was prepared by a university affiliated pharmacist and consisted of an inert compound made from white petrolatum, anhydrous lanolin and emollient cream and was identical in color and consistency to nitroglycerin ointment. Both ointment tubes were then circumferentially covered with duct tape to blind the surgeon, patient and research team. An ointment tube provided approximately 20 doses per 60 grams tubing. At the time of surgery, the research coordinator consulted the randomization list for the next treatment allocation and delivered the study drug to the operating room.

Mastectomy was performed by a member of the University of British Columbia General Surgery service, followed by immediate reconstruction by one of the five plastic surgeons...
involved in breast reconstruction program. A thin layer of ointment was applied at the
time of surgical dressing by the attending plastic surgeon concentrically from the center
of the breast to the periphery at a dose of 45mg of nitroglycerin ointment (equivalent to
7.5cm on the measuring strip [Figure 2]). The ointment and dressing was left in place for
a minimum of 48 hours. In patients undergoing bilateral breast reconstruction (often with
one side undergoing prophylactic mastectomy), only the mastectomy performed by the
general surgeon (therapeutic mastectomy) received the study drug to avoid the potential
of an increased effect of the nitroglycerin ointment from the contralateral breast. All
patients were admitted to hospital post operatively for a minimum of 24 hours.

2.5 Interim Analysis

On February 24\textsuperscript{th} 2014, after 165 patients had been randomized, the interim analysis was
conducted. All randomized patients were included in the analysis in the group to which
they were allocated (intention-to-treat). The interim report was sent to two independent
plastic surgeons outside our institution for independent review. Based the findings of the
interim report, the study was stopped early for proof of efficacy.

2.6 Statistical Analysis

To describe the patient population, descriptive statistics were generated for baseline
variables by treatment group. Continuous variables were summarized with mean (SD) or
median (10\textsuperscript{th}, 90\textsuperscript{th} percentiles) if the data were skewed. Categorical variables were
summarized with frequency (percent). Pearson’s chi-square test was used for between-
group comparisons of proportions. Point and interval estimates were calculated for
between-group differences. We also performed a secondary analysis adjusting for known risk factors for mastectomy flap necrosis. These factors were determined \textit{a priori} based on literature review and surgeon experience and included: Age $>$65, body mass index $>$ 30, active smoking, history of pre-operative radiation, mastectomy weight $>$ 800 grams, wise-pattern incision, nipple sparing mastectomy and direct-to-implant reconstruction.\textsuperscript{5-13}

We also did an exploratory analysis of whether the effect of nitroglycerin varied according to the number of risk factors. A score of one was given for each of the aforementioned risk factors. A total risk score was calculated as the sum of the eight scores. All analyses were performed using Stata 11.0 (StataCorp LP, College Station, TX) and all tests are two-sided.
3 Results

One hundred and sixty-five patients participated in the study, with 85 randomized to the nitroglycerin ointment arm and 80 to the placebo arm. Of the 85 patients in the treatment arm, one patient did not receive the allocated ointment and two patients had the ointment wiped off in the recovery room without un-blinding due to hypotension. There were no patients lost to follow-up and all randomized patients were included in their allocated group (Figure 3- CONSORT diagram).

Patient demographics and baseline characteristics were similar between the treatment and placebo group (Table 1) as were breast baseline characteristics (Table 2) and operative characteristics (Table 3).

All patients had a minimum of 27 days follow up, a period sufficient for the development of mastectomy flap necrosis. Mastectomy flap necrosis occurred in 24.2% (40/165) of cases in this cohort. Mastectomy flap necrosis was less likely in the group receiving the nitroglycerin ointment (15.3% [13/85] vs. the placebo (33.8% [27/80], p=0.006, Table 4). The difference in mastectomy flap incidence between the treatment and placebo groups was 18.5% (95% CI of 5.3% to 31%). The effect was consistent across severity of necrosis. The difference in the rate of necrosis was reflected in decreased rates of debridement and closure of the wound (Table 4). Explantation of an alloplastic device due to mastectomy flap necrosis occurred in 2.4% (4/165) of cases, two patients in each group.
A secondary analysis adjusting for BMI>30, Age>65, active smoker, preoperative radiation, mastectomy weight > 800g, wise-pattern incision, direct-to-implant reconstruction and nipple sparing mastectomy yielded a similar estimated difference of 17.5% (95 % CI: 5.0% to 30.0%). An exploratory analysis looking at the effect of nitroglycerin ointment on different risk factor groups was also performed (Table 5). The total risk factor score ranged from 0 to 4. Due to small numbers we combined the 3 and 4 categories. As expected, the risk of MFN in the placebo group increased with increasing score. The observed risk of MFN was lower in the nitroglycerin group in all risk categories.

Early complications such as seroma, hematoma, infection and early capsular contracture occurred in 25.5% (42/165) of patients and were similar in both groups (Table 6). The most common early complication was seroma which occurred in 12.7% (21/165) of patients. Severe headache was reported in 2.4% (2/85) of patients receiving nitroglycerin ointment compared to 0% in the placebo group. Hypotension was reported in two patients who received the nitroglycerin ointment. In both cases, the hypotension did not resolve with removal of the study ointment and was likely due to other factors.

The results of the interim analysis did not meet the pre-specified stopping boundary (i.e. p ≤ 0.001). However, given the large reduction in the rate of mastectomy flap necrosis in the nitroglycerin group the investigators were no longer in the state of personal equipoise and felt it unethical to continue to randomize patients. A conditional power calculation was performed; the probability of detecting a significant benefit for nitroglycerin should
the trial continue to completion with an assumed mastectomy flap necrosis rate of 25% (the observed rate) in both arms was 82%. 
4 Discussion

To our knowledge, this is the first randomized trial evaluating the use of nitroglycerin ointment in the prevention of mastectomy flap necrosis in patients undergoing mastectomy and immediate reconstruction. Our study demonstrated that the application of a single 45mg dose of nitroglycerin ointment at the time of the surgical dressing reduced the incidence of mastectomy flap necrosis by more than half. The absolute risk reduction of 18.5% translates to a number needed to treat of 5.4. In patients treated with nitroglycerin ointment we also found an approximate 50% reduction in full thickness mastectomy flap necrosis, which translates to a similar reduction in cases requiring surgical debridement and closure. In addition, after stratifying patients into risk factor subgroups, the observed reduction in MFN prevailed in all risk categories in patients treated with nitroglycerin. Given the small number of patients and events in each subgroup we were unable to determine definitively if the treatment effect might increase (or decrease) with increasing risk factors. Overall, these findings suggest that nitroglycerin ointment increases perfusion to the traumatized skin flap thereby reducing the occurrence of flap necrosis in this patient population.

The mechanism of action of topical nitroglycerin occurs through smooth muscle relaxation in the vessel wall thereby promoting both a venous and arterial dilation.17 Endothelial dependent vessel relaxation impairment is important to the development of skin flap necrosis, a process that may be mitigated by nitroglycerin or other nitric oxide donors.26 Nitroglycerin may also induce endothelial cells to synthesize prostacyclin, a known vasodilator and inhibitor of platelet aggregation, which may contribute to flap
survival by decreasing thrombosis of smaller vessels.\textsuperscript{27}

Nitroglycerin ointment was first studied in an animal model by Rohrich et al. in 1984 and was found to significantly increase axial pattern skin flap survival in both rats (89.4\% vs. 68.9\% flap area survival) and pigs (74.1\% vs. 50.5\% flap area survival) when a 30mg dose was applied preoperatively and every six hours for three days.\textsuperscript{18} In 1985, Nichter et al. studied the effects of nitroglycerin transdermal pads on random pattern flaps in rats using a 5mg daily dose for two weeks. They did not show a difference in flap survival compared to control, but this may be due to the much smaller daily dose or the transdermal delivery used in their protocol.\textsuperscript{28} Nitroglycerin ointment was first used on skin flaps in humans a year later in a trial on the penile flaps of children undergoing hypospadias repair and was found to improve flap survival.\textsuperscript{29}

Nitroglycerin ointment has also been studied in comparison to other vasodilating agents such as enteral phenoxybenzamine, enteral nifedipine as well as intravenous allopurinol and was found to be superior in treating failing random pattern skin flaps in rats.\textsuperscript{30-31} The most substantial animal study looking at the effect of nitroglycerin on random pattern skin flaps included 61 rats randomized to 1 of 6 topical treatment groups, treated immediately post-operatively and every 6 hours for a week. Although topical nitroglycerin alone improved flap survival, the combination of topical nitroglycerin and topical trolamine salicylate showed the greatest capacity for flap salvage.\textsuperscript{32}

Although the majority of animal studies have shown increased flap survival with the use
of nitroglycerin ointment, three studies have shown a lack of benefit.\textsuperscript{29,33,34} In all of these studies the dose of nitroglycerin used was low (5mg), which may be the reason a significant effect was not detected.

The doses used in previous clinical studies on nitroglycerin and mastectomy flaps ranged from a single 5mg application to a 50mg transdermal daily protocol for 5 days.\textsuperscript{23-24} The dose used in this study (45mg, 3 inches) was determined using these previous studies as a guideline as well as by consulting an academic cardiologist. We selected a single 45mg dose to keep the protocol simple yet effective and allow for patient monitoring in the case of adverse events. This dose was applied to a single breast and caution should be exercised in treating both breasts. Either doubling the dose or splitting the dose over a larger surface area may have greater effects on a patient’s blood pressure.

In this study the overall incidence of mastectomy flap necrosis in the placebo group was higher than we had estimated (33.8%), but similar to rates in the literature.\textsuperscript{35,36} This rate is also consistent with the significant rise in mastectomy flap necrosis at our institution since the adoption of nipple-sparing mastectomy and direct-to-implant reconstruction. Despite the higher risk of mastectomy flap necrosis, these newer techniques allow for better aesthetic outcomes often in a single stage and are therefore preferred by patients and surgeons.

The complications seen in this cohort were consistent with previous studies.\textsuperscript{36,37} There was a small decrease in overall complication rates in the treatment versus placebo group.
(22.4% vs. 28.8%). Explantation of a prosthetic device due to mastectomy flap necrosis occurred rarely (2.4%) so that a significant reduction of this complication could only possibly be detected in a much larger cohort. Severe headache was reported in two patients in the treatment arm and is a possible side effect of the nitroglycerin ointment. Hypotension did occur in two patients who received the nitroglycerin ointment but was likely due to pain medication and under-resuscitation as the hypotension persisted after removal of the ointment. Headache and hypotension remain possible complications of nitroglycerin ointment and patient blood pressure should be monitored in the immediate post-operative setting.

The strengths of this study include the randomized controlled-trial design; blinded ointment allocation, near perfect adherence to treatment allocation and the 100% follow-up rate. In addition, our findings are generalizable to most breast cancer patients although caution is advised in older patients and patients on anti-hypertension medication who may be more sensitive to nitrates. These patients were excluded from the study but have since been treated routinely with nitroglycerin ointment without any adverse events.

A limitation of this study is that it was conducted at a single center although three different sites were involved. Mastectomy flap necrosis is a multifactorial complication that varies greatly depending on the institution. Centers with lower rates of mastectomy flap necrosis may not see as drastic an effect with nitroglycerin ointment. However, given the simplicity and low complication profile of the intervention it remains a simple addition to other preventative measures. Further studies are needed to determine the
appropriate dose for each breast in treating bilateral mastectomy skin. Clinical studies are also needed to help elucidate if repeat application or a combination topical ointment (nitroglycerin-trolamine-salicylate) could further reduce mastectomy flap necrosis rates.
5 Figures and Tables

5.1. Figures

5.1.1 Figure 1. Superficial (left) and full thickness (right) mastectomy flap necrosis.
5.1.2 Figure 2. Nitro-Bid measuring strip for dosing the study ointment (7.5cm).25
5.1.3 Figure 3. CONSORT flow diagram.\textsuperscript{38-39}

- Assessed for eligibility (n = 175)
  - Excluded (n = 10)
    - Exclusion criteria (n = 6)
    - Declined to participate (n = 4)
  - Randomized (n = 165)

  - Allocation
    - Allocated to placebo arm (n = 80)
      - Did not receive allocated intervention (n = 0)
    - Allocated to treatment arm (n = 85)
      - Did not receive allocated intervention (n = 1)
        - Surgeon did not apply ointment

  - Follow-Up
    - Discontinued intervention (n = 0)
      - Lost to follow-up (n = 0)
    - Discontinued intervention (n = 2)
      - Low BP (n=1)
      - Low BP & headache (n=1)
      - Lost to follow-up (n = 0)

  - Analysis
    - Analysed (n = 80)
      - Excluded from analysis (n = 0)
    - Analysed (n = 85)
      - Excluded from analysis (n = 0)
5.2 Tables

5.2.1. Table 1. Patient demographics in the placebo and nitroglycerin treated groups.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo (n = 80)</th>
<th>Nitro (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (sd)</td>
<td>49.9 (9.7)</td>
<td>50.0 (9.2)</td>
</tr>
<tr>
<td>Median (P10 to P90)</td>
<td>49.0 (37.5 to 62.5)</td>
<td>49.0 (39.0 to 63.0)</td>
</tr>
<tr>
<td>Body Mass Index, mean (sd)</td>
<td>24.0 (4.9)</td>
<td>24.9 (4.6)</td>
</tr>
<tr>
<td>Median (P10 to P90)</td>
<td>22.6 (20.1 to 30.7)</td>
<td>23.8 (19.9 to 31.6)</td>
</tr>
<tr>
<td>Laterality, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>45 (56.3)</td>
<td>44 (51.8)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>35 (43.7)</td>
<td>41 (48.2)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>64 (80.0)</td>
<td>67 (78.8)</td>
</tr>
<tr>
<td>Active</td>
<td>2 (2.5)</td>
<td>0 (0.0)</td>
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<tr>
<td>Former</td>
<td>14 (17.5)</td>
<td>18 (21.2)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2 (2.5)</td>
<td>0 (0.0)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>11 (13.8)</td>
<td>8 (9.4)</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td></td>
<td></td>
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<tr>
<td>BRCA1 gene carrier</td>
<td>2 (2.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>BRCA2 gene carrier</td>
<td>1 (1.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pre-operative chemotherapy, n (%)</td>
<td>25 (31.2)</td>
<td>23 (27.1)</td>
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<tr>
<td>Pre-operative hormonal therapy, n (%)</td>
<td>5 (6.3)</td>
<td>12 (14.1)</td>
</tr>
</tbody>
</table>
5.2.2 Table 2. Breast characteristics in the placebo and nitroglycerin treated groups.

<table>
<thead>
<tr>
<th>Breast Characteristics</th>
<th>Placebo (n = 80)</th>
<th>Nitro (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for mastectomy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td>10 (12.5)</td>
<td>4 (4.8)</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>70 (87.5)</td>
<td>80 (95.2)</td>
</tr>
<tr>
<td>Pathology, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign (prophylactic)</td>
<td>10 (12.5)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Ductal carcinoma-in-situ</td>
<td>13 (16.3)</td>
<td>21 (24.7)</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>54 (67.5)</td>
<td>54 (63.5)</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>3 (3.8)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Radiation, n (%)</td>
<td>7 (8.8)</td>
<td>9 (10.6)</td>
</tr>
<tr>
<td>Previous lumpectomy, n (%)</td>
<td>24 (30.0)</td>
<td>29 (34.1)</td>
</tr>
<tr>
<td>Breast Size (cup size), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12 (15.0)</td>
<td>10 (11.8)</td>
</tr>
<tr>
<td>B</td>
<td>30 (37.5)</td>
<td>32 (37.7)</td>
</tr>
<tr>
<td>C</td>
<td>19 (23.8)</td>
<td>18 (21.2)</td>
</tr>
<tr>
<td>D</td>
<td>10 (12.5)</td>
<td>13 (15.3)</td>
</tr>
<tr>
<td>Larger than D</td>
<td>9 (11.2)</td>
<td>12 (14.2)</td>
</tr>
<tr>
<td>Breast Width, mean (sd)</td>
<td>13.8 (1.8)</td>
<td>14.0 (1.8)</td>
</tr>
<tr>
<td>Median (P10 to P90)</td>
<td>13.5 (12.0 to 16.0)</td>
<td>14.0 (12.0 to 16.0)</td>
</tr>
<tr>
<td>Breast Ptosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26 (32.5)</td>
<td>28 (32.9)</td>
</tr>
<tr>
<td>2</td>
<td>39 (48.8)</td>
<td>32 (37.7)</td>
</tr>
<tr>
<td>3</td>
<td>12 (15.0)</td>
<td>17 (20.0)</td>
</tr>
<tr>
<td>4</td>
<td>3 (3.8)</td>
<td>8 (9.4)</td>
</tr>
<tr>
<td>Previous Scar, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>36 (45.0)</td>
<td>43 (50.6)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>17 (21.3)</td>
<td>15 (17.7)</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>24 (30.0)</td>
<td>27 (31.8)</td>
</tr>
<tr>
<td>Reduction or Mastopexy</td>
<td>3 (3.7)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
### 5.2.3 Table 3. Operative factors in the placebo and nitroglycerin treated groups.

<table>
<thead>
<tr>
<th>Operative factors</th>
<th>Placebo (n = 80)</th>
<th>Nitro (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Anesthetic, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>0.25% Marcaine with epinephrine</td>
<td>75 (83.8)</td>
<td>77 (90.6)</td>
</tr>
<tr>
<td>0.25% Marcaine without epinephrine</td>
<td>5 (6.2)</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td><strong>Reconstruction Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alloplastic</td>
<td>69 (86.2)</td>
<td>59 (69.4)</td>
</tr>
<tr>
<td>Direct-to-Implant</td>
<td>43 (53.8)</td>
<td>42 (49.4)</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; stage Tissue Expander (TE)</td>
<td>19 (23.8)</td>
<td>13 (15.3)</td>
</tr>
<tr>
<td>Acellular Dermal Matrix &amp; TE</td>
<td>7 (8.8)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td><strong>Autologous</strong></td>
<td>11 (13.8)</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td>Pedicled TRAM</td>
<td>8 (10.0)</td>
<td>14 (16.5)</td>
</tr>
<tr>
<td>Deep Inferior Epigastric Perforator</td>
<td>3 (3.8)</td>
<td>9 (10.6)</td>
</tr>
<tr>
<td>Latissimus Dorsi</td>
<td>0 (0.0)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td><strong>Incision Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Sparing Mastectomy</td>
<td>60 (75.0)</td>
<td>61 (71.8)</td>
</tr>
<tr>
<td>Horizontal ellipse</td>
<td>24 (30.0)</td>
<td>30 (35.3)</td>
</tr>
<tr>
<td>Vertical ellipse</td>
<td>5 (6.3)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Wise pattern</td>
<td>31 (38.8)</td>
<td>28 (33.9)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Nipple sparing mastectomy</td>
<td>20 (25.0)</td>
<td>24 (28.2)</td>
</tr>
<tr>
<td>Peri-areolar &amp; radial lateral extension</td>
<td>8 (10.0)</td>
<td>14 (16.5)</td>
</tr>
<tr>
<td>Lateral incision only</td>
<td>1 (1.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Vertical incision</td>
<td>2 (2.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Infra-mammary fold incision</td>
<td>9 (11.3)</td>
<td>6 (7.1)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td><strong>Sentinel Lymph Node Biopsy, n (%)</strong></td>
<td>44 (55.0)</td>
<td>47 (55.3)</td>
</tr>
<tr>
<td><strong>Axillary Lymph Node Dissection, n (%)</strong></td>
<td>15 (18.8)</td>
<td>13 (15.3)</td>
</tr>
<tr>
<td><strong>Flap thickness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant dermal exposure</td>
<td>3 (4.2)</td>
<td>3 (4.3)</td>
</tr>
<tr>
<td>Patches of dermis exposed</td>
<td>17 (23.9)</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>Thick flap without dermis exposed</td>
<td>30 (42.3)</td>
<td>31 (44.3)</td>
</tr>
<tr>
<td>Moderately thick</td>
<td>16 (22.5)</td>
<td>23 (32.9)</td>
</tr>
<tr>
<td>Very thick</td>
<td>5 (7.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Missing</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td><strong>Mastectomy weight, median (P10 to P90)</strong></td>
<td>479.5 (222 to 1100)</td>
<td>497.0 (160 to 1137)</td>
</tr>
<tr>
<td>Operative factors</td>
<td>Placebo (n = 80)</td>
<td>Nitro (n = 85)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Plastic Surgeon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>2 (2.5)</td>
<td>9 (10.6)</td>
</tr>
<tr>
<td>B</td>
<td>9 (11.3)</td>
<td>10 (11.8)</td>
</tr>
<tr>
<td>C</td>
<td>40 (50.0)</td>
<td>48 (56.5)</td>
</tr>
<tr>
<td>D</td>
<td>8 (10.0)</td>
<td>12 (17.1)</td>
</tr>
<tr>
<td>E</td>
<td>21 (26.3)</td>
<td>6 (7.1)</td>
</tr>
<tr>
<td>Breast Surgeon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>23 (28.8)</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td>Y</td>
<td>23 (28.8)</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td>Z</td>
<td>21 (26.2)</td>
<td>16 (18.8)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (16.2)</td>
<td>17 (20.0)</td>
</tr>
</tbody>
</table>

*TRAM* = transverse rectus abdominis muscle
5.2.4 Table 4. Mastectomy flap necrosis in the placebo and nitroglycerin treated groups.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 80)</th>
<th>Nitro (n = 85)</th>
<th>95% CI for difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy flap necrosis, n (%)</td>
<td>27 (33.8)</td>
<td>13 (15.3)</td>
<td>5.3 to 31.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Superficial thickness</td>
<td>9 (11.2)</td>
<td>5 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full thickness</td>
<td>18 (22.5)</td>
<td>8 (9.4)</td>
<td>1.9 to 24.3</td>
<td>0.021</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debridement and closure</td>
<td>16 (20.0)</td>
<td>8 (9.4)</td>
<td>0.0 to 21.6</td>
<td>0.054</td>
</tr>
<tr>
<td>Under local anesthetic</td>
<td>11 (13.7)</td>
<td>3 (3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under general anesthetic</td>
<td>5 (6.3)</td>
<td>5 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dressings</td>
<td>27 (33.8)</td>
<td>13 (15.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explantation (loss of TE/implant)</td>
<td>2 (2.5)</td>
<td>2 (2.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.2.5 Table 5. MFN risk factor score and MFN rates in the placebo and nitroglycerin groups.

<table>
<thead>
<tr>
<th>MFN Risk Factor Score</th>
<th>N</th>
<th>Placebo</th>
<th>Nitro</th>
<th>Risk Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28</td>
<td>2/14 (14.3)</td>
<td>1/14 (7.14)</td>
<td>0.50</td>
<td>0.05 to 4.9</td>
</tr>
<tr>
<td>1</td>
<td>37</td>
<td>5/18 (27.8)</td>
<td>1/19 (5.3)</td>
<td>0.19</td>
<td>0.02 to 1.47</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>12/33 (36.4)</td>
<td>8/39 (20.5)</td>
<td>0.56</td>
<td>0.26 to 1.21</td>
</tr>
<tr>
<td>3 or 4</td>
<td>20 + 8</td>
<td>8/15 (53.3)</td>
<td>3/13 (23.1)</td>
<td>0.43</td>
<td>0.14 to 1.30</td>
</tr>
</tbody>
</table>

Mantel-Haenszel test of homogeneity P = 0.80

*MFN= Mastectomy flap necrosis*
5.2.6 Table 6. Complication rates in the placebo and nitroglycerin treated groups.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Placebo (n = 80)</th>
<th>Nitro (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication, n (%)*</td>
<td>23 (28.8)</td>
<td>19 (22.4)</td>
</tr>
<tr>
<td>Seroma</td>
<td>12 (15.0)</td>
<td>9 (10.6)</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (6.3)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>3 (3.8)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Explantation</td>
<td>2 (2.5)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.5)</td>
<td>6 (7.0)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0.0)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0.0)</td>
<td>2 (2.4)</td>
</tr>
</tbody>
</table>

*p-value = 0.35, 95% CI for difference -6.9 to 19.5
6 Conclusion

The single application of nitroglycerin ointment (45mg, 3 inches) to the breast skin in patients undergoing mastectomy with immediate reconstruction decreased the incidence of mastectomy flap necrosis by half (33.8 to 15.3%) with a number needed to treat of 5.4. Nitroglycerin ointment application on mastectomy flaps is a simple, readily available and affordable ($3) measure to prevent mastectomy flap necrosis. In high-risk patients, it can be combined with other modalities to optimize patient outcomes. The authors propose that a simple and cost-effective approach to the prevention of mastectomy flap necrosis would include the application of nitroglycerin on all patients undergoing mastectomy with immediate reconstruction.
Bibliography


15. Munabi NC. Olorunnipa OB, Goltsman D, Rohde CH, Ascherman JA. The ability of intra-operative perfusion mapping with laser-assisted indocyanine green angiography to predict mastectomy flap necrosis in breast reconstruction: a


19. Fenton C, Wellington K, Easthope SE. 0.4% Nitroglycerin Ointment In the Treatment of Chronic Anal Fissure Pain. Drugs 2006; 66 (3): 343-349


25. Nitrol 2% product monograph from Paladin Laboratories Inc.
31. Davies BW, Lewis RD, Pennington G. The impact of vasodilators on random-pattern skin flap survival in the rat following mainstream smoking exposure. Ann


Appendices

Appendix A: Pre-operative Case Report Forms

Nitro RCT – Initial Surgical Consultation

Date: mm/dd/yy DOB: mm/dd/yy Age: ___ (years)

Height: ______ Weight: ______ Children: ☐ Yes ☐ No Breast-Fed: ☐ Yes ☐ No

Reason for Breast Reconstruction:
☐ Breast Cancer ☐ DCIS ☐ Prophylactic ☐ Other, describe: __________________________

Breast Cancer:
If yes, ☐ Yes ☐ No
☐ Right ☐ Left ☐ Both

First Detected:
☐ Palpable ☐ Imaging ☐ Nipple discharge ☐ Other, describe: _______________

Biopsy:
☐ Yes ☐ No If yes, pathology [______________]

Lumpectomy:
☐ Yes ☐ No If yes, TM stage [______________]

Lymph Node Dissection:
☐ Yes ☐ No If yes, LN status [______________]

Adjuvant treatments:

Radiation: ☐ Yes ☐ No
Chemo: ☐ Yes ☐ No
Hormonal: ☐ Yes ☐ No Type: __________________________

Breast History: Abnormal development: ☐ Yes ☐ No If yes, describe: _______________

Family History: ☐ Yes ☐ No
Gene Positive: ☐ Yes ☐ No

Last mammogram: mm/dd/yy

Past Medical History:

Smoker: ☐ Yes ☐ No Current Smoker: ☐ Yes ☐ No Hypertension: ☐ Yes ☐ No Diabetes: ☐ Yes ☐ No

Cardiac/Respiratory/Renal/GI problems:
☐ Yes ☐ No If yes, describe: __________________________

Medications:
☐ Yes ☐ No If yes, please list: __________________________

Allergies:
☐ Yes ☐ No If yes, please list: __________________________

Other Surgical History: ☐ Yes ☐ No If yes, please describe: __________________________
Nitro RCT – INITIAL SURGICAL CONSULTATION

Preoperative Examination:

<table>
<thead>
<tr>
<th></th>
<th>Right Breast</th>
<th>Left Breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cup Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A – Base Width</td>
<td>cm</td>
<td>cm</td>
</tr>
<tr>
<td>B – Nipple/Infra-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary Fold</td>
<td>cm</td>
<td>cm</td>
</tr>
<tr>
<td>C – Sternal Notch</td>
<td>cm</td>
<td>cm</td>
</tr>
<tr>
<td>D – Areolar Diameter</td>
<td>cm</td>
<td>cm</td>
</tr>
<tr>
<td>E –Ptosis (I, II, III, IV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scars – mark on diagram ➔

Breast/ Axilla Masses:  □ None  □ Size & Location ____________________________

Breast Asymmetry:
1 – Larger Breast Size  □ No asymmetry  □ Right  □ Left  Est. volume Diff ______g
2 – Nipple Level Discrepancy ______ cm
3 – IMF Level Discrepancy ______ cm

Envelope Characteristics:
Envelope compliance  □ Normal  □ Loose  □ Tight
Presence of striae    □ None  □ Some  □ Many

Other Comments:
Appendix B: Surgical Case Report Form

STUDY ID#: __________________

**Nitro RCT – Surgical Worksheet**

Date of Mastectomy Surgery: [mm/dd/yy]

Plastic Surgeon: ____________________________  Breast Surgeon: ____________________________

Study Site:  
- UBC  
- VGH  
- MSJ

Admission status:  
- Admitted  
- Not Admitted

Unilateral  
- or  
- Bilateral

Study Breast:  
- Right:  
- or  
- Left:  

**Mastectomy details:**

<table>
<thead>
<tr>
<th>Right</th>
<th>Mastectomy weight: [________ ] g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>Mastectomy weight: [________ ] g</td>
</tr>
</tbody>
</table>

**Mastectomy flap thickness:**  
- Significant dermal exposure
- Patches of dermis exposed
- Thin flap w/o dermis exposed
- Moderately thick
- Very thick

**Skin incision:**  
- SSM Horizontal ellipse
- SSM Vertical ellipse
- Nipple sparing peri-areolar with radial lateral extension
- Nipple sparing radial lateral incision only
- Nipple sparing vertical incision
- Nipple sparing IMF incision
- Other incision: ____________________________

**Sentinel lymph node biopsy:**  
- Yes  
- No  

**Axillary lymph node dissection:**  
- Yes  
- No

**Local Anesthetic used:**  
- Yes  
- No. Specify amount and concentration:

**Reconstruction details:**

- Alloplastic DTI  
- Alloplastic 1st stage T/E  
- Alloplastic Allograft and T/E

Alloderm size: ____________________________  Implant: ____________________________  T/E style and fill: ____________________________

- Autologous pedicled TRAM  
- Autologous DIEP  
- Autologous LD flap (implant/T/E: ____________________________)

No. of breast drains:  
- 1  
- 2

Tension on skin closure:  
- present/  
- absent

Contralateral breast procedure:  

Incision margin revision (1-2mm):  
- Yes  
- No

**Additional comments:**
## Appendix C: Post-operative Case Report Form

### STUDY ID#: __________

### Nitro RCT – Post-operative Worksheet

**Post-operative visit**

<table>
<thead>
<tr>
<th>Interval</th>
<th>1-2 weeks</th>
<th>2-4 weeks</th>
<th>4-6 weeks</th>
<th>6-8 weeks</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
</table>

**Study Breast:** Right □ Left □

**Drains Removed:** □ Yes / □ No

If yes, after _______ days

**Signs of Seroma:** □ Yes / □ No

If yes, drained _______ cc

**MFN:** □ Yes / □ No

Size: ________ cm

- Superficial □
- Full thickness □
- Indeterminate □

**Location:**
- UMQ □
- ULQ □
- IMQ □
- ILQ □
- NAC □

**Debridement/closure:** □ Yes / □ No

If Yes, ULA □ or GA □

Details: ________________________

**Need for dressing:** □ Yes / □ No

Ointment type: __________

**Marginal necrosis:** □ Yes / □ No

Size: ________ cm

**Need for debridement/closure:** □ Yes / □ No, ULA □ or GA □

**Signs of infection:** □ Yes / □ No

If Yes, □ IV / □ PO abx

**Abx Prescribed:** __________

**Complications:**
- Hematoma □
- Malposition □
- Capsular contracture □

**Other Complications:** __________________________

**Post operative need for:**

- XRT □ Yes / □ No
- Chemotherapy □ Yes / □ No
- Hormonal □ Yes / □ No

**Need for further surgery (describe):** __________________________

**Contralateral side:** Right □ Left □

**Non operated □**

- Balancing procedure □
- Mastectomy-recon □, describe: __________________________

**Complications:**
- Seroma □
- Hematoma □
- Infection □
- Malposition □
- Capsular contracture □

**MFN □ (ST □ or FT □), size: ________ cm**

- Other □: __________________________

If complications, treatment given: __________________________

**Contralateral breast post-op need for XRT:** □ Yes / □ No

**Further procedure on contralateral breast:** □ No / □ Yes, specify: __________________________