

Effects of sodium hyaluronate compared with steroid eye drop against the degree of canalicular stenosis in breast cancer patients treated with docetaxel

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Effects of sodium hyaluronate compared with steroid eye drop against the degree of canalicular stenosis in breast cancer patients treated with docetaxel

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Abstract. Canalicular stenosis caused by inflammatory processes in the mucosa of canalicular causing thickening of the squamous epithelium, subsequently parakeratosis and hyperkeratosis of the squamous epithelium. The aim of this study was to assess the effects of sodium hyaluronate compared with steroid eye drop against the degree of canalicular stenosis in breast cancer patients treated with docetaxel chemotherapeutic agents. This study was a clinical trial with the randomized controlled trial (RCT) of 80 sample during the period August-October 2017. Bivariate analyzes used chi-square and McNemar test, and multivariate analysis used logistic regression with the backward method. A total of 20 samples with moderate degree stenosis became mild degree and 36 samples with mild degree stenosis became not stenosis after treated with sodium hyaluronate eye drops. A total of 16 samples with moderate degree stenosis became mild degree and 36 samples with mild degree stenosis became not stenosis after treated with steroid eye drops. McNemar test showed a significant difference in the degree of stenosis after treated with sodium hyaluronate ($p=0.039$) and steroid eye drops ($p=0.000$), but chi-square test showed no significant difference in the degree of stenosis between sodium hyaluronate and steroid ($p=0.302$). Multivariate analysis showed that age, duration of administration and dose of docetaxel effects in canalicular stenosis. Administration of sodium hyaluronate and steroid eye drops can improve the degree of canalicular stenosis.

1. Introduction

Canalicular stenosis is one of the complications of the use of docetaxel as a chemotherapeutic agent that is commonly used in the treatment of breast cancer patients. Canalicular stenosis becomes a major cause of epiphora in patients with breast cancer (BCP) treated with docetaxel [1-3].

Epiphora as a side effect of docetaxel therapy was first described in the 2001 Ophthalmology Journal. Since then several related reports have emerged, reported complains of epiphora appeared in 64% of patients on weekly therapy and 39% of patients on 3 weeks therapy; more than 50% patients on weekly docetaxel therapy. In B. Esmaeli et al's study, we found results showing abnormalities of the lacrimal secretory and drainage systems, such as canalicular stenosis and punctum stenosis.

Docetaxel is a taxoid chemotherapeutic agent that works by interfering with cell activity in the mitotic process [4]. Based on the Bina Esmaeli MD et all study, docetaxel is secreted in tears and therefore has a



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direct effect on the canalicular mucous, causing inflammation and fibrosis of the punctum and canalicular system. Fibrosis of the mucosal in the lacrimal system occurs secondary to the systemic effects of the drug [1,2,5]. Although excessive tearing (epiphora) reportedly associated with the use of docetaxel as chemotherapeutic agents, only little data has been obtained regarding this ocular side effects.

Up until now, there has been no study on the prevention of canalicular stenosis induced by docetaxel. As a secondary prevention, topical corticosteroids can be given when symptoms of epiphora appear. Hypothetically, eye drops containing corticosteroid can reduce mucosal inflammation and may prevent canalicular stenosis. In addition, the eye drops alone can clear the docetaxel from the ocular surface, thus prevent the occurrence of canalicular stenosis. In this study, a double-blind randomized study was conducted to determine the efficacy of corticosteroid versus artificial tears topical eye drops treatment in BCP treated with docetaxel.

2. Methods

This research was conducted at Mohammad Hoesin Hospital Palembang, started from August 2017 to October 2017. The sample of this study was all breast cancer patients using docetaxel. The examination was performed by an ophthalmologist, including visual acuity examination of the patient's eyes, slit lamp examination, funduscopy examination, intraocular pressure measurement, Schirmer's examination of the lacrimal systems and probing on the patient's canalicular. Patients were given two eye drops, which form and packaging were made identical; Artificial Tears (sodium hyaluronate, hyalub@, Cendo) and Prednisolone (P-pred@ Cendo). The two contents of the bottle are separated discreetly so that both the patient and the ophthalmologists in this did not know the contents of the bottle.

Table 1. General characteristics of research's subjects by age.

Age	Freq		Age
	N	%	
30-45 yr	52	65	30-45 yr
46-60 yr	28	35	46-60 yr
Total	80	100	Total

Table 2. General characteristics of subjects based on length of chemotherapy

Duration of Chemoth	Freq		Duration of Chemoth
	N	%	
I	0	0	I
II	16	20.0	II
III	20	25.0	III
IV	16	20.0	IV
V	16	20.0	V
VI	12	15.0	VI
Total	80	100	Total

Patients were scheduled to take the eye drops six times a day, and were evaluated by ophthalmologists at week 3,6,9 for 3 months. At each visit, patients would undergo slit lamp examination, intraocular pressure measurement, and probe on the lacrimal systems. 0 there was no canalicular stenosis, 1 mild, small puncta size but probing could be done after dilating the puncta, resulted in bony stop, 2 medium, partial probing in canalicular, no bony stop, 3 severe, probing cannot be performed, extreme pain during procedure and blood sometimes can be obtained, both upper and lower ecretory apparatus were not potent. Subjective assessment of epiphora: 0 not found euphoria, 1 mild with frequent complaints of wiping tears, 2 moderate epiphora with complaints of wiping tears throughout the day, 3 severe epiphora with severe epiphora complaints requiring the patient to wipe the tears all the time and disrupt daily activities of the patient, such as reading, driving a car and doing daily chores. Elusion criteria were

patients with an abnormal anterior segment, such as infection and inflammation, glaucoma, using soft contact lenses, lacrimal systems obstruction.

Bivariate analysis using chi-square test and McNemar test, and multivariate analysis using logistic regression backward method.

3. Results

Subject age ranged from 30-60 years old; age 30-45 years old 52 subjects (65%), 46-60 years old 28 subjects (35%).

Table 3. Docetaxel dose relationship with the degree of stenosis.

Docetaxel Dosage	Mild Stenosis		Moderate Stenosis		p
	N	%	N	%	
100 mg	20	66.7	10	33.3	0.042
105 mg	4	40.0	6	60.0	
125 mg	10	41.7	14	58.3	
130 mg	4	25.0	12	75.0	
Total	38	47.5	42		

*uji chi square (p<0.05)

Table 4. The dose of docetaxel relationship with the degree of euphoria.

Docetaxel Dosage	Mild Epiphoria		Moderate Epiphoria		p
	N	%	N	%	
100 mg	24	80.0	6	20.0	0.000
105 mg	10	100.0	0	0.0	
125 mg	12	50.0	12	50.0	
130 mg	2	12.5	14	87.5	
Total	48		60.0		

*uji chi square (p<0.05)

Table 5. Comparison of epiphora degrees before treatment.

Group	Mild Epifora		Moderate Epiphoria		p*
	N	%	N	%	
Sodium Hyaluronate	24	60	16	40	1.000
Steroid	24	60	16	40	

*Uji chi square (p < 0.05)

Table 6. Comparison of epiphoria degrees after treatment.

Group	No Epiphoria		Mild Epiphoria		p*
	N	%	N	%	
Sodium Hyaluronate	34	85	6	15	1.000
Steroid	34	85	6	15	

*Uji chi square (p < 0.05)

4. Discussion

The mean age of the study's subjects was 43.95 + 6.43 years, with age group of 30-45 years 52 subjects (65%) and age group 46-60 years as many as 28 subjects (35%). while research conducted by Esmali et al. in Texas about the docetaxel related epiphora obtained 54.3 years old average age with age range 28-83 years.[12] A total of 64 subjects in this study received education for at least 9 years, 34 subjects (42.5%) received a high school education and 30 subjects (37.5%) received the college education.[13] In

this study, 20 subjects experienced canalicular stenosis and after 3 docetaxel regiments (25%) and 16 subjects (20%) after 4 docetaxel regiments. This result was supported by Esmaeli et al. which showed that the mean interval between first-time use of docetaxel to the onset of epiphora 4 regiments (3 months). The length of chemotherapy will affect the accumulation of the dosage used up to the occurrence of canalicular stenosis or epiphora [6,12].

Table 7. Comparison of epiphora degrees after steroid administration.

Degree of Epiphoria	Degree of Epiphoria		p*
	Mild Epiphoria	Moderate Epiphoria	
Mild Epiphoria	22	2	0.013
Moderate Epiphoria	12	4	

*Uji McNemar (p < 0.05)

Table 8. Comparison of the degree of stenosis prior to treatment.

Group	Mild Stenosis		Moderate Stenosis		p*
	N	%	N	%	
Sodium Hyaluronate	20	50	20	50	0.654
Steroid	18	45	22	55	

*Uji chi square (p < 0.05)

Table 9. Comparison of the degree of stenosis after treatment.

Group	No Stenosis		Mild Stenosis		p*
	N	%	N	%	
Sodium Hyaluronate	28	70	12	30	0.302
Steroid	32	80	8	20	

*Uji chi square (p < 0.05)

Table 10. Comparison of the degree of stenosis after the administration of sodium hyaluronate.

Degree of Stenosis	Degree of Stenosis		p*
	No Stenosis	Mild Stenosis	
Mild Stenosis	18	2	0.039
Moderate Stenosis	10	10	

Table 11. Comparison of the degree of stenosis after the administration of steroid .

Degree of Stenosis	Degree of Stenosis		p*
	No Stenosis	Mild Stenosis	
Mild Stenosis	18	0	0.000
Moderate Stenosis	14	8	

*Uji McNemar ($p < 0.05$)**Table 12.** Multivariate analysis.

Variabel	Koefisien	p	Exp (B)
Age	0.132	0.031	1.142
Duration of chemotherapy	1.894	0.000	6.643
Dosage	0.072	0.021	1.075
Groups	-2.196	0.022	0.111
Constanta	-19.947	0.000	0.000

Based on the duration of the use of chemotherapy, this study obtained that the average dose accumulation used by the subjects is $442.75 + 169.73$ mg, ranging from 200-780 mg. In this study there were 20 (66.7%) subjects with mild degrees of stenosis and 10 samples (33.3%) who had moderate stenosis with docetaxel dose of 100 mg, while 4 samples (25%) had mild degrees of stenosis and 12 samples (75%) had moderate stenosis with docetaxel dose of 130 mg. Based on the chi-square test, a statistically significant correlation between docetaxel dose was used with the degree of occurrence of stenosis ($p = 0.042$). The results of this study were supported by Esmaeli et al. which received an average dose of accumulation of 690 mg, ranging from 420-1050 mg [1,3,15].

At the beginning of the study, there were 24 subjects (60%) who had mild epiphora and 16 subjects (40%) who experienced moderate epiphora in both groups, the sodium hyaluronate group, and the steroid group. After probing and given drops based on the treatment group that was sodium hyaluronate and steroid, 34 subjects (85%) no longer have epiphora and only 6 subjects (15%) had mild epiphora in both groups. Based on comparative analysis before and after treatment with McNemar test, there was statistically significant change of epiphora level in each group ($p = 0.013$), but chi-square test to assess epiphora degree before or after treatment showed no significant difference between administration sodium hyaluronate and steroid eye drops ($p = 1.000$). Similar research conducted by Leyssens et al. comparing the efficacy of topical eye medications in preventing stenosis and epiphany due to docetaxel for 26 weeks showed a reduction in the number of subjects who experienced epiphora by 5% in topical steroid eye treatment, while sodium hyaluronate did not subside.33 Esmaeli et al. confirmed that the use of topical steroids accompanied by recurrent probing and irrigation may overcome epiphoria [6,11,14].

At the beginning of the study, 20 subjects (50%) had mild stenosis and 20 subjects (50%) had moderate stenosis in the sodium hyaluronate group, while 18 subjects (45%) had mild stenosis and 22 subjects (55%) had moderate stenosis in the steroid group. Then after probing and given drops based on the treatment group, as many as 28 subjects (70%) no longer have stenosis and 12 subjects (30%) had mild degrees of stenosis in the sodium hyaluronate group, while as many as 32 subjects (80%) no longer had stenosis and 8 subjects (20%) had mild degrees of steroid in the steroid group. Based on comparative analysis before and after treatment with McNemar test, there was a statistically significant change in stenosis degree in sodium hyaluronate group ($p = 0.039$) and steroid group ($p = 0.000$), but chi-square test did not show statistically significant difference between the two groups before treatment ($p = 0.654$) and after treatment ($p = 0.302$). Similar results conducted by Leyssens et al. comparing the efficacy of topical eye medications in preventing stenosis and epiphora due to docetaxel for 26 weeks showed a reduction in the number of subjects who had stenosis by 20% in topical sodium hyaluronate medication, whereas in steroid administration the reduction was 7.5% [17].

In this study, subjects who experienced canalicular stenosis and epiphora while undergoing chemotherapy with docetaxel was recorded so that the average accumulation dose was obtained to determine which factors affect the occurrence of stenosis and epiphora. Multivariate analysis using logistic regression backward conditional method was done and obtained that the factor that influences the degrees of stenosis after the chemotherapy agent Docetaxel was the duration of the chemotherapy with the result Exp (B)6,643.

The occurrence of stenosis in BCP using a docetaxel chemotherapeutic agent may be caused by the secretion of the drug into the lacrimal systems, causing the drugs to accumulate in the canalicular mucosal

wall, which eventually gives a direct effect of irritation and inflammation leading to fibrosis in the punctum and canalicular systems [5-7].

5. Conclusions

The lack of supporting data and research on the comparison of the efficacy of topical drugs of sodium hyaluronate and steroids in reducing the degree of stenosis and the existence of different working mechanisms in both topical drugs may support the hypothesis (H^0) of this study that there is no difference in degrees of canalicular stenosis among breast cancer patients performed a probing action with sodium hyaluronate eye drops compared with steroid eye drops in breast cancer patients treated with docetaxel chemotherapeutic agents. It is hoped that in the future, other similar research will be conducted to support the results of this study and previous research.

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