The Value of Local Application of Hydrogen Peroxide Solution at the Site of Wound after Mastectomy for Breast Carcinoma in Reducing Local Recurrence of the Tumor.

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Abstract

Background: Hydrogen peroxide is produced in normal cells of the body by peroxisomes. Cancer cells have lower respiration rates than normal cells therefore they grow better under low oxygen concentration, and introducing high oxygen levels could retard their growth or kill them. On these bases hydrogen peroxide solution had been applied locally at the site of wound after mastectomy for breast carcinoma to decrease the risk of local recurrence of the tumor.

Objective: To evaluate the significance of local application of hydrogen peroxide solution at the site of wound after mastectomy for patients with breast carcinoma in reducing local recurrence of the tumor, and to observe whether it is safe or not.

Patients and Methods: One hundred female patients with breast carcinoma and underwent mastectomy in Baghdad hospitals were involved in this study. Patients were divided into two identical groups each with fifty patients. Group 1, patient's wounds were treated locally by hydrogen peroxide solution after mastectomy; whereas the other group (control) did not treat with it. Patients had been followed for survival, recurrence, and complications for 15 years.

Results: In group 1; there was no local recurrence, while in the control group, the local recurrence of the tumor was 14% .In group 1,the five, ten, and fifteen years survival were 60%, 14%, and 6% respectively without detectable complications; while in the control group, the 5 year survival was 24%, and no patient survive more than 7 years.

Conclusion: Local application of hydrogen peroxide solution at the site of wound after mastectomy for breast carcinoma is safe and may be effective in improving survival rate and reducing local recurrence of the tumor.

Key words: Breast carcinoma, local application of hydrogen peroxide solution, local recurrence.

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Introduction

Cancer cells have lower respiration rates than normal cells, therefore they grow better under low oxygen concentrations, and that introducing higher oxygen levels could retard their growth or even kill them. These facts are the major theoretical foundation for oxygen therapy and were the results of the work of Warburg, the winner of Nobel Prize for medicine in 1931 and his observations in this field [(1)].

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Hydrogen peroxide (H_2O_2) is produced normally inside certain cells of the body directly by cytoplasmic peroxisomes. Hydrogen peroxide acts as a cytotoxic, digestive, opsonic, and growth inhibitory factor.H_2O_2 induce cellular injury by lipid peroxidation, protein interaction and DNA damage; so it is a natural substance that formed inside normal cells of the body as a part of its defense mechanism [(2)].

Breast tumors are frequently infiltrated by large number of macrophages. These may contribute to carcinoma cell oxidative stress, as tumor-associated macrophages have been shown to deliver a sublethal oxidative stress to murine mammary tumor cells. This may be due to oxygen radical production by the macrophage [(3)].

The killing of cells by ionizing radiation is most likely the result of direct formation of hydroxyl radicals from the radiolysis of water [(2)].

Radiotherapy and photodynamic therapy generate oxygen radicals within the carcinoma cells [(4)]. In the same context, some anticancer therapies may add to the oxidative stress within breast carcinomas. The chemotherapeutic agents doxorubicin,mitomycin C, and cisplatin are superoxide generating agents, and part of the mechanism of the action of chemotherapy is a superoxide generating agents[(5)].

Considering these principles, hydrogen peroxide solution applied locally in the wound after mastectomy for patients with breast carcinoma using its cytotoxic activity to kill any implanted malignant cells that may fail in the wound due to manipulation of the tumor during surgery; considering that hydrogen peroxide is a natural substance that formed inside normal cells of the body causing cell injury and death, and that the cancer cells are relatively anaerobic cells and supplying higher oxygen concentrations surrounding their field cause retardation of their growth and even their death.

There are many studies which shows the effective and safe use of hydrogen peroxide (H_2O_2) in different ways for example: H_2O_2 is administered intravenously,orally,in ear drops, as a nasal spray, as a tooth gel, and via enemas as mentioned in "Clinical literature by Kurt Donsbach runs Hospital Santa Monica." Although some patients develop air embolism after intravenous infusion of hydrogen peroxide which is considered one of its complications; Donsbach claims that injected peroxide will boost oxygen levels which in turns kill cancer cells. Killing cancer cells by supplying more oxygen than they can tolerate [(6)].

Also soaking an affected body part in hydrogen peroxide solution can cause tumors to separate from the body so that they can be 'wiped away', and that drinking H_2O_2 solution can reduce the size of throat tumors.[(7)]

Local recurrence of cancer following surgery may be due to spillage of cancer cells into the operative field, these cancer cells may be seeded in the wound by direct contact with the primary tumor, with lymph nodes containing metastatic tumor, or with contaminated gloves and instruments. Cancer cells may also enter the wound via cut lymphatics and divided blood vessels [(8)].

Hence the aim of this study is to assess the efficacy of using local application of hydrogen peroxide (H_2O_2) solution peroperatively following mastectomy for breast carcinoma in reducing local recurrence of the tumor and improve long term survival of the patients "by decrease the risk of distant metastasis through the wound" and to show if there is any complications due to its use.

Patients and methods

A randomized controlled trial was conducted on 100 female patients with breast carcinoma proved by histopathological examination who had mastectomy and axillary clearance "Patey operation" in the period from 1995-2010 with age range from 28-65 years (mean age= 45.52 ± 8.71 years).The patients were divided into 2 identical groups each with 50 patients. All the patients were allocated randomly to be in group 1 (study group) in whom H_2O_2 solution applied locally at the site of the wound after mastectomy, and group 2(control) in whom no such treatment of the wound done.

Both groups are identical, regarding age group of the patient, histopathological type of the tumor, stage for stage of the breast carcinoma,

and it was as follows in each group: stage I, included 7 (14%) patients, stage II, included 16 (32%) patients, 18 (36%) patients presented with stage III, and 9 (18%) patients were with stage IV. Staging of the tumor done by means of TNM (Tumor – Node – Metastasis) [8], as shown in table 1.

All the patients were followed for 15 years for survival, recurrence and complications.

Informed written consent was taken from the patients before the use of the solution after full explanation of the mechanism of its action and its possible complications (as air embolism or any other unexpected complications).

In group 2(control) patients were submitted to mastectomy and axillary clearance "Patey mastectomy" with absolute hemostasis of the wound using ligatures and electrocautery, and the wound then closed without application of local hydrogen peroxide solution.

In group 1 (study group); after removal of the breast and clearance of the axilla; absolute hemostasis of the wound was achieved to avoid any risk of embolism by H_2O_2 solution through the capillaries as shown in figure 1.

The exposed axillary vessels were covered by dry gauze packs to prevent local damage of the wall of these vessels by the local application of H_2O_2 solution as shown in figure 2.

Thenafter, fifty ml of 7%H_2O_2 solution was applied locally to the surgical wound and allowed to cover the surgical field "the pectoralis facia, axilla, subcutaneous tissue, and the skin edges" and left at the site for two minutes 'to kill all the malignant cells that may be implanted in the wound due to manipulation of the tumor during surgery as shown in figure 3.

After two minutes of the local application of 7%H_2O_2 solution and its direct contact with the surgical field; the wound then washed with one pint of normal saline 'to clean it and to remove all the debris and killed malignant cells from the wound as shown in figure 4.

Then the wound was dried by dry gauze packs and closed with drains as in the control group.

Follow up of all the patients were done regularly for 15 years to detect any local, regional, or distant metastasis, and any possible complications that may occurred due to the local use of H_2O_2 solution at the site of the wound of the patients.

Regular follow up of the patients had been done by clinical examination,labrotery tests' blood cell count and serological tests' ,X-ray of chest and bones when needed, ultrasound of the wound and of the other breast, ultrasound of the abdomen "to detect any distant metastasis", and fine needle aspiration FNA of any suspicious mass were done.

Results

In the study group no signs of local recurrence were detected in the period of follow up of the patients for 15 years. While in the control group seven (14%) patients had local recurrence in the first postoperative year "five (10%) of them were with stage IV, and two (4%) were with stage III; and unfortunately all of them died in the first postoperative year due to distant metastasis.

The five years survival in the study group was noticed with 30(60%) patients; ten years survival was 7(14%); and the fifteen years survival was 3(6%) of patients "two of the patients were in stage I, and the other patient was in stage II; and those three patients are living for fifteen years without signs of recurrence or detectable complications due to the local application of H_2O_2 solution to the wound.

The five years survival in the control group was noticed with 12 (24%) and only two patients survived for seven years; both in stage two. No patient survived more than seven years in this group. All the mortality was due to distant metastasis.

The number of patients survival for 5, 10, and15 years postoperatively in both groups are shown in table (2).

The five years survival in the study group comparing with the control is significant "X^2=13.3"and" P=0.0003".

The ten years survival in the study group was seven (14%) of patients while the maximum survival rate in the control group was 7 years, which is also significant ' Fisher exact P= 0.01.

There are three (6%) patients in the study group survive for 15 years and they are living without obvious site of metastasis or local recurrence, 2 of them with stage I of the disease and the other patient with stage II.

The mortality in the control group in the first postoperative year was seven (14%) patients; all of them were with stage IV. While no mortality in the study group in the first postoperative year which is significant Fisher exact P =0.01.

Table (3) shows the mortality per postoperative year in the study group in comparison with the control and its significance.

All the patients in the study group tolerated the local application of H_2O_2 solution at the site of the wound after mastectomy in the way described above very well without any complain, and there were no detectable side effects or complications observed in the years of regular follow up of the patients till their mortality, and all the mortality were due to distant metastasis which were much less than in the control group.

Discussion

Breast cancer is the most common cause of death in middle-aged women in western countries, accounting for 3-5% of all deaths in women. Local spread of the tumor tends to involve the skin and to penetrate the pectoralis muscle and even the chest wall.

Cancer-en-cuirasse' when the skin of the chest is infiltrated with carcinoma and has been likened to a coat, may be associated with a grossly swollen arm, this usually occurs in case with local recurrence after mastectomy, the condition may respond to palliative systemic treatment but prognosis in terms of survival is poor.

The two basic principles of treatment of breast carcinoma are to reduce the chance of local recurrence and the risk of metastatic spread. [9]

Hydrogen peroxide is synthesized in normal cells of the body by peroxisomes to kill microorganisms because these intracellular molecules are cytotoxic and cause cell injury and death [10].

Cancer cells are relatively anaerobic and will die with higher oxygen levels. [1]

On these principles, the application of 7%H_2O_2 solution at the site of wound after mastectomy for breast carcinoma to kill any malignant cell in the wound after absolute hemostasis by ligatures and electrocautery to decrease the t incidence of embolism by hydrogen peroxide which is very important step in the study. The idea is to kill any possible implanted malignant cells in the surgical wound by the cytotoxic effect of hydrogen peroxide and its direct contact with these malignant cells in the hope that this will decrease the incidence of local recurrence of the tumor and even the regional and distant metastasis will be decreased, and so it will improve the survival rate

and the final results of the management of patients with breast carcinoma.

This study showed that it is safe to apply 7% H_2O_2 solution locally at the site of the wound after mastectomy by the same technique mentioned above; it was effective in reducing local recurrence of the tumor and improve long term survival of the patients; and its use carries no detectable local or systemic side effects. There is improvement in survival rate of the patients and low incidence of metastasis in the study group without detectable complications in the period of follow up for fifteen years.

Figure (5) shows one of the patients with advanced stage IV breast carcinoma preoperatively and two years after local application of hydrogen peroxide solution at the site of the wound after surgery without signs of local recurrence or detectable complications.

There were no available studies and researches about the local application of H_2O_2 solution locally in the wound after mastectomy in the literatures, so it is recommended that further studies and researches to be done using larger numbers of patients of identical groups of the same stage of the tumor, same histopathological disease and same age group; to show the significance and value of local application of hydrogen peroxide solution at the site of the wound to decrease the incidence of local recurrence of the tumor and improve long term survival of the patients.

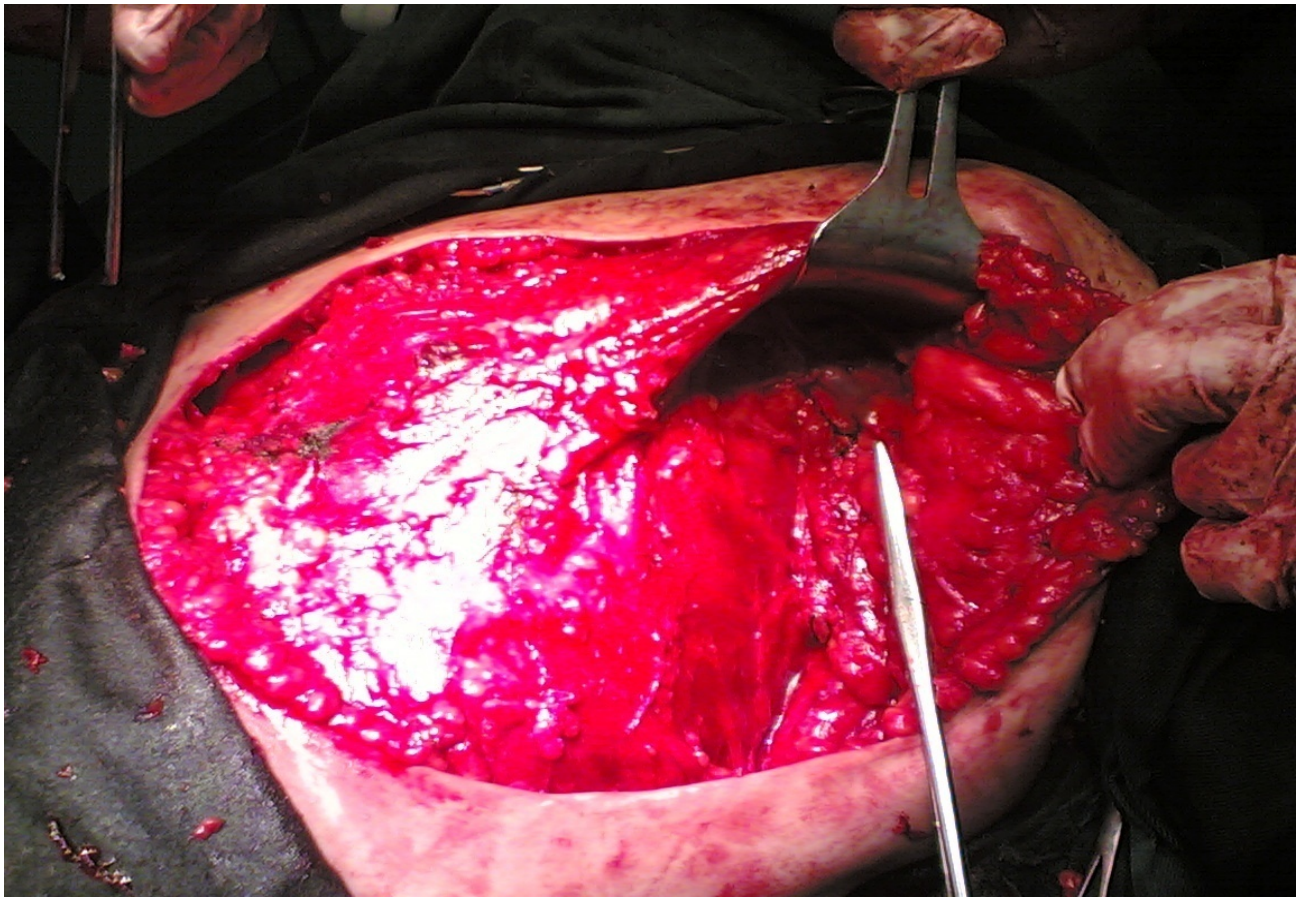

Figure1: patient with mastectomy and axillary cleareness for breast carcinoma,absolute hemostasis was achieved using ligatures and electrocautery to avoid any risk of embolism by H_2O_2 solution" the axillary vessels are marked by arrow".

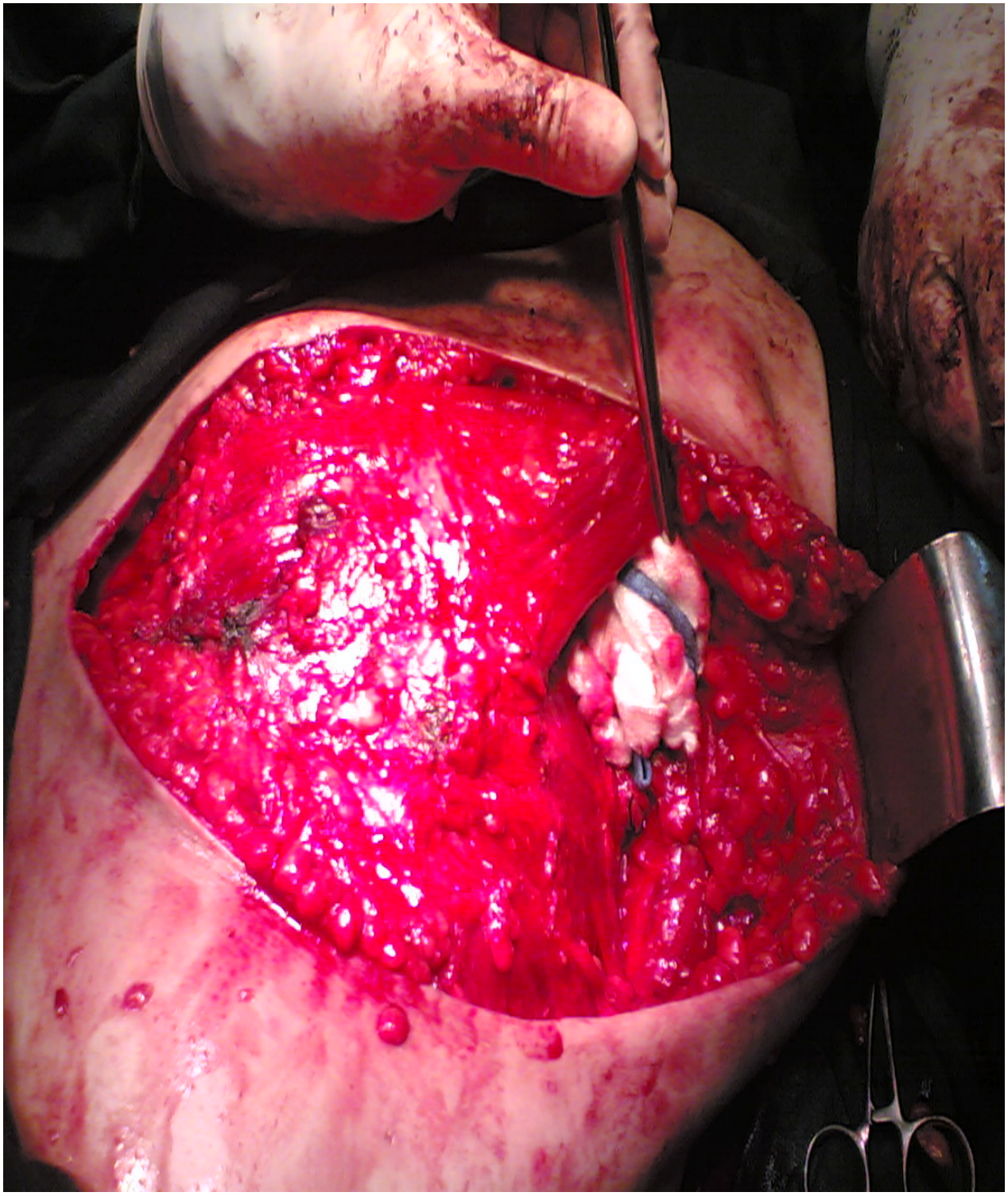

Figure 2: The same patient in figure 1, after secure haemostasis, the axillary vessels is protected by dry gauze pack before the local application of H_2O_2 solution in the wound "to avoid damage to the wall of these vessels by the solution.

Figure 3: the same patient, using fifty ml of 7% hydrogen peroxide solution to the wound in direct contact with the surgical field and skin edges and left for 2 minutes. "The axillary vessels are well protected by gauze pack"

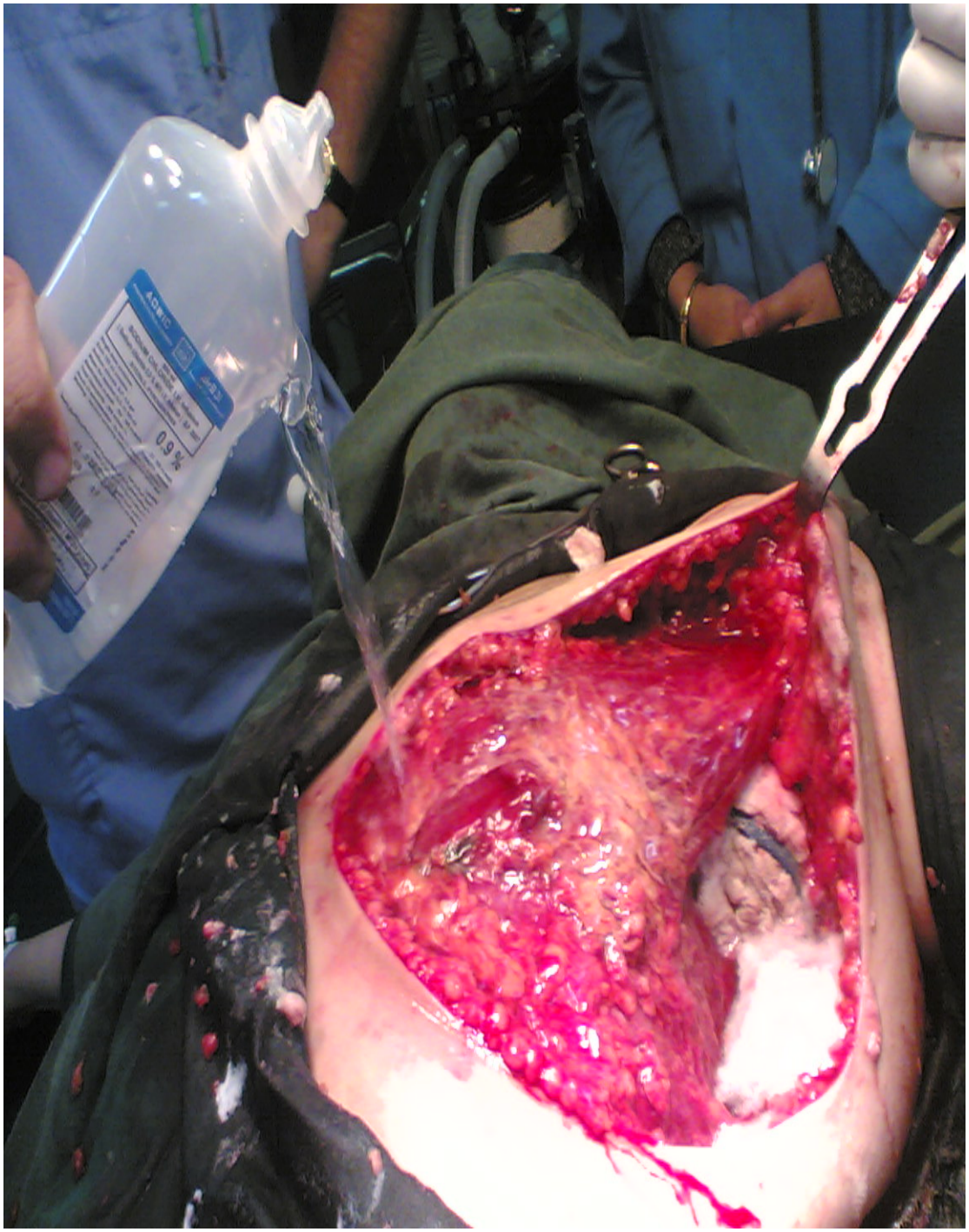

Figure 4: The same patient, after two minutes the wound washed by one pint of normal saline to remove all the debris and"the killed malignant cells" from the wound. The axillary vessels are still protected by gauze pack.

Figure 5: One of the patients with advanced stage IV carcinoma of the breast in the study group "above" and two years postoperatively "below" without local recurrence.

Table 1: Distribution of patients in the group 1(study group) and group2 (control) according to the stage of the tumor.

Stage of the tumor	Group1(study group)	Group 2(control group
Stage I	7(14%)	7(14%)
Stage II	16(32%)	16(32%)
Stage III	18(36%)	18(36%)
Stage IV	9(18%)	9(18%)
TOTAL	50(100%)	50(100%)

X^2=O.O P=1.0

Table 2: The five, ten, and fifteen year's survival of patients in both groups and its significance.

Survival	Group 1(study group)	Group 2(control group)
5 year survival	30 (60%)	12 (24%)
5 year dead	20 (40%)	38 (76%)
5 year TOTAL	50	50
Significance:	**X^2=13.3 P=0.0003**	
10 year survival	7 (14%)	0
10 year dead	43 (86%)	50 (100%)
10 year TOTAL	50	50
Significance	Fischer exact	P=0.01
15 year survival	3 (6%)	0
15 year dead	43 (86%)	50 (100%)
15 year TOTAL	50	50
Non significant	**Fischer exact P=0.1**	

Table 3: Mortality of patients in both groups per postoperative year and its significance.

Years postoperatively	Mortality in group 1	Mortality in the control	Significance
One	**nil**	**7(14%)**	**Fisher exact P = 0.01**
Two	**7(14%)**	**7(14%)**	**X^2 = 4.79 df =2 P =0.09**
Three	**8(16%)**	**14(28%)**	**X^2 =5.39 df = 2 P = 0.07**
Four	**5(10%)**	**10(20%)**	**X^2 = 11.46 df = 2 P =0.003**
Five	**7(14%)**	**6(12%)**	**X^2 =4.399 df =2 P =0.11**
Six	**2(4%)**	**4(8%)**	**Fisher exact P = 0.008**
Seven	**5(10%)**	**2(4%)**	**Fisher exact P = 0.08**
Eight	**5(10%)**		
Nine	**4(8%)**		
Ten	**4(8%)**		

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