

A critical look at the effect of hyperbaric oxygen on the ischemic nipple following nipple sparing mastectomy and implant based reconstruction: a case series

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Background: Nipple preservation provides superior aesthetic results as well as patient satisfaction in patients treated with both therapeutic and prophylactic mastectomy. Post-operative nipple ischemia and necrosis presents a unique clinical challenge that may be treated with hyperbaric oxygen therapy or conservative measures alone. To date, the efficacy of hyperbaric oxygen on post-operative nipple ischemia has yet to be evaluated.

Methods: A retrospective review of patients treated with either hyperbaric oxygen or conservative management was performed. Post-operative photographs were evaluated using a novel imaging data pathway to in both groups to determine rates of healing.

Results: Although patients treated with hyperbaric oxygen experienced rates of healing nearly twice those of patients treated with conservative measures alone, no statistical significance was found between groups in this series.

Conclusions: No significance difference was found between groups treated with hyperbaric oxygen or conservative management in this series. Further large scale, multi-center studies are warranted to further determine clinical utility and cost-effectiveness of hyperbaric oxygen for nipple ischemia following nipple sparing mastectomy (NSM) and implant based reconstruction.

Keywords: Hyperbaric oxygen; nipple ischemia; breast reconstruction

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Introduction

The advent of nipple preservation for oncologic and prophylactic mastectomy has enhanced aesthetic outcomes in breast reconstruction. Nipple sparing mastectomy (NSM) has been demonstrated to increase patient satisfaction and result in superior cosmetic outcomes compared to skin sparing mastectomy with nipple reconstruction (1,2). Over the past ten years, numerous studies have demonstrated NSM to be oncologically safe in appropriately selected

patients and a viable alternative to skin-sparing mastectomy (3-6). Based on the safety and efficacy of NSM and the possibility of aesthetic superiority, nipple preservation has become the preferred approach in the highest volume breast centers in the United States.

Although NSM is preferred in many situations, it is not without risk based on the perfusion requirements of the additional skin and nipple areolar complex (NAC). Mastectomy skin flap ischemia/necrosis is a well-known

complication following mastectomy with prevalence in the literature ranging from 2–30% (7–10). In the setting of NSM and direct to implant or autologous reconstruction, the risks of nipple ischemia may be compounded because of the added internal volume of the device or flap that may further compromise the perfusion of the tissues following NSM. Mastectomy skin flap necrosis as well as NAC necrosis may be increased in this setting (11–13).

As oncologic surgeons become increasingly comfortable with nipple-sparing mastectomy, their indications have expanded to larger and more ptotic breasts and in some patients, even previously radiated breasts (14,15). Skin flap necrosis following skin sparing mastectomy is usually managed with immediate excision and closure; however, ischemia of the NAC following NSM presents a unique challenge in that excision of the all or a portion of the areola usually results in a deforming asymmetry (10). NAC ischemia is often evident within 24–48 hours following NSM, however the degree of non-viable tissue (i.e., depth of impending tissue loss), as well as the timeline for progression or healing may be difficult to predict. It is during this time period that adjunct methods aimed at improving tissue perfusion are often attempted. Such therapies have traditionally included the application of topical vasodilators, local wound care with hydrating gels and/or antibacterial compounds; however, newer strategies such as supplemental oxygen administration and hyperbaric oxygen are now being considered more often. Unfortunately, there are few studies evaluating the role of hyperbaric oxygen for nipple ischemia following nipple-sparing mastectomy and reconstruction and of the few studies in the literature, most are isolated case reports that demonstrate eventual healing and device salvage (16–19).

Hyperbaric oxygen therapy comes at a significant cost to both the patient and the health care system as a whole. Although dive regimens vary, a standard course consists of 1–2 dives per day. Dive times range from 90 minutes to 4 hours and may continue for up to 30 days. Depending on the setting, the cost of each individual dive is approximately \$400 but may vary from \$100–1,000 (20,21). Recently, Dent *et al.* demonstrated high rates of healing in the setting of both partial and full thickness ischemia in patients treated with conservative management alone (22). Given the paucity of high quality studies and the need for additional inquiry, the purpose of this study is to critically examine the effects of hyperbaric oxygen therapy on the survival of the NAC following NSM and compare that to conservative treatment alone.

Methods

An IRB approved retrospective review was conducted to identify patients who experienced NAC ischemia following implant based breast reconstruction at MedStar Georgetown University Hospital from 2009 to 2013. Patients who were treated with or without hyperbaric oxygen therapy were included. Chart review was then performed to include weekly post-operative photographs, patient demographics, the use of adjuvant radiation therapy, smoking history, prior breast surgery, volume of breast tissue removed, initial expander fill volume, and type of mastectomy (therapeutic *vs.* prophylactic). Only patients with weekly post-operative photographs documenting the progression of NAC ischemia were included. Patients treated with HBOT received two 4-hour dives per day. Patients who received conservative management were treated with local wound care including petroleum gauze and/or topical antibiotic ointment. Post-operative photographs were then analyzed using a MATLAB (MathWorks, Natick, MA, USA) data processing pathway (*Figure 1*). Each NAC was hand defined using the image Segmenter tool producing a binary mask for each NAC at each post-operative visit (*Figure 2*, rows 2 and 3). A region of interest was then defined by visually selecting pixels in the ischemic portion of the NAC. A script based on the hue, saturation, and value of visually identified ischemic pixels was then applied to each post-operative visit cropped photograph (*Figure 2*, rows 4 and 5). Finally, by computing the number of pixels in the ischemic region of interest and dividing them by the number of pixels in the entire NAC, a percentage of ischemia relative to the whole NAC was generated. These values were then plotted to assess time to healing in each group. Treatment was discontinued once complete healing or progression to full thickness necrosis was documented.

Results

A total of 13 patients with adequate post-operative photographs for accurate documentation were included in the study. Of these, 8 patients were treated with HBOT while 5 were treated with conservative management. There were no significant differences in the prevalence of risk factors for NAC ischemia between groups (*Table 1*). Differences between prophylactic and therapeutic NSM or invasive versus *in situ* disease between groups is shown in *Table 2*. A single patient in the HBOT cohort had a free nipple graft at the time of NSM. There was no significant

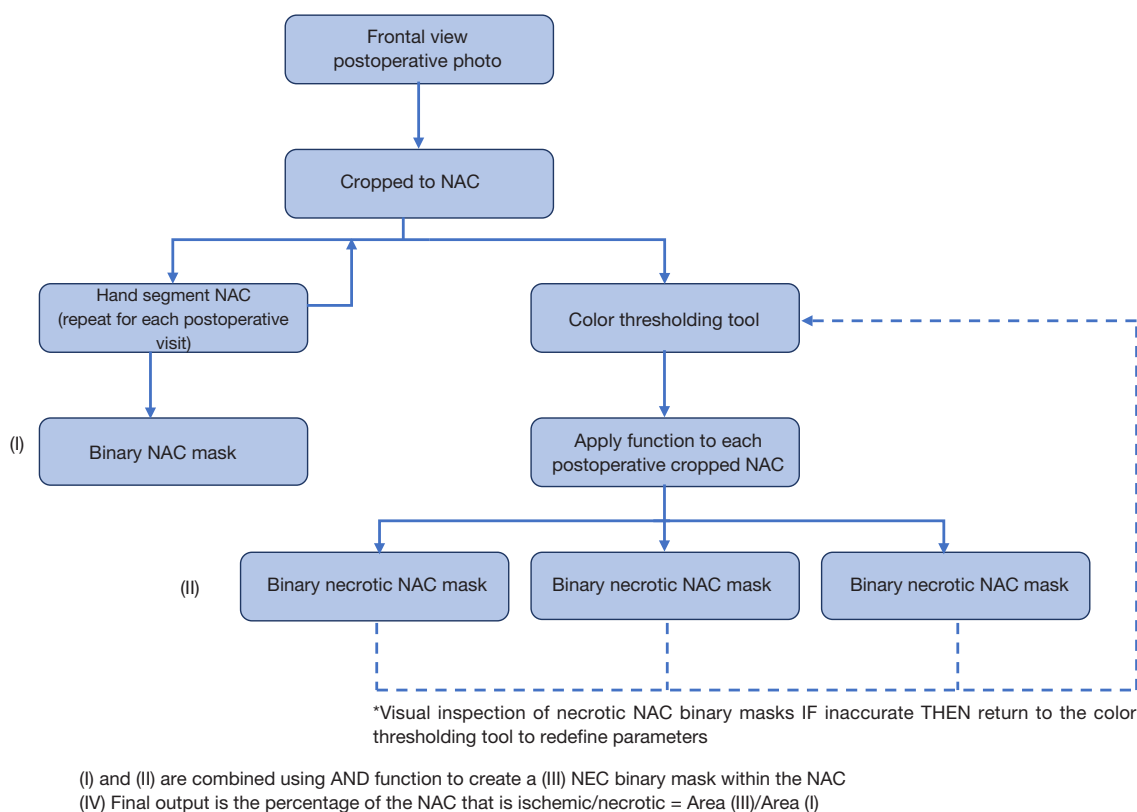


Figure 1 Data processing workflow in MATLAB (MathWorks, Natick, MA, USA).

difference between degree of initial ischemia defined as the average delta ischemia (64.9% in the HBOT groups *vs.* 61.7% in the non-HBOT group, $P=0.85$) All patients in both groups, demonstrated good healing of the NAC. The average time (days) to complete healing was 35.9 days in the HBOT group and 65.4 days in the non-HBOT group. This difference was not found to be statistically significant (Figure 3).

Discussion

One of the most devastating complications following nipple-sparing mastectomy is partial or total loss of the NAC. The psychological advantages of nipple preservation have been demonstrated in numerous studies based on body image, self-esteem, and retention of an important aesthetic structure (1,23). Given that many women are choosing NSM for prophylactic and therapeutic indications, it is prudent for surgeons to do everything possible to preserve the vascularity of the NAC. This can be accomplished intraoperatively as well as postoperatively. Intraoperative

maneuvers include optimizing incision location to minimize disruption of perfusion, maintaining the normal subcutaneous layer of the breast to avoid injury to the subdermal plexus of vessels, and assessment of perfusion to the NAC following NSM technology focused on visualization of blood flow and perfusion (22,24). Studies have demonstrated that these techniques can be beneficial postoperative maneuvers to improve the circulation to the NAC include nitro paste and HBO. The effect of nitro paste is to vasodilate and to improve the circulation.

Postoperative nipple ischemia can manifest in various ways and can be secondary to arterial or venous insufficiency. Arterial insufficiency may result in a pale NAC, whereas venous insufficiency often manifests in a congested appearance. The first step in the assessment of nipple perfusion is to make sure that this is not a pressure related phenomenon such as an implant that is too large or abnormal pressure around the nipple. Operative exploration may sometimes be indicated. If reversible causes are ruled out, then secondary maneuvers such as nitro paste or HBO are considered. This study has demonstrated that although

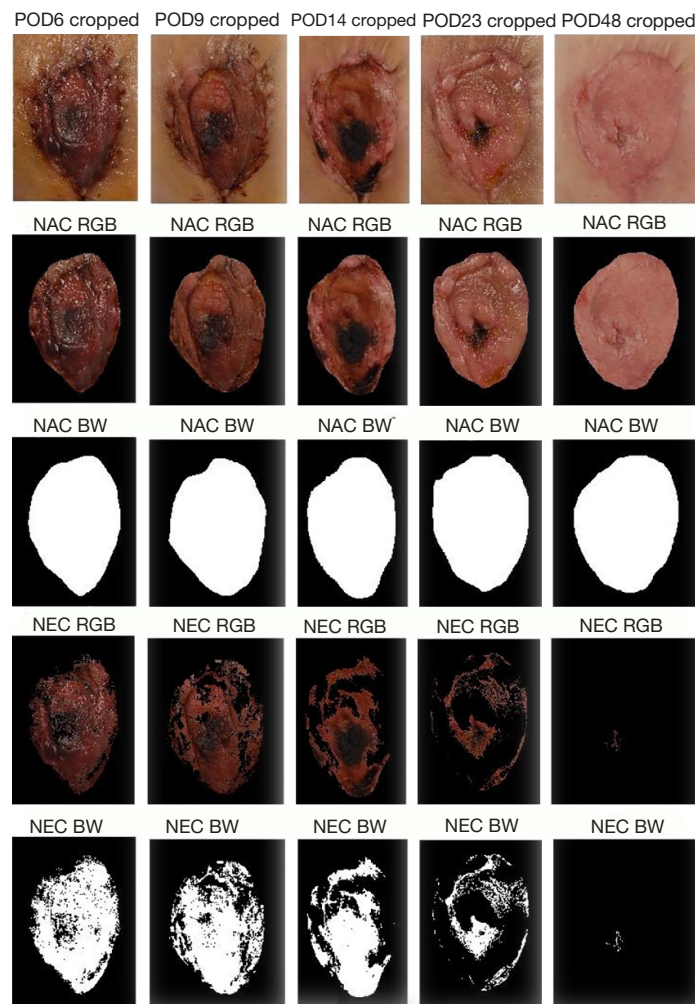


Figure 2 Data processing outputs.

Table 1 Patient demographics

Demographics	Non-HBOT	HBOT	P value
No. of patients (n)	5	8	
No. of nipples (n)	8	10	
Mean age (year)	43.8	46.7	0.68
Mean BMI, kg/m ²	22.2	26.4	0.21
Peri-operative radiation therapy (%)	0	12.5	0.39
Postoperative radiation therapy (%)	20	0	0.29
Smoking (%)	0	25	0.18
Previous breast surgery (%)	20	25	0.66

HBO therapy did not prove to be advantageous for the ischemic NAC following NSM compared to conventional management based on eventual healing, it did appear to accelerate the rate at which the ischemic tissues recovered.

Hyperbaric oxygen therapy has been studied in animal models, and several mechanisms have been proposed to support its use in wound management. First, HBOT raises dissolved plasma oxygen concentration from 0.3 to nearly 7%, thus increasing the diffusion distance of O₂ in the interstitial space by 4x–5x (25,26). Zamboni *et al.* found using *in vitro* and *in vivo* animal studies that ischemia-reperfusion injury was minimized through a nitric oxide mediated mechanism that resulted in decreased polarization of the CD18 on neutrophils (Zamboni2). Additionally, several animal studies have shown the benefit of HBOT in neovascularization of ischemic tissue flaps (27-29).

The main limitation of the current study is the small sample size given the relatively low rate of NAC ischemia. A further limitation of this study is the variability in degree and presentation of NAC ischemia between patients.

Although not standardized in this study, it is our general practice to refer patients with more severe ischemia to HBOT. Although the patients treated with HBOT on average achieved complete healing in nearly half the time, this was not statistically significant. The considerable healthcare cost and time investment with HBOT must be weighed against the potential benefit of more rapid healing, return to work, and faster initiation of adjuvant radiation therapy. To this end, further larger scale studies are warranted. This initial case series may aid surgeons in patient counseling and decision making when HBOT is available. Furthermore, this series demonstrates the clinical utility of a data processing pathway using MATLAB (MathWorks) software to assess the progression of ischemic tissue. This may prove useful in future studies pertaining to mastectomy/NAC ischemia.

Conclusions

Ischemia of the NAC following NSM and reconstruction remains a challenging problem. Hyperbaric oxygen therapy has been shown to increase tissue oxygenation, prevent ischemia-reperfusion injury, and improve neovascularization in in-vitro as well as in animal studies. In the current study, we were not able to demonstrate a statistically significant benefit in patients treated with HBOT *vs.* conservative treatment for NAC ischemia. Further large-scale studies are warranted to further determine clinical utility and cost-effectiveness of HBOT for nipple ischemia following NSM and implant based reconstruction.

Table 2 Operative treatment details

Variables	Non-HBOT, n (%)	HBOT, n (%)
PPx mastectomy	3 (60%)	6 (75%)
Tx mastectomy	2 (40%)	2 (25%)
DCIS/LCIS	1 (20%)	1 (12%)
IDC/ILC	10 (20%)	25 (12%)

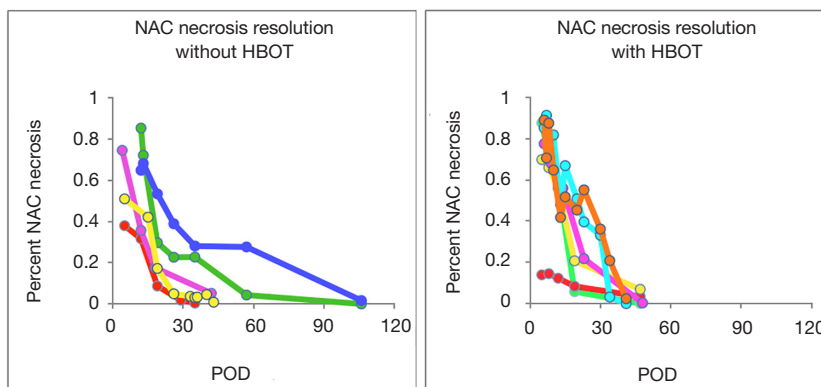


Figure 3 Time to complete healing between groups.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The IRB used was the Georgetown University Institutional Review Board (No. 2016-0999).

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