Perioperative hyperbaric oxygen treatment and postoperative complications following secondary breast reconstruction after radiotherapy: a case-control study of 45 patients

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Abstract
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Introduction: Radiotherapy reduces the risk of locoregional recurrence of breast cancer. As a side-effect, tissue can become hypocellular, hypovascular, and hypoxic and late radiation tissue injury can develop months or years later. Radiotherapy increases the risk of complications following secondary breast reconstruction. Hyperbaric oxygen treatment (HBOT) improves oxygenation of irradiated tissue and induces neovascularisation. This study evaluated whether the incidence of complications following secondary breast reconstruction after radiotherapy is decreased with perioperative HBOT.
Methods: In this retrospective case-control chart review study, patients who underwent perioperative HBOT (n = 15) were compared to lifestyle-matched (n = 15) and radiation damage-matched (n = 15) patients who underwent secondary breast reconstruction without HBOT.
Results: The HBOT group had significantly more severe radiation damage of the breast than the lifestyle- and radiation-damage-matched control groups (scoring grade 1–4, mean 3.55 versus 1.75 and 2.89 respectively, P = 0.001). Patients underwent on average 33 sessions of HBOT (18 sessions preoperatively and 15 sessions postoperatively). There was no significant difference in the incidence of postoperative complications between the HBOT group, lifestyle-matched group and radiation damage-matched group. Logistic regression analysis showed a lower risk of postoperative complications in patients who underwent HBOT.
Conclusions: Although the HBOT group had more radiation damage than the control groups, the incidence of postoperative complications was not significantly different. This implied a beneficial effect of HBOT, which was supported by the logistic regression analysis. Definitive conclusions cannot be drawn due to the small sample size. Future research is justified, preferably a large randomised controlled trial.

Introduction

Breast reconstruction following breast-conserving therapy or mastectomy is a common procedure in women with breast cancer. If radiotherapy is indicated as part of their cancer treatment, the breast reconstruction will be delayed in most patients, and thus, secondary breast reconstruction will be performed. Radiotherapy reduces the risk of locoregional recurrence of the disease, leading to an increased overall survival rate, both after breast-conserving treatment and mastectomy.[1] The average radiotherapy dose is 50 Gray.[2] Although radiotherapy improves overall survival, it has various side-effects. Radiotherapy causes cellular depletion, microvascular impairment, fibroblast dysfunction, extracellular matrix alterations and growth factor derangement.[3] This results in hypocellular, hypovascular and hypoxic tissue.[4]

Acute side-effects of radiotherapy, that occur within days or weeks, are dose- and time-dependent and include erythema, inflammation, oedema from leaking capillaries and desquamation. Delayed effects of radiotherapy occur months or even years later and are known as late radiation tissue injury (LRTI). LRTI consists of soft tissue fibrosis, skin atrophy, epithelial ulceration, skin necrosis, major vessel rupture and impaired wound healing.[5,6] LRTI decreases the ability of the tissue to heal following a breast reconstruction, which predisposes to postoperative complications.

Breast reconstructions in the irradiated breast have higher complication rates and poorer aesthetic outcomes compared to reconstructions in non-irradiated breasts (relative risk of 2.58 [95% CI 1.86–3.57]).[7,8] Autologous reconstructions are preferred over reconstructions with implants since the

latter have a high incidence of capsular contracture (up to 40–50%).[9–13]

However, in autologous reconstructions, vascular changes of the recipient site increase the risk of perioperative vascular complications such as arterial or venous thrombosis and the need to re-perform the anastomosis.[14] Other radiotherapy-related complications in autologous reconstructions include fat necrosis, fibrosis, atrophy and flap contracture.[15–17] Therefore, breast reconstructions in irradiated tissue remain challenging.

Hyperbaric oxygen treatment (HBOT) consists of breathing 100% oxygen in a hyperbaric chamber at a pressure of 202.6–253.3 kPa (2.0–2.5 atmospheres absolute). Each treatment session has a duration of about 2 hours. The treatments are given five days per week for a total of 30–40 sessions (6–8 weeks, excluding weekends). HBOT improves oxygenation of the hypoxic radiated tissue, resulting in oedema reduction, phagocytosis activation, anti-inflammation, neovascularisation, osteogenesis and stimulation of collagen formation by fibroblasts.[18] These processes could be of value to reduce complications following secondary breast reconstruction in the previously irradiated breast. Previous studies have shown that LRTI symptoms of the breast improve following HBOT.[19–21] Reduction of pain and hypersensitivity of the affected breast and fewer skin problems in the affected area are reported, as well as a reduction of pain and swelling in the affected shoulder, arm and hand.[21] Apart from LRTI of the breast, HBOT is used for several other indications, such as the treatment of necrotizing soft-tissue infections, osteomyelitis, acute thermal burn injury, crush injury, chronic ulcer due to diabetes, compromised grafts and flaps, radiation cystitis, proctitis and enteritis and other late radiation tissue injury.[18,22]

Several case reports and a rat model study describe the beneficial effect of HBOT on skin flap ischaemia after mastectomy, skin flap necrosis after mastectomy with direct reconstruction with implants, and skin survival after a transverse rectus abdominus myocutaneous (TRAM) flap.[23–30]

Based on this literature, HBOT could have a beneficial effect on postoperative complications of secondary breast reconstruction. However, evidence about the use of HBOT specifically in secondary breast reconstruction is limited to one case-control study with five patients (10 breasts).[31] Therefore, the aim of this study was to investigate whether the incidence of complications following secondary breast reconstruction decreased with perioperative HBOT.

Methods

A retrospective cohort study was conducted, using the STROBE statement guidelines.[32] Approval of the medical ethical committee was obtained (file number 2018-4394). Written informed consent was obtained from all subjects.

PATIENT SELECTION

All patients referred by the Department of Plastic Surgery in the Radboudumc (Nijmegen, the Netherlands) to the Da Vinci Clinic (Arnhem, the Netherlands) to undergo perioperative HBOT for secondary breast reconstruction after radiotherapy were included. All of these patients underwent radiotherapy because of breast cancer and substantial radiation damage was seen upon referral for the secondary breast reconstruction.

To add a control group to the study, the main factors influencing the outcome of breast reconstruction were determined based on literature and expert opinion.[33,34] Demographic factors and radiation damage developed after radiation were determined as principal factors influencing the outcome of breast reconstruction. To take both factors into account, two control groups were created. Patients with a history of secondary breast reconstruction following radiotherapy because of breast cancer were extracted from a Radboudumc database. Exclusion criteria were no radiotherapy, perioperative HBOT, patients who already underwent HBOT in the past, patients with certain co-morbidities (history of thoracic surgery, history of a major vascular event, immunosuppressive treatment, or pre-existent coagulation disorders) and patients who were deceased at the time of the study.

The first control group was case-matched with the HBOT group based on year of birth, body mass index (BMI), co-morbidities (hypertension, diabetes mellitus, a history of deep vein thrombosis (DVT), pulmonary embolism or thrombosis elsewhere, use of platelet aggregation inhibitors, use of anticoagulants) and smoking status. For each of the patients of the HBOT group, the best match was chosen and included.

The second control group was matched based on radiation damage. For every woman in the HBOT group, the radiation damage was classified by the reviewer (EM) using the toxicity scoring system of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.[35] Again, the best match based on this score was chosen and included in the second control group.

OUTCOMES AND ASSESSMENT

The electronic medical records of the Radboudumc of all patients were retrospectively reviewed by one independent reviewer (EM). For the HBOT group, the medical records of the Da Vinci Clinic were also reviewed by the same reviewer. Outcomes and relevant data as described were recorded in an online database (Castor EDC, Amsterdam, the Netherlands).[36]

The primary outcome of this study was the number of postoperative complications of the breast, as described in postoperative clinical notes. Postoperative complications

were defined as the need for reoperation, postoperative bleeding, infection, flap loss and wound healing problems with necrosis. A complication was registered if any of the terms above were mentioned in the clinical notes. Postoperative bleeding was registered as a complication if bleeding occurred which required surgery to stop the bleeding. Infection was registered as a complication if the term infection was mentioned, or if infection symptoms (erythema, swelling, increase of temperature, pus discharge) were described with the prescription of antibiotics. Necrosis was registered as a complication if a necrosectomy was performed.

Other perioperative outcomes such as type of reconstruction, duration of surgery and duration of ischaemia of the deep inferior epigastric artery perforator (DIEP) flap and postoperative recovery days in the hospital were also recorded.

Other relevant data recorded included patient demographics, risk factors, and disease characteristics including radiation damage and treatment characteristics. The following risk factors were noted; hypertension, diabetes mellitus, a history of deep vein thrombosis (DVT), pulmonary embolism or thrombosis elsewhere; use of platelet aggregation inhibitors, use of anticoagulants, smoking history, and obesity (body mass index [BMI] ≥ 25.0). The amount of radiation damage was classified using the scoring system as previously mentioned.[35] To classify each patient, clinical notes of physical examination, as well as preoperative photographs, were reviewed to estimate the grade of radiation damage.

Follow up assessments of patients were very different. Therefore, outcome measures were scored up to 6 months postoperative. All patients had at least two follow up assessments in this period.

In the HBOT group, the number of sessions of HBOT and side effects were also recorded.

STATISTICAL ANALYSIS

SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, V.A., NY: IBM Corp.) was used for statistical analysis. A Kruskal-Wallis one-way analysis of variance was performed per patient to compare the medians of the three groups. The Kruskal-Wallis analysis was performed on patient characteristics, perioperative outcomes, postoperative complications, time of ischaemia (when applicable), bilateral reconstruction, surgery time and length of hospital stay, and was analysed for each type of reconstruction separately. Bonferroni correction was performed to correct for multiple testing.

A multivariate logistic regression analysis was performed to test the research hypothesis regarding the relationship between the likelihood of postoperative complications based on treatment with or without HBOT and the amount of radiation damage. The presence or absence of postoperative complications was the dependent variable. Treatment with or without HBOT and amount of radiation damage were independent variables.

The following equation was used:
$\log[Y/1\text{-}Y] = \beta_0 + \beta_1 * \text{HBOT} + \beta_2 * \text{radiation damage}$.

Y = postoperative complications, coded as 0 = no postoperative complications and 1 = postoperative complications, HBOT is coded as 0 = no HBOT and 1 = HBOT, and radiation damage is coded following the earlier mentioned toxicity score, ranging from 0 = no radiation damage to 4 = grade 4 radiation damage. Thus, the predicted logit of postoperative complications was found to be: – 2.282–0.362* HBOT + 0.254*radiation damage.

In all statistics, a *P*-value of ≤ 0.05 was considered as significant.

Results

In total, the patient population consisted of 45 women. In the HBOT group, five patients were excluded due to incomplete data sets. A remaining total of 15 eligible patients where a full data set was available were included. In the control groups, 30 patients were included, 15 in each group. Patients in the HBOT group had undergone HBOT and reconstructive surgery in the period between 2013 and 2017. Patients in the control groups had undergone reconstruction surgery in the period between 2016 and 2018.

PATIENT CHARACTERISTICS

Patient characteristics are presented in Table 1. Reconstructions performed in the groups were: DIEP reconstruction, both unilateral and bilateral; latissimus dorsi (LD) reconstructions, both with and without implants; and one reconstruction with implants following tissue expanders.

There were no significant differences between the demographics of patients. Despite an attempt to match the HBOT group with one of the control groups, there was a significant difference between the groups in the amount of radiation damage, the HBOT group had the most radiation damage (mean radiation damage score 3.55 in the HBOT group versus 1.75 in the lifestyle-matched group and 2.89 in the radiation-damage-matched group, $P < 0.001$). Median scores are presented in Table 1.

HBOT SESSIONS

On average, 33 sessions of HBOT were given to patients (mean of 18.4 preoperatively and 14.7 postoperatively, range of 14–50 sessions). There was no correlation between number of sessions and radiation damage. Three patients failed to complete the prescribed number of sessions. Reasons for not finishing the complete treatment (treatment

Table 1
Baseline patient characteristics. All three groups *n* = 15. DIEP – deep inferior epigastric artery perforator flap; IQR – interquartile range

Patient characteristics	Lifestyle-matched group Median (IQR) or *n* (%)	Radiation damage-matched group Median (IQR) or *n* (%)	HBOT group Median (IQR) or *n* (%)	*P*-value
Age at surgery	54 (47–61)	58 (50–64)	55 (47–61)	0.547
Body mass index	27 (26–30)	26 (24–29)	26 (24–28)	0.642
Never smoked	7 (47%)	10 (67%)	7 (47%)	0.456
Risk factors	1 (1–2)	2 (1–2)	1 (0–2)	0.215
Radiation damage Grade 0 Grade 1 Grade 2 Grade 3 Grade 4	1 (1–2) 1 (13%) 4 (27%) 2 (13%) 1 (7%) 1 (7%)	3 (2–3) 0 (0%) 0 (0%) 4 (27%) 7 (47%) 3 (20%)	4 (3–4) 0 (0%) 0 (0%) 0 (0%) 7 (47%) 6 (40%)	< 0.001
Chemotherapy	13 (87%)	12 (80%)	14 (93%)	0.862
Hormone therapy	7 (47%)	5 (33%)	5 (33%)	0.691
Axillary lymph node dissection	9 (60%)	4 (27%)	7 (47%)	0.314
DIEP unilateral	10 (67%)	7 (47%)	5 (33%)	0.192
DIEP bilateral	5 (33%)	3 (20%)	4 (27%)	0.717
Latissimus dorsi	0 (0%)	5 (33%)	5 (33%)	0.430
Tissue expanders	0 (0%)	0 (0%)	1 (7%)	0.368

Table 2
Postoperative complications. Note that percentage calculations are on a small denominator (*n* = 15 all groups)

Postoperative event	Lifestyle-matched group *n* = 15 *n* (%)	Radiation-damage-matched group *n* = 15 *n* (%)	HBOT group *n* = 15 *n* (%)	*P*-value
No complications	12 (80)	13 (87)	12 (80)	0.925
Repeat surgery	2 (13)	1 (7)	2 (13)	0.797
Postoperative bleeding	0 (0)	0 (0)	1 (7)	0.387
Infection	2 (13)	1 (7)	2 (13)	0.797
Necrosis	1 (7)	0 (0)	1 (7)	0.387
Flap loss	1 (7)	0 (0)	1 (7)	0.633

as prescribed at intake, range 30–40 prescribed sessions) were severe flu, not feeling well and surgery performed earlier than planned. During HBOT, two patients suffered from trouble equalising middle ear pressure, three from myopia, and five from tiredness. All of these side effects were reversed after the treatment.

PRIMARY OUTCOME: POSTOPERATIVE COMPLICATIONS

Complications are presented in Table 2. Overall, there were no significant differences in the occurrence of postoperative complications between groups. Reasons for repeat surgery were necrosis, suspicion of venous congestion, arterial problems or postoperative bleeding. All complications occurred within the first three postoperative months.

According to the multivariate logistic regression model, the logit of a patient having postoperative complications was positively related to radiation damage (0.254) and negatively related to HBOT (-0.362), as can be seen in Table 3. In other words, the higher the radiation damage, the more likely it is that a patient would have postoperative complications. And given the same radiation damage score, patients receiving HBOT were less likely to have postoperative complications. However, with *P*-values of 0.528 and 0.684 respectively, these results were not significant.

PERIOPERATIVE PARAMETERS

Time of surgery of all reconstructions, time of ischaemia of the unilateral and bilateral DIEP and amount of recovery days in the hospital were all not significantly different between the three groups. Perioperative parameters are presented in Table 4.

Table 3

Logistic Regression Analysis of the relationship between the likelihood of postoperative complications based on treatment with or without HBOT and the amount of radiation damage. [a] – variables entered on step 1 were HBOT, radiation damage; Beta – coefficient for the constant (intercept); CI = confidence interval; df – degrees of freedom for the Wald Chi-Square test; Exp (β) – exponentiation of the β coefficient (odds ratio); SE – standard error; Wald – Wald Chi-Square that tests the null hypothesis that the constant equals 0

Variables in the equation		Beta	SE	Wald	df	*P*	Exp (beta)	95% CI for Exp (beta)	
								Lower	Upper
Step 1[a]	HBOT	-0.362	0.890	0.165	1	0.684	0.697	0.122	3.984
	Radiation damage	0.254	0.403	0.399	1	0.528	1.290	0.586	2.839
	$Beta_0$	-2.282	1.096	4.330	1	0.037	0.102		

Table 4

Relevant perioperative parameters including total surgery time for the DIEP and LD flap reconstructions, time of ischaemia of DIEP reconstructions, and total recovery days in the hospital for all reconstructions. DIEP – deep inferior epigastric artery perforator reconstruction; LD – latissimus Dorsi reconstruction

Parameter	Lifestyle-matched group Mean (SD)	Radiation damage-matched group Mean (SD)	HBOT group Mean (SD)	*P*-value
DIEP unilateral (hours)	7.3 (1.3)	7.2 (1.3)	7.0 (1.5)	0.673
DIEP bilateral (hours)	9.5 (0.7)	11.1 (3.6)	9.3 (3.3)	0.651
LD (hours)	-	2.7 (0.8)	3.8 (2.0)	0.299
Time of ischaemia DIEP unilateral (minutes)	72.0 (24.9)	57.0 (20.1)	61.0 (25.9)	0.485
Time of ischaemia DIEP bilateral (minutes)	69.0 (18.2)	36.0 (14.0)	59.0 (7.4)	0.350
Total hospital days	5.8 (1.2)	5.1 (1.2)	5.6 (3.1)	0.581

Discussion

Radiotherapy plays an essential role in the treatment of women with breast cancer by increasing the overall survival rate.[1] However, radiotherapy can lead to hypocellular, hypovascular, hypoxic tissue and LRTI, which decreases the ability of the tissue to heal.[4]

As a consequence, breast reconstructions in the irradiated breast have higher complication rates compared to reconstructions in the non-irradiated breast (relative risk of 2.58, 95% CI 1.86–3.57).[8] HBOT can decrease the effects of LRTI by improving oxygenation of the damaged tissue, resulting in neovascularization, anti-inflammation and stimulation of collagen formation by fibroblasts.[19] This is one of the first studies examining the effect of HBOT on perioperative outcomes and postoperative complications of secondary breast reconstruction after radiotherapy.

Using logistic regression analysis, a beneficial effect of HBOT was demonstrated on postoperative complications of breast reconstruction after radiotherapy, although this effect was not significant. However, there was a significant difference in the amount of radiation damage, with a higher score in the HBOT group ($P < 0.001$). Although the aim was to form a control group as similar as possible, it was not possible to find an equal number of patients with grade 4 radiation damage as in the HBOT group.

The finding that, despite the HBOT group having significantly more radiation damage, the postoperative complications and perioperative outcomes in all groups were not significantly different, supports the conclusion that HBOT provided a beneficial effect. HBOT was well tolerated with no major side effects occurring. The average number of sessions of HBOT was 33, which is similar to the average number of sessions that have been given in other studies for other chronic indications, including LRTI.[37,38]

In the literature, there is evidence for a beneficial effect of HBOT on wound healing processes,[22] however, there is little evidence for the effect of HBOT on postoperative outcomes. A randomised controlled trial examining the influence of HBOT on split-thickness skin grafting showed an increased survival of skin graft surface area of 29% with the use of HBOT. Complete take of the skin graft was 64% in the HBOT group versus 17% in the control group.[39] Another study reported a significantly lower postoperative infection rate in neuromuscular surgery, with 5.5% infections in the HBOT group versus 16.6% infections in the non-HBOT group.[40]

A major limitation of this study was the significant difference in the amount of radiation damage between patients. Although all other patient characteristics (age at surgery, BMI, smoking history, risk factors) and neoadjuvant therapy (chemotherapy, hormone therapy, axillary lymph node

dissection) were not significantly different, the significant difference in the amount of radiation damage created selection bias.

Another limitation of this study was its retrospective design. Not all notes were recorded in a standardised fashion. Therefore, the grade of radiation damage had to be estimated based on clinical notes and preoperative photographs. The interpretation of minor versus major complications was in some cases challenging. To retain objectivity, complications were only registered if there was a clear outcome measure, for example, a necrosectomy in case of necrosis. However, this method can possibly lead to bias. The study was also small.

This study provides evidence that HBOT may reduce postoperative complications in women undergoing secondary breast reconstruction in the irradiated breast. Embedding HBOT as a method of work-up treatment in cases of heavily irradiated secondary reconstruction may be considered. More research is needed in a larger patient group to evaluate the effect of HBOT on perioperative and postoperative outcomes. For a future study, a large randomised controlled trial would be preferable.

Conclusion

Although the group that underwent HBOT had more radiation damage than the control groups, the incidence of postoperative complications was not significantly different. This implied a beneficial effect of HBOT. However, explicit conclusions cannot be drawn due to the small sample size. Future research is justified, preferably a large randomised controlled clinical trial.

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