

Original Research Article

Correlation between C-reactive protein, intravenous hydrocortisone, systemic tranexamic acid and post mastectomy seroma

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ABSTRACT

Background: Breast cancer is the second leading cause of death among women worldwide. Formation of a seroma most frequently occurs after mastectomy and axillary surgery. The objective was to find the correlation between the formation of post modified radical mastectomy seroma and C-reactive protein (CRP) and the effect of preoperative intravenous (IV) hydrocortisone, systemic tranexamic acid.

Methods: This prospective study was conducted at Menoufia university hospital on female patients with primary operable breast cancer who were divided to two groups; each included 30 patients: group I received general anesthesia with hydrocortisone therapy (Solu-Cortef 100 mg solution once), systemic tranexamic acid (kapron 5 ml once) and group II received general anesthesia without hydrocortisone nor tranexamic acid. CRP serum levels before surgery and 24 hour after the procedure. All patients were followed up postoperatively for registration of the total drainage volume until drain removal, timing of drain removal, incidence of seroma formation and management of seroma.

Results: Our results revealed that a significant difference between both groups as regard CRP, the incidence of seroma, time of removing the drain and total collection of the drain in favor to those who received IV hydrocortisone and systemic tranexamic acid.

Conclusions: Induction of IV hydrocortisone, systemic tranexamic acid with general anaesthesia during modified radical mastectomy (MRM) are significantly decreasing the level of CRP, the incidence of seroma, time of removing the drain and total collection of the drain.

Keywords: CRP, Hydrocortisone, Mastectomy, Seroma, Tranexamic acid

INTRODUCTION

Breast cancer is the second leading cause of death among women worldwide. Surgical treatment of breast cancer is breast conservative surgery (BCS) or modified radical mastectomy (MRM) with axillary lymph node dissection (ALND). The most frequent postoperative complication of MRM and ALND is seroma formation. The seroma formation especially its duration affects the postoperative adjuvant therapy as well as renders the patient prone for nosocomial infections.¹

Seroma is caused by lymphatic channel disruption and the formation of a large space between the deep fascia during flap elevation. Several factors have been detected in seroma fluid that support this assumption. These factors are high levels of IgG, leukocytes, granulocytes, proteinases, proteinase inhibitors and different kinds of cytokines.²

Seroma formation increases chances of infection, delays wound healing, flap necrosis, persistent pain, dehiscence of the wound and thus prolong the convalescence period.³

With the steep increase in breast cancer incidence globally and regionally, there has been a trend toward reducing patient morbidity by meticulous surgical techniques to obviate complications like seroma formation; use to pre-operative steroids seems to be convenient, cost effective and shows promising results in trials.⁴

Many efforts have been put worldwide to reduce the chances and duration of seroma formation. The body mass index, use of electrocautery for dissection, early drain removal, low vacuum drains, obliteration of dead space and delayed shoulder physiotherapy are most of the hypothesized method but consensus is still lacking and seroma continues to remain a risk to both the surgeon and patients.⁵

Surgical techniques to preserve the lymphatics and secure the closure of the donor site can reduce seroma formation.⁶

Our study was established to find the correlation between the formation of post MRM seroma and CRP and the effect of preoperative intravenous hydrocortisone, systemic tranexamic acid.

METHODS

Study design

The study design was a randomized controlled trial (RCT).

Study setting

This study was conducted at El-Menoufia university hospital.

Study period

The study period was from January 2020 to April 2021.

Ethical consideration

Ethical scientific committee of Menoufia university approved the study protocol and informed consent was taken from the patients before their enrollment in the study.

Sample size

Minimum sample size calculated was 54 females with breast cancer according to,

$$n \geq \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (\sigma_1^2 + \sigma_2^2/r)}{(\mu_1 - \mu_2)^2},$$

where,

n=sample size,

$Z_{1-\alpha}$ =Z score for CI 95% and equals 1.96,

$Z_{1-\beta}$ =Z score for power of the study 80% and equals 0.84,

σ =estimated standard deviation:estimated mean.

Total sample size required was 60 females with breast cancer after adding 6 females for drop-out rate (drop-out rate equals 10% of calculated sample size). This sample was divided into two equal groups.

The cases were divided into two groups: group I, patients received general anesthesia with hydrocortisone therapy (SoluCortef 100 mg solution once), systemic tranexamic acid (kapron 5 ml once); group II, patients received general anesthesia without hydrocortisone nor tranexamic acid.

Inclusion criteria

Female patient with operable cancer breast prepared for MRM was included in the study.

Exclusion criteria

Patients with recurrent breast lesion, breast reconstruction, conservative breast surgery and patients receive neo-adjuvants therapy were excluded from the study.

Methodology

Preoperative

All our patients were females and had undergone detailed history was taken and general and local examination; preoperative imaging and laboratory workup were done.

Venous samples were collected 24 hour before the procedure and for measuring CRP serum levels before surgery.

Operative

Drug induction: Patients received general anesthesia with hydrocortisone therapy (Solu-Cortef 100 mg solution once), systemic tranexamic acid (kapron 5 ml once).

The operation: MRM was done.

Postoperative

Postoperative medical treatment

CRP was measured 24 hours after surgery. The drainage was observed every 12 hours and measured the output. Antibiotics, anti-inflammatory (IV hydrocortisone),

sedatives and treatment of postoperative hemorrhage (tranexamic acid) were given.

Outcome within one month

Complications like prolonged drainage state, wound infection were there. Length of stay in hospital due to seroma formation.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean±standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: independent-samples t test of significance was used when comparing between two means. Chi-square (χ^2) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and

the margin of error accepted was set to 5%. So, the p value was considered significant as the following: probability (p value): $p < 0.05$ was considered significant.

RESULTS

On comparison between CRP preoperative and CRP postoperative our results showed that, in group I, CRP decreased with a median from 0.84 mg/l to 0.76 mg/l. In group II, CRP increased with a median from 0.86 mg/l to 0.88 mg/l, with statistically significant difference ($p < 0.001$) (Table 1).

As regard seroma incidence among studied patients, our results reported that there was statistically significant difference between studied groups as 70% of group I and 43.3% of in group II had seroma, ($p < 0.037$) (Table 2).

Our results showed statistically significant in postoperative follow up of studied groups, regard time of removing the drain and total collection of the drain, ($p < 0.010$) (Table 3).

Table 1: Preoperative and postoperative CRP in studied groups.

CRP		Preoperative n=30	Postoperative n=30	t test	P value
Group I	Mean±SD	0.84±0.03	0.76±0.05	8.08	<0.001**
	Range	0.76-93	0.64-0.87		
	Median	0.84	0.76		
Group II	Mean±SD	0.85±0.03	0.88±0.10	6.91	<0.001**
	Range	0.77-0.94	0.80-0.96		
	Median	0.86	0.88		

Group I=patient received hydrocortisone therapy and systemic tranexamic acid; group II=patient not received hydrocortisone therapy and systemic tranexamic acid; **high-significant t=paired t test.

Table 2: Seroma incidence among studied patients.

Seroma	Group I; n= 30		Group II; n=30		χ^2	P value
	N	%	N	%		
Presence	9	30	17	56.7	4.34	0.037*
Absent	21	70	13	43.3		

χ^2 =Chi-square test; *significant.

Table 3: Postoperative follow up of studied groups.

Postoperative follow up	Group I; n=30	Group II; n=30	t test	P value
Drain removal in days				
Mean±SD	9.6±2.13	11.2±2.41	2.65	0.010*
Range	6-13	7-15		
Median	10	11		
Total drain collection (cc)				
Mean±SD	1229.3±196.8	1696.5±182.1	9.5	<0.001**
Range	1000-1750	1200-1880		
Median	1135	1745		

Group I=patient received hydrocortisone therapy and systemic tranexamic acid; group II=patient not received hydrocortisone therapy and systemic tranexamic acid; t=Student's t test; *significant; **high significant.

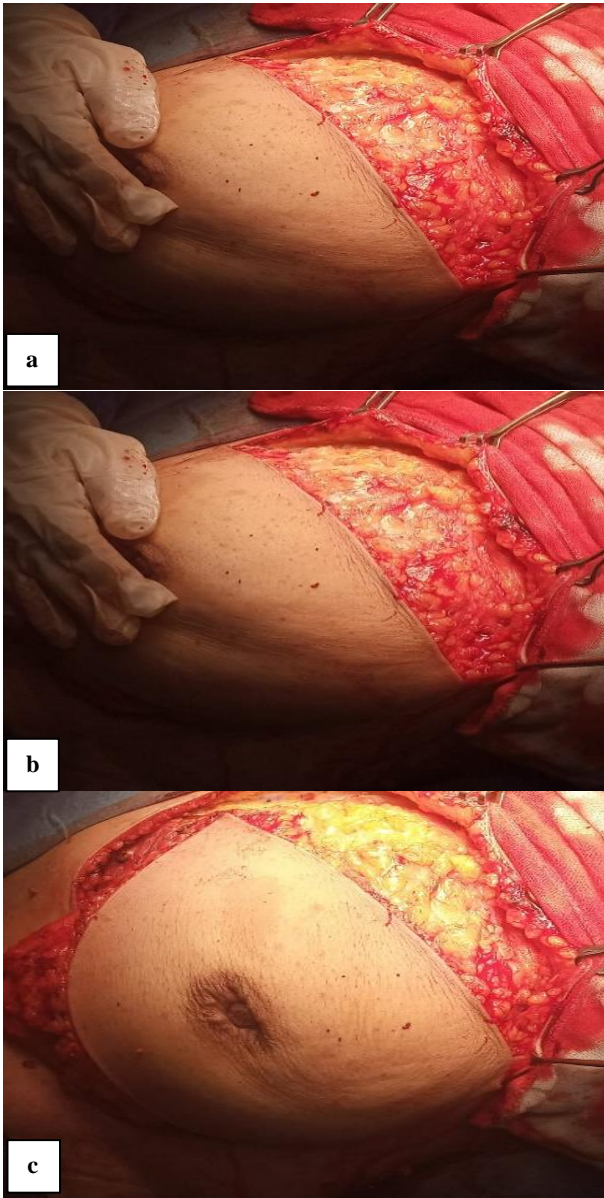


Figure 1 (a-c): Dissection of the lower flap of the breast.



Figure 2: Subcutaneous closure of the incision in the breast.

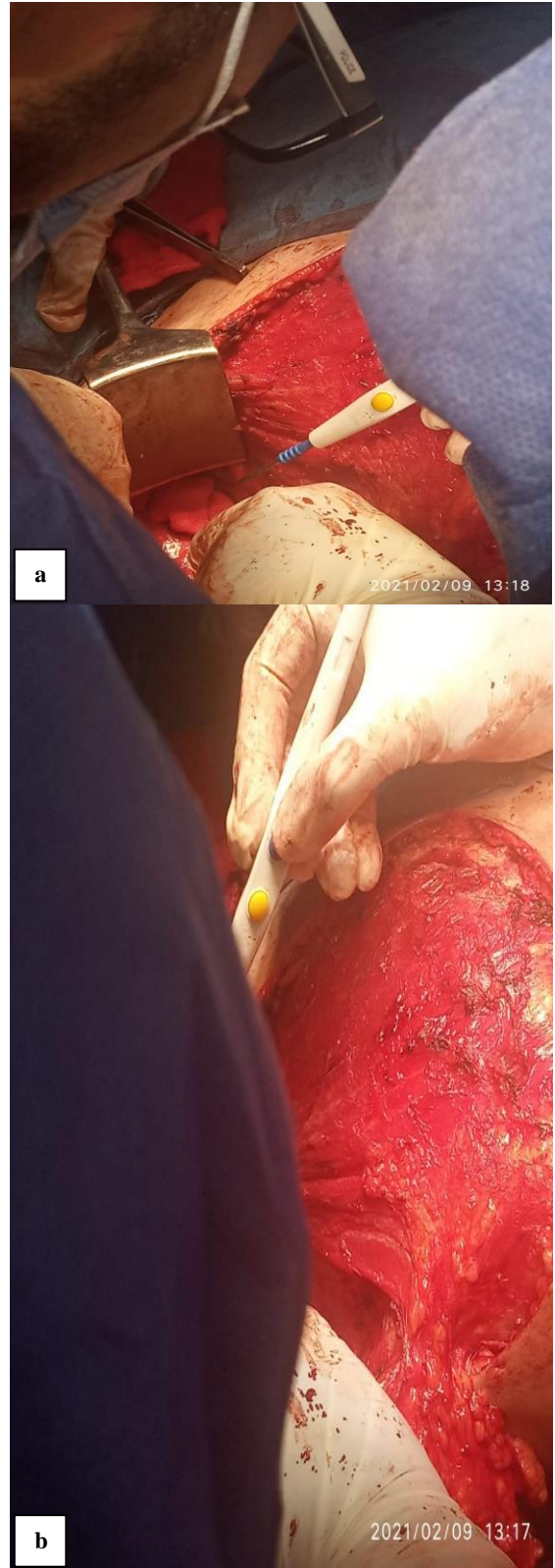


Figure 3 (a and b): Exploration of the axilla.

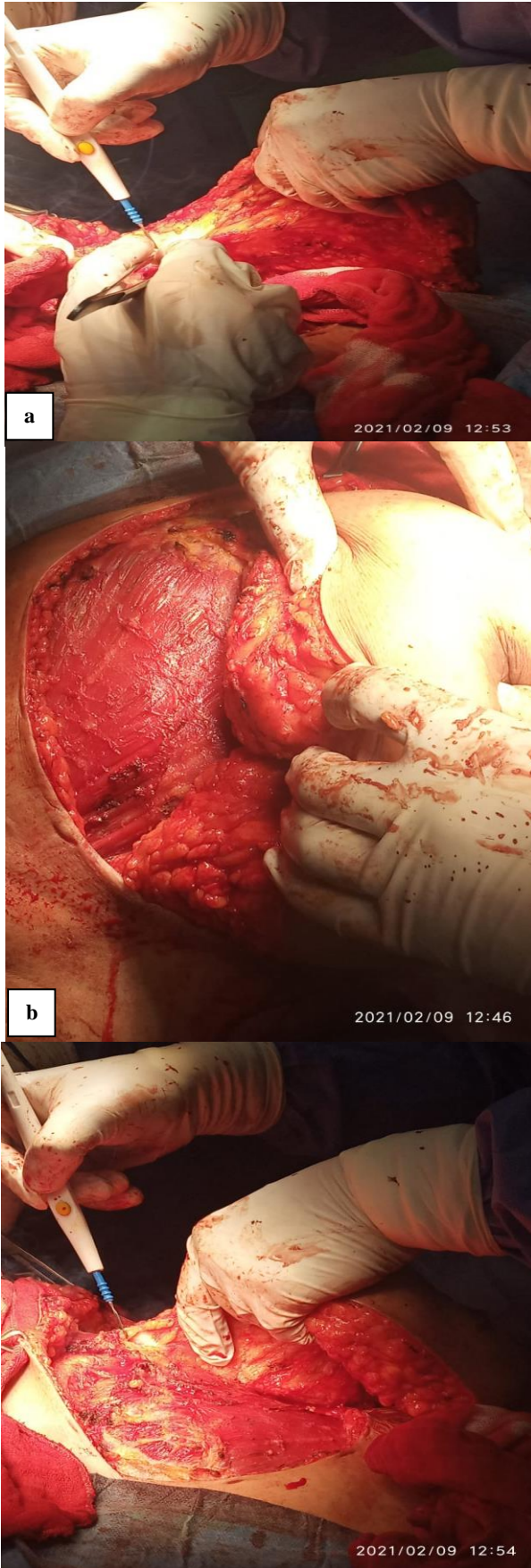


Figure 4 (a-c): Dissection of the upper flap of the breast.

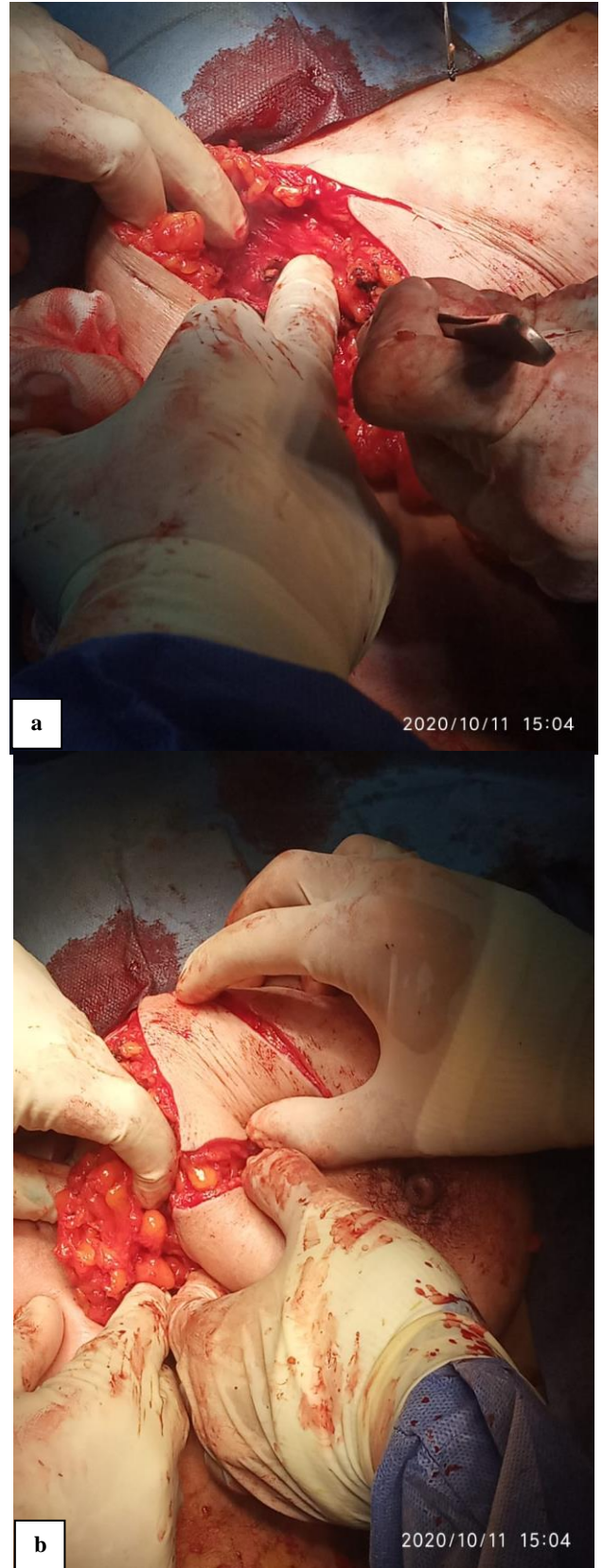


Figure 5 (a and b): Targeting of the malignant mass in the breast.



Figure 6: Dissection of the mammary glands for exploration of the axilla.

DISCUSSION

Seroma is extremely common after breast surgery and this could be because of the inflammatory response during wound healing. Several factors such as CRP had been detected in the seroma fluid that supports this assumption; therefore, inhibition of the inflammatory response by using hydrocortisone might decrease seroma formation.⁷

Seroma occurred in a range of 10 to 85% of the cases, which may be responsible for an increased morbidity by complications like disunity of surgical flap, infection and delay in administering adjuvant therapies.⁸

Systemic tranexamic acid as an antifibrinolytic agent may control fluid accumulation in the dead space under the skin flaps and in the axillary fossa after mastectomy.⁹

As regard seroma, in our study (60 cases), it occurred in 9 cases (30%) in patients who received IV hydrocortisone therapy and systemic tranexamic acid (30 cases) and occurred in 17 cases (56.7%) in patients who didn't receive IV hydrocortisone therapy and systemic tranexamic acid (30 cases). There was a significant difference between both groups, ($p < 0.037$).

Similarly, Qvamme et al reported that hydrocortisone administration significantly reduce the duration of seroma formation (46% of cases presented by seroma), number of aspirations, mean seroma volume, total cumulative seroma volume.¹⁰ In addition, Shyamsundar had the same

results that injection of hydrocortisone significantly reduced seroma formation.¹¹

A retrospective cross-sectional study by Hashemi et al on 158 patients who underwent surgical therapy for breast cancer with either MRM or breast preservation (BP) was carried out.¹² Seventy three percent underwent MRM and the remaining 27% received BPS. Seroma occurred in 35% of patients. In multivariate logistic regression analysis an association of postoperative seroma formation was noted with modified radical mastectomy ($p < 0.04$).

In an observational study, 150 patients who underwent breast surgery at the university hospital of Örebro, their charts were studied in order to extract the clinical information. The incidence of seroma following breast surgery was 49% (74/150 patients). A statistically significant association was found between seroma formation and MRM ($p < 0.009$), a study done by Andersson et al.¹³

However, in another study Pan et al found that a total of 72 patients (70%) developed seroma postoperatively and they were all treated with aspiration.¹⁴ A statistically significant association was found between seroma formation and MRM (72/102 patients) ($p < 0.008$).

The difference between our study and the last three studies was that patients in their study didn't receive hydrocortisone nor tranexamic acid. Also, in Hashemi et al study, patients were followed up with a chemotherapy, although our patients didn't receive chemotherapy.¹²

As regard mean amount of drain output, in our study (60 cases), it resulted in a mean \pm SD was 1229.3 \pm 196.8 and a median 1135 cc in patients who received systemic tranexamic acid and resulted in a mean \pm SD 1696.5 \pm 182.1 and a median 1745 cc in patients who didn't receive systemic tranexamic acid. There was a highly significant difference between the two groups, ($p < 0.001$).

In a similar study Knight et al results showed that perioperative and postoperative administration of systemic tranexamic acid 1 gm 3 times daily resulted in a significant reduction in the mean postoperative drainage volume (from 1800cc to 1200 cc) ($p < 0.001$).¹⁵

Eldesouky et al made a prospective COHORT study on 115 patients with breast cancer who underwent MRM.⁹ Topical tranexamic acid was used to moisten the area in some patients to assess its effect on total wound drainage and seroma formation in follow up period of 1 month. The mean amount of wound drainage was significantly lower in the study group as compared with the control group (798.06 \pm 107.3 versus 1067.1 \pm 188.6 ml; $p < 0.005$).

Similarity between our study and Eldesouky et al COHORT study was that applying tranexamic acid as a systemic or topical can reduce the incidence of seroma and decrease the total amount of drainage. In our study

addition of IV hydrocortisone increased the inhibitory effect tranexamic acid in (the formation of seroma, total amount of drainage, postoperative level of CRP).

In our study CRP decreased with a median from 0.84 mg/l to 0.76 mg/l in patients who received IV hydrocortisone therapy and systemic tranexamic acid however CRP increased with a median from 0.86 mg/l to 0.88 mg/l in patients who didn't receive IV hydrocortisone therapy and systemic tranexamic acid. There was a highly significant difference between the two groups, ($p < 0.001$).

In accordance, Talha et al made a study on 80 female patients.⁷ Postoperative serum levels of IL-6 and CRP showed a significant decrease in patients who received general anesthesia with hydrocortisone (40 patients) compared with patients who didn't receive general anesthesia with hydrocortisone (40 patients), ($p < 0.001$).

However, in Karunanithi et al study, CRP remained stable in the serum for at least 3 days at 15-25°C.¹⁶ The measuring range of CRP was 0-220 mg/l, the normal value of CRP being < 5 mg/l. A significant difference in serum CRP levels between patients with lymph node metastasis and those without lymph node metastasis ($p < 0.001$). The median levels of CRP increased with increasing stage and also noted significant differences between the CRP level and cancer stage.

Kozomara et al showed that there was a statistically significant increase in the levels of CRP (5.97 mg/l) compared to preoperative values (3.24 mg/l).¹⁷ Levels of CRP of patients statistically increased rapidly after operation (58.74 mg/l), continued to grow even 48 hours after surgery (96.37 mg/l) and 72 hours after surgery reach its maximal values (112.74 mg/l) ($p < 0.001$).

Also, in another study was done by O'Riain et al 30 women with biopsy-proven breast cancer requiring mastectomy with axillary node clearance were enrolled in a prospective, randomized study, to receive general anesthesia (GA) and postoperative opioid patient-controlled analgesia (PCA) (GA group) or combined GA and paravertebral anesthesia with continuous postoperative paravertebral analgesia (GA-PVAA group). The group GA-PVAA had lower serum cortisol and CRP at 4 hours than group GA (322±152 versus 544±216 µmol/l, respectively, $p < 0.006$). There were no significant differences in glucose or cortisol at 24 hours. CRP, however, was increased in the GA group at 4 hours and 24 hours compared with the GA-PVAA group (4 hours: 5.7±2.9 versus 2.6±1.5, $p < 0.002$; 24 hour: 30.0±7.2 versus 23.3±6.0, $p < 0.04$, respectively), a study done by O'Riain et al.¹⁸

The difference explained their level of CRP was increased postoperatively, was that patients in their study weren't given IV hydrocortisone and systemic tranexamic

acid with the induction of general anesthesia and before the surgery.

Regarding to time length for the drain in our study drain time length in days ranges from 6-13 days with a median 10 days in patients who received IV hydrocortisone therapy and systemic tranexamic acid however drain time length in days ranges from 7-15 days with a median 11 days in patients who didn't receive IV hydrocortisone therapy and systemic tranexamic acid. There was a significant difference between two groups, ($p < 0.010$).

Uslukaya et al reported that there was a positive correlation between the histopathologic features of the tumor, size of removed breast tissue (BS), tumor size (TS), number of totally removed lymph nodes (TLN) and metastatic lymph nodes (MLN) and the drain indwelling time (DIT).¹⁹

Similarly, Eldesouky et al found that the mean duration of drainage was also lower in the study group as compared with the control group (9.85±1.66 versus 11.67±1.9 days; $p < 0.005$); this difference was significant.⁹

However, in Barwell et al study, suction drains were removed at the ward after a median of 4 days (range 1-7 days) for wide local excision of breast carcinoma and the median of suction drain removing for mastectomy with axillary dissection was about 12 days (range 10-14 days).²⁰

Compared to Barwell et al who made a study on 63 patients after wide local excision of breast carcinoma with axillary dissection, the difference was due to their patients had wide local excision of breast carcinoma, however in our study patients underwent MRM.²⁰ Also in their study, their patients didn't receive IV hydrocortisone nor tranexamic acid with GA.

On comparison short-term versus long-term axillary drainage in women treated for lymph node positive breast cancer. Andeweg et al reported that, the short-term drainage group consisted of 37 patients and the long-term drainage group of 40 patients.²¹ Overall incidence of seroma formation was 40% and more frequently in the short-term drainage group ($p < 0.01$).

However, a study was done to determine the impact of adopting a no drains policy on symptomatic seroma formation rates.

Taylor et al in their study on 247 women who underwent MRM and axillary LN Dissection (group 1), 184 MRM±sentinel lymph node biopsy (SLNB)/axillary node sampling (ANS) (group 2) and 165 ALND±WLE (group 3).²² Within each group, the presence or absence of a drain did not find a significant difference between three groups in the rate of incidence of seroma, wound

infection rates. In all three groups, the presence of a drain was associated with a longer hospital stay ($p < 0.001$).

Limitations

We exclude patients with breast reconstruction, conservative breast surgery, patients who received neo-adjuvants therapy. As they didn't undergo a MRM and the percentage of seroma formation in these cases was less than what we expected from MRM.

In our study we tried to observe the efficiency of IV hydrocortisone and systemic tranexamic acid on seroma formation which was clearly occur after MRM.

CONCLUSION

Induction of IV hydrocortisone, systemic tranexamic acid with GA during MRM may significantly decrease the level of CRP, the incidence of seroma, time of removing the drain and total collection of the drain.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Abass MO, Gismalla MDA, Alsheikh AA, Elhassan MMA. Axillary lymph node dissection for breast cancer: efficacy and complication in developing countries. *J Glob Oncol.* 2018;4:1-8.
2. Srivastava V, Basu S, Shukla VK. Seroma formation after breast cancer surgery: what we have learned in the last two decades. *J Breast Cancer.* 2012;15(4):373-80.
3. Suresh BP, Sachin HG, Naidu M, Gopalkrishna V. A study to evaluate the factors influencing seroma formation after breast cancer surgery at tertiary care centre. *Int Surg J.* 2018;6(1):278-82.
4. Khan MA. Effect of preoperative intravenous steroids on seroma formation after modified radical mastectomy. *J Ayub Med Coll Abbottabad.* 2017;29(2):207-10.
5. Szecei BP, Larsen J, Horby J, Axelsson CK. Seroma production after breast cancer surgery has a pro-inflammatory component. *Open Breast Cancer J.* 2012;4(1):11-7.
6. Suh YC, Oh TM, Lee YH, Kim EK, Han HH, Eom JS. Effects of hydrochlorothiazide on drainage volume and seroma formation in deep inferior epigastric perforator flap breast reconstruction:

- Randomized controlled trial. *J Plast Reconstr Aesthet Surg.* 2020;73(4):663-72.
7. Talha A, Ramadan R, Abdelhamid S, Hamdi S. Postmastectomy seroma: how much is it affected by serum levels of IL-6 and CRP and how much is it reduced by intravenous hydrocortisone injection?. *Egypt J Surg.* 2015;34(1):17-21.
8. Douay N, Akerman G, Clement D, Malartic C, Morel O, Barranger E. Seroma after axillary lymph node dissection in breast cancer. *Gynecologie Obstetrique Fertilité.* 2008;36(2):130-5.
9. Eldesouky MS, Ashour HS, Shahin MA. Effect of topical application of tranexamic acid on reduction of wound drainage and seroma formation after mastectomy. *Egypt J Surg.* 2019;38(4):772.
10. Qvamme G, Axelsson CK, Lanng C, Mortensen M, Wegeberg B, Okholm M, et al. Randomized clinical trial of prevention of seroma formation after mastectomy by local methylprednisolone injection. *Brit J Surg.* 2015;102(10):1195-203.
11. Shyamsundar R. A study on local injection of methylprednisolone acetate to prevent seroma formation after mastectomy. *Madras Med Coll.* 2020.
12. Hashemi E, Kaviani A, Najafi M, Ebrahimi M, Hooshmand H, Montazeri A. Seroma formation after surgery for breast cancer. *World J Surg Oncol.* 2004;2(1):1-5.
13. Andersson VJ. Seroma formation following breast surgery-incidence and risk factors. *Örebro Univ Sch Med.* 2016.
14. Pan XF, Huan JL, Qin XJ. Potential risk factors for the development of seroma following mastectomy with axillary dissection. *Mol Clinic Oncol.* 2015;3(1):222-6.
15. Knight H, Banks J, Muchmore J, Ives C, Green M. Examining the use of intraoperative tranexamic acid in oncological breast surgery. *Breast J.* 2019;25(5):1047-9.
16. Ravishankaran P, Karunanithi R. Clinical significance of preoperative serum interleukin-6 and C-reactive protein level in breast cancer patients. *World J Surg Oncol.* 2011;9(1):1-6.
17. Kozomara D, Galić G, Brekalo Z, Šutalo N, Kvesić A, Šoljić M. A randomised two-way comparison of mastectomy performed using harmonic scalpel or monopolar diathermy. *Collegium Antropologicum.* 2010;34(1):105-12.
18. O'Riain SC, Buggy DJ, Kerin MJ, Watson RW, Moriarty DC. Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2. *Anesth Analg.* 2005;100(1):244-9.
19. Uslukaya Ö, Türkoğlu A, Gümüş M, Bozdağ Z, Yılmaz A, Gümüş H, et al. Factors that affect drain indwelling time after breast cancer surgery. *J Breast Health.* 2016;12(3):102.
20. Barwell J, Campbell L, Watkins RM, Teasdale C. How long should suction drains stay in after breast

surgery with axillary dissection?. *Ann Royal Coll Surg England.* 1997;79(6):435.

21. Andeweg CS, Schriek MJ, Heisterkamp J, Roukema JA. Seroma formation in two cohorts after axillary lymph node dissection in breast cancer surgery: does timing of drain removal matter? *Breast J.* 2011;17(4):359-64.
22. Taylor JC, Rai S, Hoar F, Brown H, Vishwanath L. Breast cancer surgery without suction drainage: the

impact of adopting a 'no drains' policy on symptomatic seroma formation rates. *European J Surg Oncol (EJSO).* 2013;39(4):334-8.

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