EVALUATION OF AXILLARY DRAINAGE FLUID AFTER LYMPH NODE DISSECTION IN BREAST CANCER

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ABSTRACT

Breast cancer is gradually becoming the most common type of cancer in women. Axillary lymph node dissection is a key component of surgical management of breast cancer. Axillary lymph node dissection is however associated with several complications such as oedema of upper limb, decreased movements at the shoulder and paraesthesia of the medial arm and axilla. One of the most common sequelae of axillary lymph node dissection is seroma formation, which delays recovery and increases morbidity. To effectively manage this complication, it is paramount to understand the aetiology of seroma formation.

AIMS AND OBJECTIVES

To evaluate the composition of axillary drainage fluid in terms of total protein, albumin, globulin and lipid content and to study the change in composition of drainage fluid with prolonged drainage.

MATERIAL AND METHODS

30 patients who underwent modified radical mastectomy were evaluated in terms of axillary drain fluid output, total protein, albumin, globulin, cell counts, lipid profile (Cholesterol, HDL, LDL) and culture and sensitivity of axillary drain fluid on post-operative day 3, 5 and 7.

RESULTS

Axillary fluid is inflammatory in origin up to day 5. On day 7, the inflammation abates and the fluid becomes lymphatic. Prolonged axillary drainage has no relation to BMI.

KEYWORDS

Axillary Drainage Fluid, Breast Cancer, Axillary Lymph Node Dissection, Seroma.

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INTRODUCTION

Breast cancer is a major public health problem for the women throughout the world. Currently, India reports roughly 1,00,000 new cases of breast cancer annually.[1] It is becoming most common type of cancer in women, especially in metropolitan cities like Delhi and Mumbai.[1]

Though sentinel lymph node biopsy has evolved as an integral part in the management of carcinoma breast, especially in cases of early breast cancer, but Axillary Lymph Node Dissection (ALND) is still an important cornerstone in providing staging and prognostic information. The largest benefit from ALND are seen in ER positive women with small primary tumour who might not be candidates for adjuvant chemotherapy if their lymph nodes test is negative; however, virtually no beneficial result in ER negative women.[2]

Since the time of Halstead who carried out first mastectomy in 1882, surgeons have faced several complications of surgery such as necrosis of flap, breakdown of wound, haematoma, seroma and infection increasing the morbidity of the patients.

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ALND is particularly associated with arm oedema, decreased range of shoulder movements, paraesthesia of the medial arm and axilla.[3]

Seroma is accumulation of serous fluid that develops following the formation of skin flaps during mastectomy or in axillary dead space in post-operative period. Traditionally, a lymph leakage from upper extremity through the transected axillary lymphatic channels is believed to be an important factor in fluid secretion and seroma formation and post-operative arm use in acting as a pump that forces large quantities of lymph into the empty axillary fossa.[4]

Hence, seroma is an important complication of ALND delaying recovery and adds to morbidity. There have been various methods for preventing seroma, such as prolonged suction drainage, shoulder immobilization, peri-operative use of tranexamic acid, octreotide usage, dressing compression, tissue sealers, etc.; but these methods for the prevention and treatment of seroma remain varied and inconclusive. Seroma may prolong recovery, length of hospital stay, delay the initiation of adjuvant therapy, predispose to wound infection, delay wound healing and has also been linked to arm lymph oedema and enhancement of the health budget.[5][6]

To break this cycle and understand the aetiology of post-operative seroma/lymphorrhea, six studies were carried out that have investigated the composition of axillary drainage fluid.[7-12] Bonnema et al, did a laboratory analysis of 16 patients and came to conclusion that seroma fluid seemed to be a peripheral lymph like fluid.[7] Taydeh et al did a laboratory analysis on 2 patients. He found that the aspirates had the

characteristics of lymph.[8] Watt Boolsen et al studied 27 patients. He found the axillary fluid to be an exudate.[9] McCaul et al studied 18 patients. He however reached the conclusion that axillary fluid is similar in composition to that of inflammatory exudates.[10] Wu et al in 2003 did an analysis on 16 patients concluding that axillary fluid is an exudate.[11] Jain et al in 2004 evacuated 37 cases and found it to be of inflammatory origin.[12]

Hence, two of them found it to be lymph on basis of biochemical and cytological parameters, but the other four found it to be an inflammatory exudate, but none of them have reached a definite consensus about the aetiology and nature of the fluid.

Some recent studies have evaluated the role of cytokines to find the origin of prolonged axillary drainage after axillary lymph node dissection. These studies have used cytokines like IL-β, TNF-α, interferon γ. In general, the level of cytokine increases along with the duration of axillary drainage.[13-15]

MATERIAL AND METHODS

A prospective observational study was undertaken in 30 female patients of carcinoma breast who underwent modified radical mastectomy following tissue diagnosis by fine needle aspiration cytology or Tru-cut biopsy.

Exclusion Criteria

1. Prior axillary surgery
2. Prior axillary radiotherapy
3. Concurrent treatment with skin graft surgery.
4. Simultaneous breast construction surgery.

Initial Workup

All the patients in the study underwent complete physical examination, complete blood count and biochemical tests, ultrasonography of abdomen, chest X-ray and ECG.

METHODS/PARAMETERS TO BE EVALUATED

The Patients Were Evaluated as follows:

1. Estimation of height, weight and Body Mass Index.
2. Preoperative evaluation of patient's blood parameters – complete haemogram, total protein, serum albumin, serum globulin and A:G ratio calculated.
3. Complete lipid profile including cholesterol, triglyceride, LDL, HDL done.
4. Repeat evaluation of all blood parameters as listed at point 2 above were done on post-operative day 5.
5. Axillary drainage fluid evaluation for cell counts, total counts, differential cell counts, proteins, triglycerides and cholesterol on post-operative day 3, 5 and 7.
6. Axillary drain fluid for culture and sensitivity on day 5.
7. The daily axillary drain output, the number of days of drainage and total axillary drainage for each patient were recorded. As the facilities for quantitative measurement of IL-γ, TNF-α and Interleukin 6 are not available in PGIMS Rohtak, so only the above parameters were used for evaluation.

The axillary drain was removed only when the daily drainage was reduced to less than 10 mL/24 hours.

OBSERVATION AND RESULTS

Thirty patients with established diagnosis of breast cancer attending the surgery OPD of Pt. B. D. Sharma Post Graduate Institute of Medical Sciences, Rohtak from November 2011 to January 2014, who underwent modified radical mastectomy with axillary lymph node dissection were included in the study.

PATIENT CHARACTERISTICS

Age

The age of the patients varied between 34 years to 65 years with mean age of 51±6.7 years and median age of 52.5 years. Majority of patients presented in the age group of 41 to 60 years (90%), only 6.7% cases presented before 40 years and 3.3% presented after 60 years signifying incidence of carcinoma breast higher in between 41 to 50 years in the present study [Table 1].

Sex

All 30 patients included in study were females.

Duration of Symptoms

The duration of symptoms varied from 1 month to 12 months with the mean duration of 3.6±2.4 months and median of 3 months; 23 patients (76.7%) noticed lump in last 4 months, 5 patients (16.6%) noticed lump in last 5 months, 2 (6.7%) patients noticed lymph in last 2 months. Above mentioned pie chart signifies that majority of the patients (76.7%) presented within 4 months of onset of symptoms signifying concern on seeking medical advice about the carcinoma breast in the present study. According to GLOBOCAN, high mortality in cases of breast cancer in India was attributed to late presentation, but in our study 76.6% presented within 4 months which can be due to better literacy rate as most of the patients evaluated belonged to urban strata [Table 2].

Menstrual History

The age of menarche ranged between 13-15 years with the mean age of 13 years and 6 months and median age of 14 years. Out of 30 patients, 12 patients (40%) were pre-menopausal and 18 (60%) patients attained menopause (Menopause is defined retrospectively as the time of the final menstrual period followed by 12 months of amenorrhoea, post-menopause describes the period following the final menses) at the time of presentation of lump [Table 3].

Use of Hormonal Pills

None of the patients included in the study had history of intake of oral contraceptive pills and no menopausal patients took hormone replacement therapy.

Family History

None of the thirty cases taken gave history of breast lump or cancer in the first degree and second degree relatives like mothers and sisters.

Body Mass Index

In the study group none of the patient was underweight, 7 (23.3%) patients were in normal BMI group, 7 (23.3%) patients were overweight whereas majority (16 patients/53.3%) were obese according to the Indian guidelines of obesity; [68] However, in accordance to WHO guidelines, [67] none of the patients belonged to the obesity group (BMI >30). This suggests good nutrition status in the present study irrespective of cancer [Table 4].

Tumour Characteristics

Staging of Tumour

On analysis of the T staging of the tumour at presentation, 22 patients (73.3%) belonged to stage T2, 7 (23.3%) belonged to T3 and 1 (3.3%) patient belonged to T4 stage [Table 5].

Axillary Fluid Analysis
After modified radical mastectomy, the operated area was drained using negative suction drain number 14 or 16, one drain was kept below the flap and the other in axilla.

The Parameters Were Assessed and Recorded as Follows
Amount of Axillary Drain Fluid
Total axillary drain output varied between 210 mL to 1100 mL with mean output of 499±229.6 mL and median output of 435 mL. Duration of axillary fluid drainage was between 8 to 10 days with the mean duration of 8.8±1 days and median duration of 8.5 days [Table 6].

Daily Axillary Fluid Output
Axillary fluid output quantified on day 3, 5 and 7. On day 3, the mean output was 59.3 mL, on day 5 was 34.8 mL and 20.3 mL on day 7. This showed a constant decrease in the amount of axillary fluid.

Amount of Total Axillary Fluid with Age
ANOVA test was applied and p value is 0.448 (insignificant). The above table suggests consistent increase in the axillary fluid with increase in age. However, due to small sample size (<5) in 61-70 years, the significance of this interpretation could not be clearly established [Table 7].

Correlation of Axillary Fluid with BMI
14 patients (46.4%) in the study had normal BMI and remaining 13 patients were overweight according to the Indian standard for obesity. ANOVA test was applied and p value is 0.858 (Insignificant) suggesting no association of BMI with axillary drain output in study group. ANOVA test was applied and p value evaluated (p=0.315; insignificant) suggesting no association of BMI with duration of axillary fluid in present study [Table 8].

Correlation of Axillary Fluid Output with T Staging
According to the data collected, mean output of patients in T2 stage was 450.9±226.4 mL, mean output of patients in T3 was 597.8±182.3 mL and mean output of patients in T4 stage was 865 mL. ANOVA test was applied and p value is 0.037 (significant) suggesting a constant increase in the axillary fluid output with increase in T staging [Table 9].

Axillary Fluid Culture and Sensitivity
10 mL of axillary fluid was taken on postoperative day 5 and sent for culture and sensitivity. The fluid culture of all the patients taken for the study was reported sterile.

Pattern of Change in Blood Cells in Axillary Fluid on day 3, 5 and 7
The axillary fluid was taken on post-operative day 3, 5 and day 7 and sent for blood cell count. On day 3, mean number of Red Blood Cells (RBC) in a sample was 1185±205 cells/cu. mm, White Blood Cells (WBC) was 357±16 cells/cu. mm. In that mean of polymorphs was 74±3 cells/cu. mm and lymphocytes was 24±3 cells/cu. mm. On day 5, mean number of red blood cells in a sample was 715±131 cu. mm, White Blood Cells (WBC) was 379±46 cells/cu. mm. In that mean of polymorphs was 64±2 cells/cu. mm and lymphocytes was 34±2 cells/cu. mm. On day 7, mean number of red blood cells in a sample was 234±123 cells/cu. mm, White Blood Cells (WBC) was 264±21 cells/cu. mm. In that, mean of polymorphs 50±1 was cells/cu. mm and lymphocytes was 48±1 cells/cu. mm [Table 10].

ANOVA test was applied and p values of the change in pattern was calculated as <0.05 (Significant). The above data suggests an initial increase in RBC count on day 3, which constantly reduces on day 5 and 7. The WBC count increased on day 5 and reduced on day 7. On evaluation of WBCs, the polymorphs predominated on day 3 and day 5 suggesting inflammatory response to the intervention, whereas on day 7 the polymorphs reduced and the fluid was rich in lymphocytes which increased constantly from day 3, 5 and 7 suggesting the possibility of lymphatic origin.

Pattern of Change in Total Protein, Albumin and Globulin in Axillary Fluid on day 3, 5 and 7
The axillary fluid was taken on post-operative day 3, day 5 and day 7 and biochemical analysis was done to evacuate protein, albumin and globulin in the drain fluid and Albumin-Globulin ratio was calculated. On day 3, the mean total protein was 3.3±0.19 g/dL. On evaluating further, the mean albumin was 2.1±0.07 g/dL and globulin was 1.2±0.7 g/dL. Albumin-to-globulin ratio was calculated. Mean A:G was 1.7±0.13. On day 5, the mean total protein was 2.75±0.07 g/dL. On evaluating further, the mean albumin was 1.6±0.1 g/dL and globulin was 1.2±0.10 g/dL. Albumin-to-globulin ratio was calculated. Mean A:G ratio was 1.4±0.21. On day 7, the mean total protein was 1.73±0.08 g/dL. On evaluating further, the mean albumin was 0.8±0.06 g/dL and globulin was 0.8±0.08 g/dL. Albumin-to-globulin ratio was calculated, mean A:G was 0.99±0.14. [Table 11].

ANOVA test was applied and p values of the change in pattern was calculated p=<0.05 (significant). On day 3, total protein, albumin and globulin had peak levels and showed constant decrease in the values on day 5 and 7 fluid. This suggests that the fluid on day 3, which was rich in protein more towards exudative side probably secondary to inflammatory response; it is the exudative nature which reduced as the fluid was evaluated on day 5 and day 7.

Pattern on Change in Lipid Profile in Axillary Fluid on day 3, 5 and 7
The axillary fluid was taken on post-operative day 3, day 5 and day 7 and biochemical analysis was done to evaluate levels of triglyceride, cholesterol, HDL and LDL. On day 3, the mean triglyceride was 25±2.7 mg/dL, the mean cholesterol level was 51.3±3.9 mg/dL, the mean HDL was 18.2±0.76 mg/dL and mean LDL was 31.3±2 mg/dL. On day 5, the mean triglyceride was 29±2.1 mg/dL, the mean cholesterol level was 59±4.7 mg/dL, the mean HDL was 15±0.81 mg/dL and mean LDL was 40±3.6 mg/dL. On day 7, the mean triglyceride was 34±4.3 mg/dL, the mean cholesterol level was 48±2.2 mg/dL, the mean HDL was 10±0.67 mg/dL and mean LDL was 32±1.3 mg/dL [Table 12].

ANOVA test was applied and p values of the change in pattern was calculated p = <0.05 (significant). The above data suggested that the levels of triglyceride and LDL increased constantly from day 3 to 7, whereas the level of cholesterol in axillary fluid initially increased on day 5 when compared to day 3, but reduced on day 7. However, the level of HDL showed a declining tread on day 3 to 7. Constant increase in triglyceride and LDL levels suggests that the fluid taken for

evaluation on day 7 was rich in lymph when compared to fluid on day 5 than on day 3.

Age Group	Patient	Percentage
31-40	2	6.7%
41-50	12	40%
51-60	15	50%
61-70	1	3.3%
Total	**30**	

Table 1

Duration of Symptoms	Patients	Percentage
1-4 months	23	76.7%
5-8 months	5	16.6%
9-12 months	2	6.7%

Table 2

Menopausal History	Patients	Percentage
Pre-menopausal	12	40%
Menopausal	18	60%

Table 3

BMI (Indian Guidelines)	Patients	Percentage
<18.5 kg/m^2	0	0
18.5-22.9 kg/m^2	7	23.3%
23.0-24.99 kg/m^2	7	23.3%
>25 kg/m^2	16	53.3%

Table 4

T Stage	Patients	Percentage
T2	22	73.3%
T3	7	23.3%
T4	1	3.3%

Table 5

	Mean	Median	Range
Day 3	59.3 mL	65 mL	30-90 mL
Day 5	34.8 mL	30 mL	15-90 mL
Day 7	20.3 mL	20 mL	10-40 mL

Table 6

Age	Patients	Fluid Amount
31-40	2	327.50±60.104
41-50	12	555.67±251.480
51-60	15	564.33±221.060
61-70	1	670.00
Total	**30**	**499.00±229.649**
P value		0.448

Table 7

BMI (kg/m^2)	Patients	Output	Duration
18.5-22.99	7	457.86±212.6	9.0±1
23.0-24.99	7	525.00±141.7	9.3±0.9
>25	16	505.63±273.2	8.6±1.1
Total	30	499.00±229.6	8.8±1.1
P value		0.858	0.315

Table 8

T Stage	Patients	Drain Output
T2	22	450.9±226.4
T3	7	597.8±182.3
T4	1	865
Total 30	**30**	**499.00±229.6**
P value		0.037

Table 9

	RBC	WBC	Polymorph	Lymphocyte
Day 3	1185±205	357±16	74±3	24±3
Day 5	715±131	379±46	64±2	34±2
Day 7	234±123	264±21	50±1	48±1
P Value	<0.05	<0.05	<0.05	<0.05

Table 10

	Total Protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)	A:G
Day 3	3.3±0.19	2.1±0.07	1.2±0.7	1.7±0.13
Day 5	2.75±0.07	1.6±0.1	1.2±0.10	1.4±0.21
Day 7	1.73±0.08	0.8±0.06	0.8±0.08	0.99±0.1
P value	<0.05	<0.05	<0.05	<0.05

Table 11

	Triglyceride (mg/dL)	Cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Day 3	25±2.7	51.3±3.9	18.2±0.76	31.3±2
Day 5	29±2.1	59±4.7	15±0.81	40±3.6
Day 7	34±4.3	48±2.2	10±0.67	32±1.3
P value	<0.05	<0.05	<0.05	<0.05

Table 12

DISCUSSION

Modified radical mastectomy forms the mainstay of the management of carcinoma breast. Prolonged axillary fluid drainage following axillary lymph node dissection is the most common sequelae (30%), which delays the recovery, makes the patient prone for local infection and prolongs the hospital stay enhancing the health budget. Hence, a prospective study was carried out to understand the composition and change in pattern of axillary fluid.

In India due to lack of awareness, health education and unavailability of effective screening programmes, 70% of the patients present at the locally advanced stage. However, in our study 73% patients presented in T2 stage suggesting good awareness/concerns on seeking medical advice about the disease.

In our study group, the mean BMI of the patient was 25.1 kg/m^2. Its association with total axillary fluid was quantified using ANOVA test. The p value was 0.858, which is insignificant. There is no association of BMI with the amount of axillary fluid and duration of output. This finding is in contrast to findings of Douay N et al, who reported BMI as an important high risk factor in patients who developed prolonged axillary drainage.

The age of presentation of the patients in our study group was between 34 years to 65 years with the mean age of 51±6.7 years and median age of 52.5 years. It was observed that the axillary fluid output increased constantly with increase in age, but the p value of the study was insignificant (p=0.448). The insignificance of this data could be attributed to the small sample size in group (61-70 years). This finding was consistent with the study conducted by Burak W.E. Jr. et al and Menton M. et al and Wings et al who concluded age as very important risk factor associated with prolonged axillary drainage. However, a study conducted by Unalp H.R. et al

advocated no relationship between the age of patient and the axillary drain output.

In our study, 73.3% patients presented in T2 stage. This suggests early reporting to the medical facility due to good awareness, possibly because of better literacy rate and large number of patients belonging to urban profile. When the drain output was compared with the T staging, it was found that the drain output increased consistently with increase in T stage of the patient with the p value of 0.037 (significant). Hence, our study is in line with the association of T stage with the axillary output, which is also in line with the study conducted by Lumchi F. et al, which reported tumour size as a risk factor for prolonged axillary drainage.

On analysing the biochemical and cytological parameters of axillary fluid, it was found that the predominant cells in the axillary fluid (After red blood cells) were polymorphs (Neutrophils = 74 on day 3 and 64 on day 5) suggesting that the axillary drain fluid is an exudate and not lymph. Moreover, high value of total protein (Day 3 = 3.3 g/dL and Day 5 = 2.75 g/dL) supports the above hypothesis. Also the value of cholesterol (Day 3 = 59.3 mg/dL and Day 5 = 53 mg/dL) (as done in 17 patients) and persistent rise in LDL levels further strengthens the finding that axillary fluid is inflammatory in origin that arises during the initial phase of wound repair.

However, on day 7, the lymphocytes (n=48) dominated the axillary fluid cytology with constant reduction in total protein. This suggests that the overriding inflammation related to surgical trauma abates by seventh day and only lymphatic fluid drainage remains to be drained. By this observation, it can be deduced that if the inflammatory fluid is prolonged by seventh day, then the patient needs to be evaluated for the cause and treatment needs to be considered depending upon the cause. The constant rise of triglycerides in fluid also favours the above finding about the Day 7 fluid.

Hence, the study clearly indicates that axillary fluid is inflammatory to start with, but later only lymphatic fluid is found if drainage is prolonged. Measures to reduce the initial phase of inflammation can be adapted by use of anti-inflammatory drugs in the initial post-operative period. Halstead advocated use of interrupted suture between skin and fascia to obliterate the dead space. However, the use of compression bandage on flap and axilla or use of fibrin glue, tissue adhesive and sclerosing agents may help obliterate the space and reduction of lymph in free space, which may be coupled with limiting the use of upper limb to reduce the afferent lymph from upper limb.

CONCLUSION

Axillary fluid is inflammatory in origin up to day 5. On day 7, the inflammation abates and the fluid becomes lymphatic. Prolonged axillary drainage has no relation to BMI.

REFERENCES

1. Chopra R. The Indian scene. J Clin Oncol 2001;19(18):106S-111S.
2. Dees EC, Shulman LN, Souba WW, et al. Does information from axillary dissection change the treatment in clinically negative patients with breast cancer? an algorithm for assessment of impact of axillary dissection. Ann Surg 1997;226(3):279-86.
3. Reimer T, Fitkaub R, Markmann S, et al. How important is axillary node status for adjuvant treatment decisions at a breast cancer multidisciplinary tumour board? a survival analysis. Ann Surg Oncol 2008;15(2):472-7.
4. Schultz I, Barholm M, Grondal S. Delayed shoulder exercises in reducing seroma frequency after modified radical mastectomy: a prospective randomized study. Ann Surg Oncol 1997;4(4):293-7.
5. Banerjee D, Williams EV, Ilott J, et al. Obesity predisposes to increased drainage following axillary node clearance: a prospective audit. Ann R Coll Surg Engl 2001;83(4):268-71.
6. Chow LW, Loo WT, Yuen KY, et al. The study of cytokine dynamics at the operation site after mastectomy. Wound Repair Regen 2003;11(5):326-30.
7. Bonnema J, Lightenstein DA, Wiggers T, et al. The composition of serous fluid after axillary dissection. Eur J Surg 1999;165(1):9-13.
8. Tadych K, Donegan WL. Post mastectomy seroma and wound drainage. Surg Gynaeco Obstet 1987;165(6):483-7.
9. Watt Boolson S, Nielsen VB, Jensen J, et al. Post mastectomy seromas a study of nature and origin of seromas after mastectomy. Dan Med Bull 1989;36(5):487-9.
10. McCaul JA, Aslaam A, Spooner RJ, et al. Aetiology of seroma formation in patients undergoing surgery for breast cancer. Breast 2000;9(3):144-8.
11. Wu FP, Hoekman K, Meijer S, et al. VEGF and endostatin levels in wound fluid and plasma after breast surgery. Angiogenesis 2003;6(4):255-7.
12. Jain PK, Sowdi R, Anderson AD, et al. Randomized clinical trial investigating the use of drains and fibrin sealant following surgery for breast cancer. Br J Surg 2004;91(1):54-60.
13. Baker EA, Kumar S, Melling AC, et al. Temporal and quantitative profiles of growth factors and metalloproteinases in acute wound fluid after mastectomy. Wound Repair Regen 2008;16(1):95-101.
14. Folkman J. Endogenous angiogenesis inhibitors. APMIS 2004;112(7-8):496-507.
15. Loo WT, Sasano H, Chow LW. Pro-inflammatory cytokine, matrix metalloproteinases and TIMP-1 are involved in wound healing after mastectomy in invasive breast cancer patients. Biomed Pharmacother 2007;61(9): 548-52.