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# Mastectomy Flap Necrosis: The Role of Cilostazol in Prevention

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## ABSTRACT

Flap necrosis in post mastectomy patient, either partial or full is a serious complication of breast cancer surgery. While in developed countries, it mostly follows skin sparing or nipple sparing mastectomy or mastectomy with immediate reconstruction, in India, MRM is the main perpetrator. It brings forth a number of problems like wound problems, delay in adjuvant therapy, anxiety and unanticipated financial burden. Talking of solution, prevention is the best and adoption good surgical practice including good tissue respect and avoidance of certain traumatic techniques can minimise the incidence. But once happened, wound can be managed both operatively and non-operatively. Cilostazol, a selective inhibitor of cellular phosphodiesterase type 3 (PDE3) is known to improve blood supply, especially in the microcirculation and also promotes cutaneous oxygen supply. With an aim to determine its role in prevention and management of Mastectomy Skin Flap Necrosis (MSFN), we conducted a study over a meticulously selected 60 patients of Carcinoma breast, slated for modified radical mastectomy (MRM), randomly divided them into two groups of 30 each, one group received Cilostazol, at a dose of 100mg orally twice daily for 1 month, starting from first post-operative day, while the other group did not. It showed that Cilostazol significantly reduced the incidence of flap necrosis in our study population (p=0.032 with little side effects. Hence, Cilostazol can be recommended as a safe and efficacious post-operative drug in all cases of MRM, especially in high risk patients, to reduce the incidence of flap necrosis.

***Key Words:*** MRM, Mastectomy Skin Flap Necrosis (MSFN), Cilostazol

## INTRODUCTION

Breast being an important part of female form and identity, any untoward event related to it adds to female anxiety. And talking of anxiety, CA breast probably tops the list. It is the most common cause of cancer in women accounting for about one-third of all cancer in women and second leading cause of cancer deaths in women today, after lung cancer.

One of the cornerstones of breast carcinoma treatment is surgery and Modified Radical Mastectomy (MRM) is the most common surgery performed in CA Breast patients. One of the important post-operative complications of MRM is flap necrosis. Mastectomy Skin Flap Necrosis (MSFN) has a reported incidence of 5%-30% in the literature but it is often an underappreciated problem1. It may present as partial or full-thickness necrosis. Predictive patient risk factors include smoking, diabetes, obesity, radiotherapy, previous scars and severe medical comorbidity. MSFN ensues when the blood supply to the skin flaps is insufficient to meet their metabolic needs due to insufficient arterial flow, inadequate venous drainage, or a combination of both.

MSFN leads to a number of challenges, including wound management problems, delay to adjuvant therapy,

aesthetic compromise, implant extrusion/infection and financial loss. At present, there is no definite preventive therapy available, resulting in significant physical and psychological morbidity once flap necrosis occurs. [1]

As Cilostazol improves blood supply, especially in the microcirculation and also promotes cutaneous oxygen supply, we aim to determine its role in prevention and management of MSFN. We conducted this study to see if Cilostazol can be implemented as a novel and effective therapy for the management of MSFN, thus reducing post-operative morbidity and improving the quality of life. No such study reports are available from India, especially from the eastern zone [MEDLINE Search].

## MATERIALS AND METHODS

We selected all patients of suspected or already diagnosed case of breast Carcinoma visiting general surgery OPD or admitted in the Indoor department under General Surgery, Medical College & Hospital, with a plan of MRM. Eventually 60 patients were selected during the study of January 2018 to June 2019 excluding those patients who have history of any skin diseases predisposing to flap necrosis, patients who have collagen vascular diseases, peripheral vascular diseases, patients who have received neoadjuvant chemotherapy (post NACT), and patients with significant medical comorbidities like heart disease, uncontrolled diabetes mellitus, chronic kidney disease, bleeding diathesis. Pregnant patients and patients who did not give consent were also kept out of the study.

This is an institution based non-randomized clinical trial. We divided those patients into two groups, and to obtain statistically significant results, each group should have a minimum of 30 patients.

All patients underwent MRM with uniform technique (no diathermy, only scissor dissection, skin closure with skin staplers). After MRM, the post-operative patients were randomly divided into two groups of 30 each, group A and group B. While all patients of Group A received Cilostazol from the immediate post-op period, Group B patients did not. The usual dose is 100 mg twice daily 30 minutes before or 2 hours after a meal. Cilostazol was continued for 1month, during which we followed up the patients and observe for the incidence of MSFN, and compared the results between two groups. Flap care was done uniformly to both groups, including daily cleansing with only normal saline, application of Mupirocin ointment. Stapler removal was done on 14th post-op day.

Specimens obtained were evaluated grossly and appropriate sections were taken both from tumour areas and apparently normal areas of the specimen. The slides after proper preparation and staining were studied and evaluated using light microscopy to identify the histological type of lesion and also to classify the cases of breast carcinoma as per Nottingham's modification of Bloom Richardson's grading system. Sections from apparently normal area were used as negative control.

Others factors like the tumour location, the histopathology and the Immunohistochemistry of the cancer cells were also compared between the two groups, to identify any possible association with increased incidence of MSFN.

Post MRM, the patients were followed up for 1 month for the study. Further routine follow up were done at 3 months, 6 months and 12 months. May-June 2019 was for data interpretation and statistical analysis.

## STATISTICAL METHODS

Each analysis was performed in a per-protocol manner. Distributions of numerical variables in both groups were expressed as mean ± standard deviation, and skewed data were reported as median (interquartile range). Chi-square or Fisher's exact test were performed for comparing categorical variables between groups, whereas the Mann-Whitney U test or unpaired Student's t-test were performed for

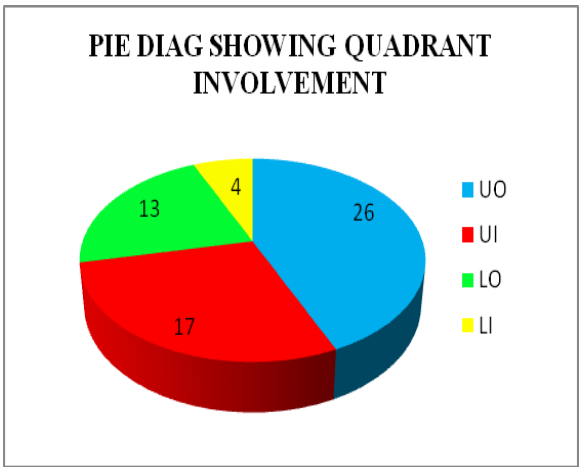
comparing numerical variables, as appropriate. Differences between baseline and post-treatment values were analyzed by the Wilcoxon signed- rank test or paired Student's t-test, as appropriate. A Pearson's Coefficient (p value) <0.05 (2-sided) was considered to indicate statistical significance. All statistical analyses were performed using SPSS for Windows (Version 16.0, SPSS Inc., Chicago, IL, USA).

## RESULT AND ANALYSIS

We compared all the cases of two groups in respect to following factors.

While comparing age, religion between the two groups, we did not find any co relation with increased incidence of flap necrosis

But affected quadrant had significant correlation with higher incidence of flap necrosis (p=0.045), with 10 out of 22 (45.45%) flap necrosis occurring in upper outer quadrant mass. Involved quadrant also had significant correlation with depth of necrosis (p=0.004) with 10 out of 17(58.82%) superficial necrosis occurring in upper outer quadrant and 3 out of 5(60%) deep necrosis occurring in upper inner quadrant. Involved quadrant also had significant correlation with extent of necrosis (p=0.019).




| CROSS TABULATION OF AFFECTED QUADRANT WITH FLAP NECROSIS | | | | |
|---|---|---|---|---|
| | | FLAP NECROSIS | | Total |
| | | YES | NO | |
| AFFECTED QUADRANT | UPPER OUTER | 10 | 16 | 26 |
| | UPPER INNER | 8 | 9 | 17 |
| | LOWER OUTER | 1 | 12 | 13 |
| | LOWER INNER | 3 | 1 | 4 |
| Total | | 22 | 38 | 60 |

Although duration and progression of lump did not have any significant correlation with flap necrosis (p=0.108), however, progression did have significant correlation with depth of necrosis (p=0.050) with all 5 (100%) cases of deep necrosis occurring in patients having rapid progression.

Same in case of skin lesions which otherwise don't seem to affect risk of flap necrosis, but it had significant correlation with depth of necrosis, with majority of superficial necrosis, i.e. 8 out of 17 (47.06%) occurring in normal skin, but 3 out of 5 (60%) of deep necrosis occurring with peau d' orange skin (p=0.010). Skin changes also had significant correlation with extent of necrosis, as in 2 out of 3 (66.67%) patients having necrosis of 5cm had peau d' orange skin (p=0.004).

Lump size also showed correlation with depth and extent of necrosis.

It is mentionable that in 13 out of 22 pt of FN, the mass had fixity to skin showing significant correlation with extent of necrosis (p=0.030), with no significant correlation with depth of necrosis (p=0.068)

In our study, majority, i.e. 24 (40%) patients had single palpable ipsilateral axillary lymph node. The number of palpable axillary lymph nodes did not have any significant correlation with flap necrosis (p=0.169), neither with extent of necrosis (p=0.276). However, number of lymph nodes showed significant association with the depth of necrosis (p=0.004), with all 5

(100%) patients having deep necrosis presenting with 2 palpable lymph nodes.

Majority of patients, i.e. 22 (36.7%) belonged to TNM stage of cT2N1Mx which had no bearing on chances of flap necrosis (p=0.080) and their extent (p=0.520). However, there seemed to be a correlation with depth of necrosis, with all 5 (100%) patients having deep necrosis, presenting with stage cT4bN1Mx (p=0.006).

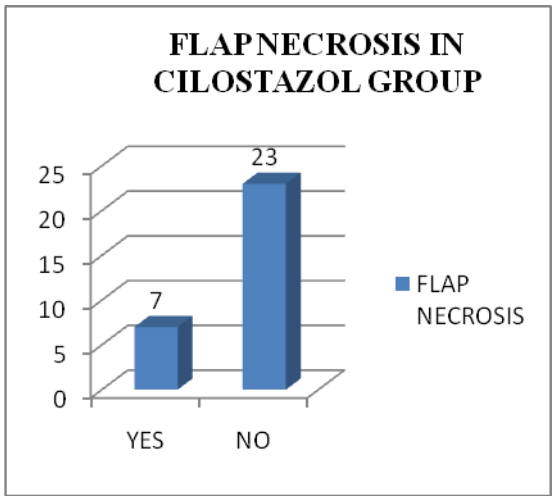
| CROSS TABULATION OF STAGING WITH DEPTH OF NECROSIS | | | | | |
|---|---|---|---|---|---|
| | | DEPTH OF NECROSIS | | | TOTAL |
| | STAGING | SUPERFICIAL | DEEP | NA | |
| | cTisN1M0 | 0 | 0 | 1 | 1 |
| | cT1N0M0 | 0 | 0 | 5 | 5 |
| | cT1N1M0 | 0 | 0 | 4 | 4 |
| | cT2N0M0 | 3 | 0 | 9 | 12 |
| | cT2N1M0 | 9 | 0 | 13 | 22 |
| | cT3N1M0 | 1 | 0 | 1 | 2 |
| | cT4bN1M0 | 4 | 5 | 5 | 14 |
| TOTAL | | 17 | 5 | 38 | 60 |

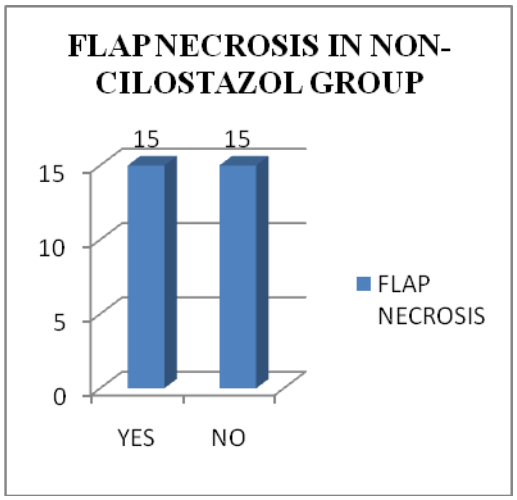
Anaemia showed significant correlation with flap necrosis (p=0.000) with 12 out of 22 (54.54%) patients of flap necrosis had anaemia. Anaemia also correlated with depth of necrosis (p=0.000), with all 5 (100%) cases of deep necrosis and 7 out of 17 (41.18%) cases of superficial necrosis had anaemia. Anaemia also had significant correlation with extent of necrosis (p=0.000), with 2 out of 3 cases of 5cm necrosis occurring in patients having anaemia.

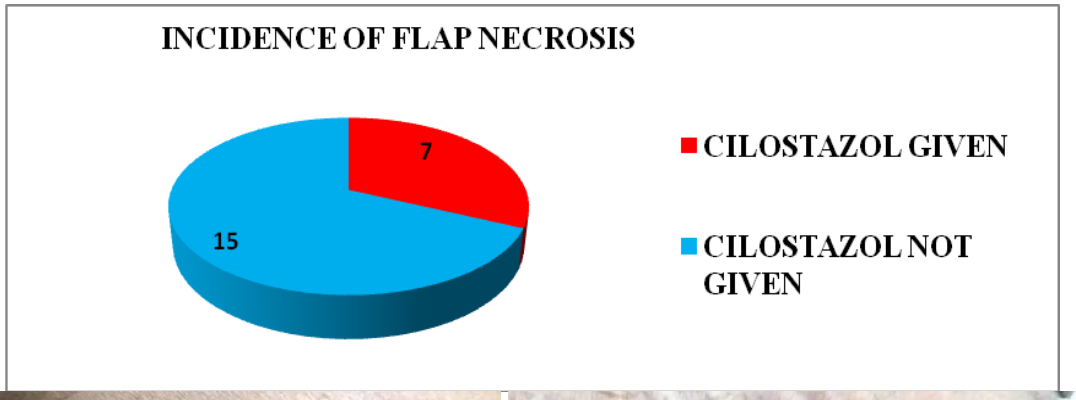
USG BIRADS score also significantly correlated with extent of necrosis (p=0.000) with all 3(100%) cases of 5cm necrosis occurring in patients having USG BIRADS score of 6.

**CILOSTAZOL**

Now, the cornerstone of present study the effect is evaluation of role of Cilostazol in prevention of flap necrosis. 30 (50%) randomly selected patients were given Cilostazol from post-operative day 1 and for 30 days. The remaining 30 (50%) patients were not given Cilostazol. Cilostazol significantly reduced the incidence of flap necrosis in our study population (p=0.032). Equally interesting to note is that non-Cilostazol showed significant correlation with depth of necrosis (p=0.027), with all 5 (100%) patients having deep necrosis and 10 out of 17 (58.8%) patients with superficial necrosis belonging to non-Cilostazol group. However, extent of necrosis (p=0.212) showed no association with the drug.






**Deep necrosis and crust formation without Cilostazol Superficial Necrosis Showing Rapid Healing with Cilostazol**

## DISCUSSION

MSFN is a phenomenon, occurring more commonly than appreciated. But one of the difficulties in reviewing the literature is that most studies, however considerable, are in developed countries like UK or US where almost all reported cases are results of skin sparing mastectomy(SSM),or nipple sparing mastectomy(NSM) or mastectomy with immediate reconstruction. [1]

Andin regards to latter, implant-based reconstruction accounts for approximately a third of all breast reconstructions in the UK [2] and around three-quarters of all reconstructions in the US. [3] Complications can occur in up to 40% of cases [4] and 40% of patients may require revision surgery. [5]

Matsen et al have recently published a prospective study of total of 606 consecutive mastectomies (SSM =84% and NSM =16%) with immediate reconstruction (implant or expander based =94% and autologous =6%) were performed. [6] A total of 85 (14%) cases experienced some form of MSFN. In all, 46 (8%) MSFN were mild, 6 (1%) were moderate and 31 (5%) were severe. The median size of the necrotic tissue, reported as the largest single dimension, was 3 cm (range: 0–24 cm), 9 cm (range: 1.5–15 cm) and 8 cm (range: 0.5–26 cm), respectively.

Another large retrospective review of 718 patients undergoing mastectomy and immediate breast reconstruction in British Columbia documented 12.9% of MSFN. [7] But it is relevant to note, all these MSFN, in the form scarring (thinner or thicker) or distorted skin envelope over implants or those related to extrusion of implant are not comparable with our study results, which dealt with MRM without any reconstruction.

The second inconsistency is the definition of MSFN. It may be partial or full-thickness necrosis. Now, superficial wound breakdown may be managed very differently (e.g. with local wound care) than full-thickness necrosis which may demand further surgery 1. The prolonged wound management with skin flap necrosis, including outpatient appointments, dressings and equipment and possibly repeat

admission and surgery if indicated all produce an additional financial burden on health care resources. [8]

In our study, the mean age was 52.67 yrs. 24 (40%) patients of the study population were in the age group 41-50yrs which corroborates with high-risk group in India, which is 43-46 years unlike in the west, where women aged 53-57 years are more prone to breast cancer. [9] However, advancing age alone does not appear to be a risk factor for surgical complications following MRM (including MSFN) according to a retrospective series from Los Angeles. [10]

The incidence of flap necrosis was 36.7% (22 out of 60) in our study population, which almost matched with the existing literature (ranging from 5% to30%), albeit towards the higher end. [1, 2]

Patient risk factors as evident in multiple studies include smoking, age, hypertension, previous scars, radiotherapy, diabetes, obesity, increased breast volume and severe comorbidities [1, 11, 12] most of which were excluded in our study.

Surgical factors increasing the risk of MSFN include higher mastectomy weight, incision type, including the Wise pattern mastectomy incision; over thinning of flap and perhaps the mastectomy technique itself. A balance must be there between achieving clear resection margins respecting oncological adequacy while not making the flaps so thin that they risk flap necrosis. This is achieved through careful adherence to the oncoplastic plane between the subcutaneous fat and the breast parenchyma. Subcutaneous tissue thickness can be extremely variable and does not correlate with BMI, patient age or the thickness in the other breast. [13] Along with meticulous surgical technique, a good knowledge of the blood supply to the skin and nipple of the breast may help to avoid MSFN in Skin Sparing Mastectomy (SSM) and Nipple Sparing Mastectomy (NSM). [14] Techniques such as careful tissue handling (especially while raising the mastectomy flaps), holding skin margin using skin hook, and avoiding tension during closure surely minimize risk of MSFN. It has also been suggested that the use of diathermy rather than scalpel dissection may increase the MSFN rate presumably via coagulation injury to the adjacent subdermal plexus. However, in a retrospective study of 151 SSMs, there was no significant difference between diathermy and scalpel dissection. [15]

A number of methods and devices have been used to assess tissue perfusion intra-operatively in order to predict and avoid mastectomy flap necrosis, but none have achieved universal acceptance. Traditional yet more popularly used clinical methods of assessing skin flap viability include review of skin colour, capillary refill, skin temperature and dermal bleeding but it has its own limitations, which has led to the development of several technologies that can be used intra-operatively, including handheld Doppler, laser Doppler flowmetry, fluorescein angiography and indocyanine green angiography. [1,16,17]

Interestingly, Gdalevitch et al [10] from the University of British Columbia have recently reported the results of an RCT into the effects of applying Nitroglycerin ointment (a potent topical vasodilator of both arteries and veins) to mastectomy skin flaps following immediate reconstruction which showed a significant reduction in MSFN in the group receiving the Nitroglycerin ointment (15.3% flap necrosis rate) versus placebo (33.8% flap necrosis rate, p=0.006). [18]

MSFN can be managed operatively or non-operatively. Operative management first necessitates debridement of necrosed tissue and then several options to deal with the skin loss, including re-suturing, replacing skin (with grafting or flaps), conversion to another breast reconstruction (where indicated) and allowing healing by secondary intention. No clearly defined course of action exists, with management often decided on a case-by-case basis, in line with the surgeon's preference.

Non-operative management remains the favoured course of action for MSFN following simple mastectomy, or with autologous reconstruction, with skin grafts reserved for massive skin necrosis. [19]

Cilostazol is a selective inhibitor of cellular phosphodiesterase type 3 (PDE3) resulting in suppressed degradation and increased concentrations of cyclic adenosine-3′,5′-monophosphate (cAMP) in platelets and blood vessels which in turn causes an increase in the active form of protein kinase A (PKA), which directly inhibits platelet aggregation. PKA also prevents the activation of myosin light-chain kinase that is responsible for smooth muscle contraction, thereby exerting its vasodilatory effect. The role of Cilostazol in improving microcirculation is said to be due this vasodilatation. Cilostazol also improves fracture healing by accelerating both bone formation and callus remodelling. [20]

In one study, use of cilostazol significantly increased plasma protein complex proprotein convertase subtilisin/ kexin type 9 (PCSK9) concentrations, high-density lipoprotein cholesterol levels, and number of circulating endothelial progenitor cells (EPCs), and decreased triglyceride levels. Cilostazol treatment was significantly and independently associated with an increase in plasma PCSK9 levels in patients with peripheral artery disease or at a high risk of cardiovascular disease regardless of background statin use and caused an improvement in some metabolic disorders and levels of vasculo-angiogenic biomarkers. [21]

Cilostazol might provide additional cellular and proangiogenic effects, including protection of endothelial cells (ECs) from apoptosis by stimulating the extra-cellular signal regulated kinase (ERK) 1/2 and p38 MAPK signalling, [22,23] stimulation of the release of angiogenic factors, [22] and improved endothelial function of ECs, [22,23] thereby potentially enhancing angiogenesis.

Many pharmacological agents have been introduced to improve ischemia of flap in experimental studies, however, clinical outcome are still controversial. These agents include sympatholytics, vasodilators, calcium channel blockers, anticoagulants, volume expander agent, prostaglandin inhibitors and botulinum toxin A. Nitric oxide has an important role in flap physiology after flap elevation and is the final mediator to affect vascular smooth muscle, causing arterial vasodilation. Many studies reported effect of cilostazol on nitric oxide production and showed that cilostazol potentiates interleukin-1 –beta (IL-1beta) induced Nitric Oxide (NO) production, at least partially through a cAMP-dependent pathway. Cilostazol also might attenuate cytokine-induced expression of the inducible NO synthase protein expression (iNOS) and increase in the accumulation of nitrite, a stable metabolite of NO. [24, 25]

Because of all these aforesaid changes effected by cilostazol in vascular smooth muscle cells, angiogenesis and microcirculation both in vivo and vitro as observed in numerous studies, it is expected to increase the chances of survival of skin flap and this was reflected in our study.

## CONCLUSION

MSFN, a more frequent phenomenon than what is reported, is a serious challenge to clinicians. Knowing the risk factors (like smoking, obesity, diabetes etc) and careful preoperative planning such as modification of those factors (where feasible) may minimise the chances. Equally important is a good surgical technique armed with good knowledge of anatomy. But when unavoidable, use of Cilostazol can give a promising outcome.

Cilostazol, at a dose of 100mg orally twice daily for 1 month, starting from first post-operative day, significantly reduced the incidence of flap necrosis in our study population ($p=0.032$). No significant side effects of Cilostazol were observed in our study population. Thus Cilostazol can be recommended to be routinely used as a safe and efficacious post-operative drug in all cases of MRM, especially in high risk patients, to reduce the incidence of flap

necrosis. Several other factors were also identified which were significantly associated with incidence of flap necrosis, like involvement of upper outer quadrant of breast, skin fixity, painful lump at presentation, anaemia at presentation, USG/Mammography BIRADS score, Immunohistochemistry, Tumour Grade, BR Score, Ki67 Score, etc. Besides, some factors, though not directly associated with flap necrosis seemed to have correlation with depth and/ or extent of flap necrosis but larger randomized trial is required to substantiate those outcome.

Our study also had some limitations. This study takes into consideration the various patient parameters which may contribute to flap necrosis after MRM. However, the outcome might differ depending on the surgical techniques, which are variable and individual dependant.

We have included cases only admitted under our unit, and not taken cases from other units because we wanted uniform intra-operative surgical techniques and post-operative management protocol for all the patients, as much as possible. However, this has restricted our sample size to 60.

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