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COMPARATIVE STUDY ON THE ROLE AND EFFICACY OF COUMARIN DERIVATIVES AND OCREOTIDE IN THE REDUCTION OF SEROMA IN POST OP MODIFIED RADICAL MASTECTOMY PATIENTS

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ABSTRACT:

OBJECTIVES: Breast cancer, with an annual incidence of 2.1 million new cases, is one of the most prevalent carcinomas worldwide. Breast cancer treatment entails the use of surgery, radiotherapy as well as chemotherapy. However while treating for breast cancer, complications are an inevitable occurrence of which post operative seroma is an issue for all patients and practitioners. Hence the key objective of this study aims to investigate, compare and determine any significant differences in seroma formation following the administration of octreotide and coumarin derivatives in postoperative Modified Radical Mastectomy (MRM) patients.

METHODS: This single-center cross-sectional study was conducted in the Department of General Surgery at Saveetha Medical College Hospital. 50 breast carcinoma patients who met the study criteria and underwent MRM from June 2023 to June 2024 were taken up for the study. After detailed history, examination and necessary investigations, these patients were divided into two groups of 25, each

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receiving one of the study drugs. Parameters analyzed included age, diagnosis, drug adverse reactions, discharge day, drain collection volume and drain duration.
RESULTS: The study demonstrates that elderly patients were the most common group involved. The study findings indicate that both Tablet Lympedim and Injection Octreotide are effective in managing postoperative conditions in breast carcinoma patients. However, Tablet Lympedim was associated with earlier drain removal and discharge, suggesting a potential advantage in terms of recovery time. The safety profiles of both drugs were similar, with no significant difference in the rate of adverse reactions.

KEY WORDS: Breast carcinoma, Modified radical mastectomy, seroma, post operative complications

INTRODUCTION

Breast cancer is the second cancer type in women, taking 26% of all female cancers not including non-melanoma skin and in situ cancers. Breast cancer treatment involves surgery, radiotherapy and chemotherapy. Breast conserving surgery, simple mastectomy skin sparing mastectomy, Patey's Modified radical mastectomy (MRM), Scanlon MRM, Auchincloss MRM and Halstead radical mastectomy are the methods of handling invasive breast carcinoma. Given, there are the following possibilities of radiotherapy, brachytherapy, intensity- modulated radiotherapy with or without axillary dissection. Post treatment complications are inevitable, with postoperative seroma remaining the most common challenge for both patients and practitioners. Hence, this study addresses one of the most important and troublesome complications viz seroma formation post mastectomy and the various risk factors which predispose to their occurrence, in patients who underwent MRM in our institution.

MATERIALS AND METHODOLOGY

The research conducted was a single center cross-sectional study. It was conducted in the Department of General Surgery, Saveetha Medical College Hospital, Thandalam. Overall out of 96 breast carcinoma patients who underwent modified radical mastectomy from June 2023 to June 2024, 50 patients between 40 -70 years were included in this study after the exclusion criterias were applied. A detailed history, physical examination of the patient, followed by routine blood analysis, radiological and histopathological investigations was done.

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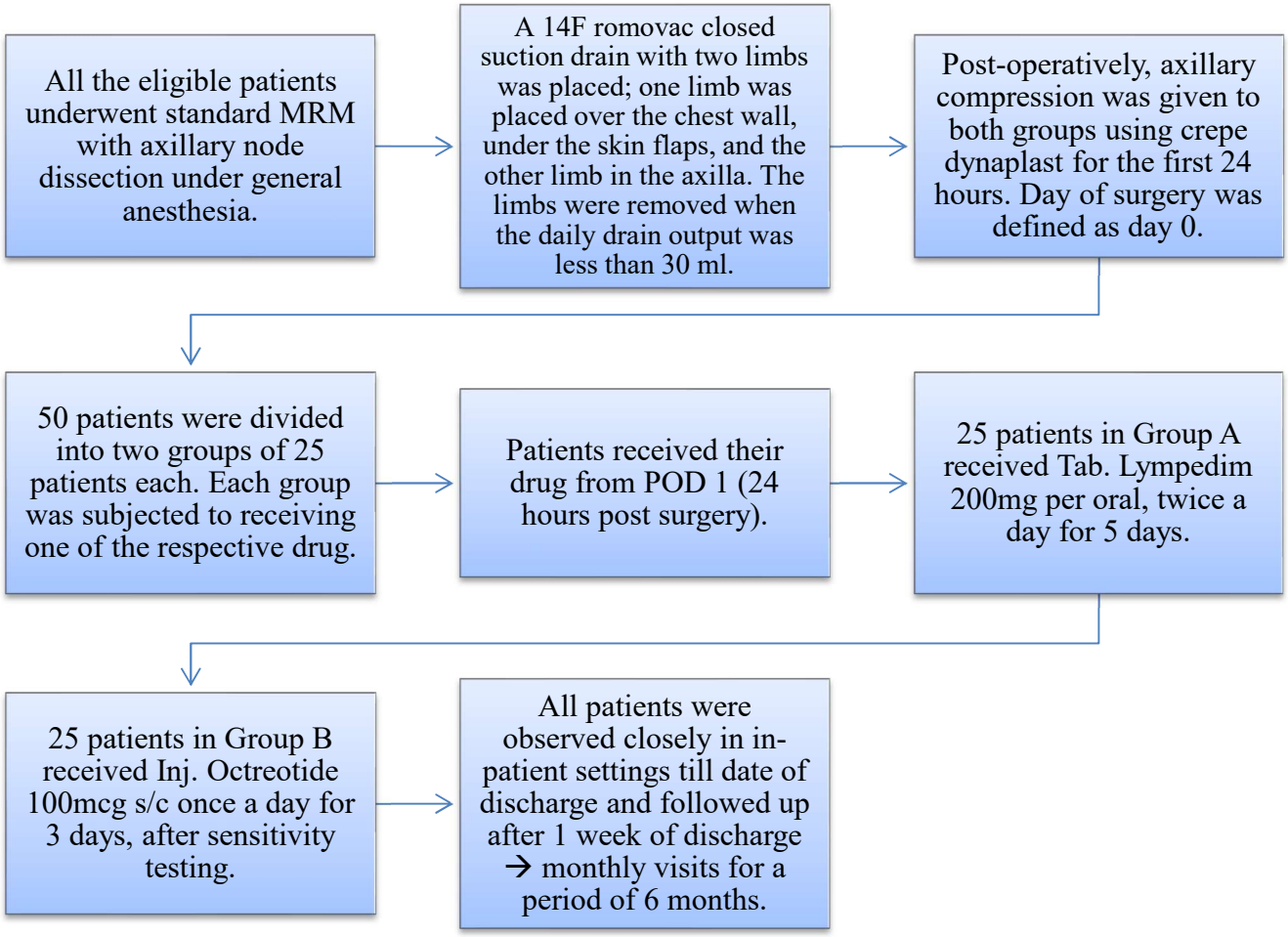

FIGURE 1: METHODOLOGY USED IN THE STUDY

INCLUSION CRITERIA	**EXCLUSION CRITERIA**
Patients diagnosed with primary breast cancer, including early-stage and locally advanced disease.	Patients with metastatic breast cancer.
Patients scheduled to undergo modified radical mastectomy without reconstruction.	Patients undergoing Breast Conservation Surgery/ who underwent previous breast surgery on the same side/ have undergone neoadjuvant chemotherapy.
Age range of 40 to 70 years.	Pregnant or breastfeeding patients.
Patients who agreed to be part of the study after explaining to them the nature of the study being conducted.	Patients with a history of previous radiation therapy to the chest area.

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Patients willing and able to comply with postoperative follow-up visits	Patients with significant coagulation disorders/ uncontrolled bleeding tendencies.
	Patients who are known type 2 diabetes mellitus patients.
	Patients with impaired liver and cardiac function - unstable angina, Myocardial infarction, abnormal cardiac conduction, cardiac arrhythmia.
	Patients with immunocompromised conditions or chronic infections that may impact wound healing.
	Patients with contraindication to ocreotide and coumarin analogues

TABLE 1: INCLUSION AND EXCLUSION CRITERIA

STATISTICS AND DATA ANALYSIS

Data collected was entered, categorized and coded in MS Excel. All analysis was performed using SPSS software version 26.0. Descriptive statistics were for age, diagnosis and adverse reactions of the drug were expressed in terms of frequencies and percentage. Other parameters like day of discharge, amount of drain collection, number of days of drain were expressed in terms of mean and standard deviation. The association between the diagnosis of the patient with the study groups receiving two different drugs were analysed by Chi-Square/Fischer's test. The association between the number of patients receiving the drug and adverse reactions of the drug was analysed by Chi-Square/Fischer's test. The association between the day of discharge and day of drain removal (t value) was analysed by independent T test. The association between the amount of drain and post operative days (f value) were analysed using repeated measures ANOVA. P value of <0.05 was considered statistically significant. Appropriate graphs and charts were used wherever necessary. The results obtained from this study are expressed in the following order.

		Frequency (n)	Percent (%)
Age in years	40 – 50	16	32
	51 – 60	24	48
	61 – 70	10	20

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TABLE 2: AGE DISTRIBUTION OF THE PARTICIPANTS IN THE STUDY

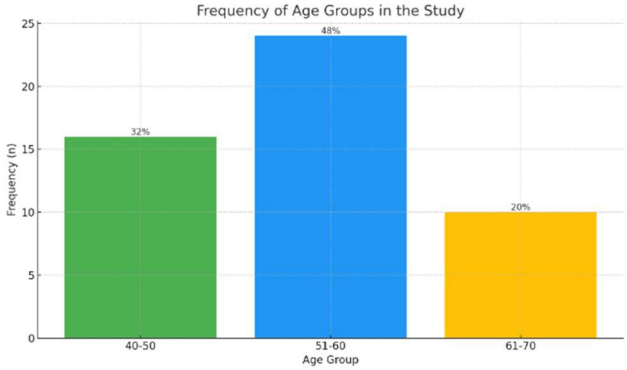

FIGURE 2: AGE DISTRIBUTION OF THE PARTICIPANTS IN THE STUDY

The participants between the years 40 and 50 are 32% of this study population. While the age group between 51 - 60 has the maximum number participants in the study with about 48% followed by 20 in the 61 - 70 years category. The mean age of the study participants was 54.64 years with a standard deviation of 7.99 suggesting an increased prevalence in the 51 to 60 years age group, which in consistent with previous epidemiological data.

Frequency (n)	Percent (%)	
LEFT BCA	**27**	**54.0**
RIGHT BCA	**23**	**46.0**

TABLE 3: DIAGNOSIS OF THE STUDY POPULATION

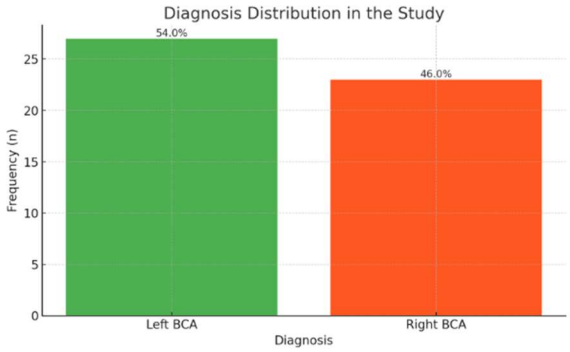

FIGURE 3: DIAGNOSIS OF THE STUDY POPULATION

The graph displays the distribution of diagnoses among the 50 participants in the study. It shows that 27 participants (54%) were diagnosed with left breast cancer (BCA), while 23 participants (46%) were diagnosed with right breast cancer (BCA). This indicates that more than half of the study participants had left breast cancer, with a slightly smaller proportion having right breast cancer.

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			DRUG			
			TAB LYMPEDIM	INJ OCTREOTIDE	X^2	P value
DIAGNOSIS	LEFT BCA	Count	15	12	0.725	0.395
		% within DRUG	60.0%	48.0%		
		% of Total	30.0%	24.0%		
	RIGHT BCA	Count	10	13		
		% within DRUG	40.0%	52.0%		
		% of Total	20.0%	26.0%		

TABLE 4: DIAGNOSIS DISTRIBUTION AND DRUG ALLOCATION

Statistical test used : Chi-square test/ Fischer's exact test

*P value - <0.05 – statistically significant

For patients with left BCA, 60% received Tab Lympedim, while 48% received Inj Octreotide. For those with right BCA, 40% were treated with Tab Lympedim, and 52% received Inj Octreotide. The chi-square test showed no statistically significant difference in the distribution of these diagnoses between the two drug groups (p = 0.395).

	Frequency	Percent
Yes	18	36.0
No	32	64.0
Total	50	100.0

TABLE 5: FREQUENCY AND PERCENTAGE OFADVERSE DRUG REACTIONS SEEN IN THE TWO STUDY GROUPS

	DRUG			
	TAB LYMPEDIM	INJ OCTREOTIDE	X^2	P value

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DRUG ADVERSE REACTIONS	YES	Count	8	10	0.347	0.769
		% within DRUG ADVERSE REACTIONS	44.4%	55.6%		
	NO	Count	17	15		
		% within DRUG ADVERSE REACTIONS	53.1%	46.9%		

TABLE 6: ASSOCIATION BETWEEN DRUG AND ADVERSE DRUG REACTIONS SEEN IN THE TWO STUDY GROUPS

Adverse drug reactions were observed in 36% of the patients overall. Among those receiving Tablet Lympedim, 44.4% experienced adverse reactions, while 55.6% of those on Injection Octreotide did. However, the difference in the rate of adverse reactions between the two drugs was not statistically significant (p = 0.769).

	N	*Minimum*	*Maximum*	*Mean*	*Std. Deviation*
DRAIN REMOVAL DAY	***50***	***5***	***12***	***7.16***	***1.490***
DISCHARGE POD	***50***	***5***	***14***	***8.02***	***1.857***

TABLE 7: DESCRIPTIVE STATISTICS ON DRAIN REMOVAL DAY AND DAY OF DISCHARGE

For drain removal day, the mean value is 7.16 days, with a standard deviation of 1.49 days. This indicates that, on average, the day of drain removal for the sample of 50 patients falls around the 7th day, with most values ranging approximately between the 5th and 9th days. In contrast, day of discharge has a higher mean value of 8.02 days, with a larger standard deviation of 1.857 days. This suggests that patients are typically discharged around the 8th day, with a slightly wider spread of discharge days, approximately between the 6th and 10th days.

	DRUG	**Mean**	**Std. Deviation**	**T value**	**Degrees of freedom**	**P value**
DRAIN REMOVAL DAY	**TAB LYMPEDIM**	**6.32**	**1.108**	**4.802**	**48**	**<0.001**

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	INJ OCTREOTIDE	**8.00**	**1.354**			
DISCHARGE POD	**TAB LYMPEDIM**	**6.92**	**1.115**	**5.174**	**48**	**<0.001**
	INJ OCTREOTIDE	**9.12**	**1.810**			

TABLE 8: ASSOCIATION BETWEEN FOR DRAIN REMOVAL DAY AND DISCHARGE POST-OPERATIVE DAY (POD) FOR TAB LYMPEDIM AND INJ OCTREOTIDE

Patients treated with Tab Lympedim had their drains removed earlier, with a mean of 6.32 days postoperatively, compared to 8.00 days for those receiving Inj. Octreotide. This difference was statistically significant ($p < 0.001$). Similarly, the mean discharge day for patients on Tab Lympedim was 6.92 days, significantly earlier than the 9.12 days for those on Inj Octreotide ($p < 0.001$).

	DRUG	**Mean**	**Std. Deviation**	**F Value**	**Degrees of freedom**	**P Value**
POD 1	**TAB LYMPEDIM**	**136.56**	**13.156**	**0.441**	**2.5**	**0.692***
	INJ OCTREOTIDE	**148.24**	**18.729**			
POD 2	**TAB LYMPEDIM**	**90.12**	**14.016**			
	INJ OCTREOTIDE	**105.52**	**20.193**			
POD 3	**TAB LYMPEDIM**	**68.76**	**14.391**			
	INJ OCTREOTIDE	**82.28**	**15.802**			
POD 4	**TAB LYMPEDIM**	**47.36**	**11.176**			
	INJ OCTREOTIDE	**60.44**	**13.814**			
POD 5	**TAB LYMPEDIM**	**31.36**	**9.797**			
	INJ OCTREOTIDE	**44.80**	**10.790**			

TABLE 9: ASSOCIATION BETWEEN FOR TABLET LYMPEDIM AND INJECTION OCTREOTIDE OVER POST-OPERATIVE DAYS (POD 1 TO POD 5)

Test used: Repeated measures ANOVA
Greenhouse-Gressier correction applied(∑-0.636)
p value >0.05- Statistically not significant

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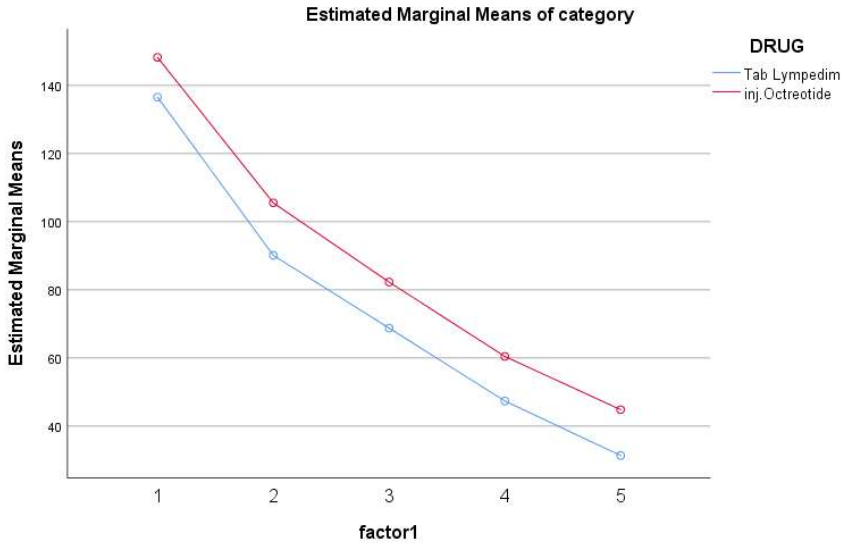

FIGURE 4: MEAN VALUES OF TWO DRUGS, TAB LYMPEDIM AND INJ OCTREOTIDE, MEASURED OVER FIVE POST-OPERATIVE DAYS (POD 1 TO POD 5)

The plot provides a clear visual representation of the trends and variability in drug effectiveness over time (from POD 1 to POD 5), demonstrating a general decline in mean values for both drugs as the days progress.

DISCUSSION

Seroma, a frequent complication after mastectomy and axillary surgery, is defined as a serous fluid collection under skin flaps or in the axillary dead space. It is considered multifactorial, with incidence rates globally ranging from 3% to 85%. Many now view seroma as a common surgical side effect rather than a complication, as it occurs even with thorough axillary clearance. Seroma can delay drain removal, wound healing, and subsequent adjuvant therapy, and may necessitate reoperation (1). It is hypothesized as an inflammatory exudate formed during early wound healing due to fibronolytic activity in serum and lymph. Evidence of low fibrinogen levels in seroma, compared to lymph, supports its lymphatic origin.

Factors Contributing to Seroma Formation and Reduction Techniques

Surgical Factors

1. **Surgical Techniques**: Radical mastectomy and extensive axillary clearance increase seroma risk. The number of lymph nodes removed during axillary clearance is proportional to the incidence of seroma. However, preservation or removal of pectoralis fascia does not significantly affect seroma rates. Sentinel lymph node biopsy, as shown by Purushotam et al., has a lower seroma incidence than traditional axillary dissection.
2. **Surgical Devices**: Various devices aim to reduce blood loss and operative time, each with different effects on seroma formation. While electrocautery raises seroma risk, ultrasonic devices, such as harmonic scalpels, have been associated with lower seroma rates. Studies

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comparing conventional scalpels with vessel-sealing systems yield mixed results, with some suggesting vessel-sealing systems reduce seroma incidence.

3. **Dead Space Obliteration**: Techniques to close the wound bed and axillary dead space aim to reduce seroma. Mechanical methods include suturing skin flaps to chest wall muscles, which has been shown to decrease seroma formation compared to conventional skin closure. Compression garments, however, do not reduce seroma or drainage volume. Chemical approaches like fibrin glue, light-activated fibrin sealants and transdermal Photo polymerised adhesive and other fibrin-based adhesives inhibit fibrinolytic activity, theorized to reduce seroma (2). Sclerosants like tetracycline and hypertonic saline are also used, with tetracycline showing promising results, though pain is a noted side effect.
4. **Somatostatin and Octreotide**: Somatostatin receptors have been discovered in lymphatic tissue. Normally they suppress growth hormone (GH) secretion. While most commonly used as antisecretory or anti-motiliy agents of the gastrointestinal tract, somatostatins are thought to reduce seroma formation mostly due to its anti-secretory effects, even though exact mechanisms are not well understood yet. Octreotide, a synthetic somatostatin analogue, 20 times more potent than somatostatin itself, has been studied in axillary lymph node dissection to reduce the duration and volume of lymphorrhea. It has a t1/2 life of 90 minutes. It has adverse effects like nausea, vomiting, abdominal discomfort, hypotension, bradycardia and dysglycemia due to its weak insulin inhibitory action. Hence it is preferred use this drug with caution or avoid in case of patients with diabetes mellitus. It also causes gall bladder dyskinesia, cholestatic hepatitis and hypothyroidism.

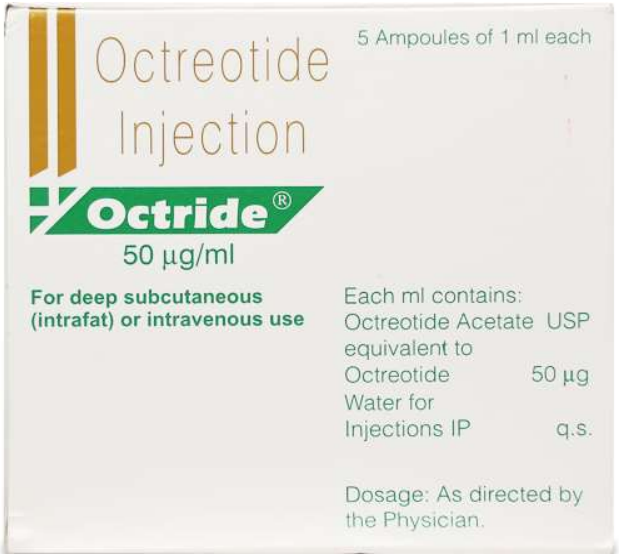

FIGURE 5: INJECTION OCTREOTIDE

5. Coumarin Analogues: Another drug that has been used in the reduction of seroma post mastectomy is coumarin analogue. It is a 5,6 - benz alpha pyrone or 1,2 – benzopyrone. A number of synthetic techniques like Pechmann, Perkin, Knoevenagel, Wittig and Claisen have

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been seen in the coumarin synthesis and hence the ability to synthesize analogs with antibreast cancer activity (3). Investigations into the biological properties of coumarins have found that they can target multiple cancer pathways, including aromatase inhibition, kinase inhibition, cell cycle arrest, and angiogenesis suppression (4).

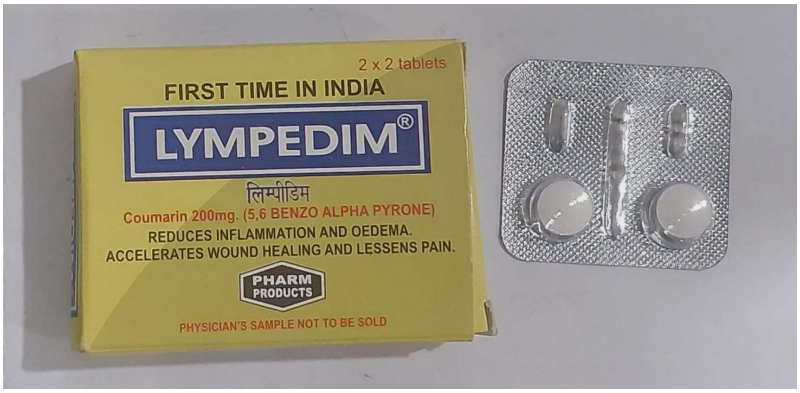

FIGURE 6: COUMARIN ANALOGUE - TABLET LYMPEDIM

It works by enhancing proteolytic activity of macrophages and exerts a positive myotropic effect on lymphangion which are anatomical functional contractile units of the lymphatic system. Due to the lack of hydroxyl group in carbon 4 of its chemical structure, it has no anticoagulant activity. Coumarins are commonly found to be used for treating renal cell cancer, prostate cancer, leukemia etc (5). This drug also the ability to counteract the side effects of radiotherapy. Recent studies have shown their use in the reduction of seroma formation after mastectomy procedures. It is administered in a dose of 30mg/day to 400mg/day. Though found to be cost effective compared to other treatments, the drug produces minor side effects such as GI complaints (nausea, vomiting, epigastric discomfort) and headache.

Postoperative Care and Physiotherapy

1. **Shoulder Mobilization**: The timing of shoulder mobilization post-mastectomy affects seroma rates. Early mobilization, though often recommended, may increase seroma risk, as supported by multiple randomized controlled trials. Conversely, delayed mobilization reduces seroma formation at the cost of temporary shoulder dysfunction but does not impact long-term mobility.
2. **Drain Management**: Drains are critical for seroma prevention, with various types used, including corrugated, closed, and closed suction drains. Studies show that closed suction drains promote quicker healing with lower infection rates. High vacuum suction drains have mixed outcomes, with some studies suggesting increased leakage compared to low vacuum systems. Bourke et al conducted a study where he found no difference between using corrugated wound drainage and closed suction drainage (6). Whitfield and Rainsbury conducted a study comparing closed suction drainage and closed siphon drainage and also found no statistical significant difference (7).

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3. **Early Discharge with Drain In Situ vs. Late Discharge**: Early discharge with a drain still in place is safe if patients are adequately educated and supported. Studies indicate that early discharge reduces seroma incidence and shortens hospital stay. For example, Holcombe et al. observed an 18% seroma rate with early discharge, compared to 34% with standard treatment, alongside a 5-day reduction in hospital stay.

Timing of Drain Removal

1. **Early vs. Late Removal**: Drain removal is typically based on drainage volume thresholds, such as less than 250 ml over three consecutive days or 20-50 ml over 24 hours. Research suggests that about 74% of seroma volume is drained within the first 48 hours. In a study by Somer's et al., patients who had drains removed after day one showed no significant difference in drainage volume, supporting early removal.
2. **Impact on Seroma Aspiration and Resolution**: Studies on timing indicate early drain removal reduces seroma formation without increasing aspiration needs. For instance, Parikh et al.'s randomized trial showed more seroma fluid in patients with prolonged drain use. Fii et al. also found no significant difference between 48-hour and standard removal groups in seroma rates.

This study aimed to evaluate the effectiveness and side effects of two drugs, Tablet Lympedim and Injection Octreotide, in breast carcinoma patients who underwent MRM. The study included 50 patients, aged 40 to 70, and focused on various parameters such as postoperative days (POD), drain removal day and day of discharge.

Participants aged between 40 and 50 years constitute 32% of the study population. The age group with the highest representation is 51 to 60 years, accounting for about 48% of the participants, followed by the 61 to 70 years category, which makes up 20%. The mean age of the study participants is 54.64 years, with a standard deviation of 7.99. This indicates a higher prevalence in the 51 to 60 years age group.

	TAB. LYMPEDIM	**INJ. OCTREOTIDE**
SEROMA LEVELS **POD 1** **POD 5**	**136.56 (SD = 13.156)** **31.36 (SD = 9.797)**	**148.24 (SD = 18.72** **44.80 (SD = 10.790)**
DAY OF DRAIN REMOVAL	**6.32 days** **SD = 1.108**	**8.00 days** **SD = 1.354**
DAY OF DISCHARGE	**6.92 days** **SD = 1.115**	**9.12 days** **SD = 1.810**
($p < 0.001$) - statistically significant difference		

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Tablet Lympedim may facilitate quicker recovery and earlier hospital discharge compared to Injection Octreotide		
ADVERSE DRUG REACTIONS (36%)	**44.4%**	**55.6%**
(p = 0.769) – not statistically significant difference Both drugs have a similar safety profile		
COST	**Rs. 16 – 18/ tablet**	**Rs. 312 per 50 mcg**

Table 10: COMPARATIVE ANALYSIS OF THE TWO DRUGS

STUDY	PARTICIPANTS	INTERVENTION	OUTCOMES
Carcoforo et al (RCT) (8)	**261**	**0.1mg Octreotide thrice a day for 5 days post-op Control group received no drug**	**Seroma: 94.6 ± 19ml/day, Duration: 16.7 ± 3.0 days; Control: 65.4 ± 21.1ml/day, Duration: 7.1 ± 2.9 days; p < 0.0001 (no significance)**
Prajapati et al (RCT) (9)	**Not specified**	**Octreotide + standard care vs standard care**	**Significant reduction in seroma formation, hospital stay; No significance in wound infections**
Burgos et al (10)	**77**	**Coumarin analogues (90mg/day and 135mg/day)**	**Progressive decrease in seroma, no significant difference between doses; Metrorrhagia and increased bleeding during menses**

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Clodius et al (11)	**Not specified**	**Coumarin analogue**	**Lymphedema reduction by 0.5cm per 10 months; Significant compared to control**

TABLE 11: SUMMARY OF OTHER SIMILAR STUDY'S PARTICIPANTS, INTERVENTIONS AND OUTCOMES

RECOMMENDATIONS:

Multi centric, large scale studies can be put forward, across various strata of people from different region and dietary practices with a diverse population in terms of age, co-morbidities and stages of breast cancer can be considered to provide a more comprehensive understanding on the different surgical methods, the post operative medical care and its reflection on the management and reduction of seroma formation in post operative mastectomy patients making it more applicable for the general population. Implementing randomized controlled trials (RCTs) would help in reducing bias and establishing a causal relationship between the drugs and the observed outcomes as RCTs are the gold standard for clinical research and would strengthen the evidence base.

LIMITATIONS:

The possible limitations of the study includes smaller study population undergoing modified radical mastectomy consenting for the study. Also, the study is a single centered study which compromises the population diversity and regional variations. A longer follow-up would be beneficial to understand the long-term effects and potential late onset adverse reactions of the drugs.

CONCLUSION:

Prolonged post operative seroma can delay the onset of adjuvant chemotherapy. It can also cause wound infection, flap necrosis and other complications post operatively. Effective control of post operative seroma formation has been achieved by giving coumarin derivatives. Though statistically great difference has not been observed between the two groups receiving Tablet Lympedim and Injection Octreotide, lesser seroma formation, side effects and economic feasibility is observed in the above said study. Hence it can be very safely advocated for use in most of the breast cancer patients which have been included in the study. These results can help inform clinical decisions regarding the postoperative management of breast carcinoma patients undergoing modified radical mastectomy. However, future studies with larger sample sizes and longer follow-up periods are recommended to further validate these findings.

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