Effects Of Sodium Hyaluronate Compared with Steroid Eye Drop Against The Degree Of Canalicular Stenosis In Breast Cancer Patients Treated With Docetax

by medsosnya.dezca@gmail.com 1

Submission date: 15-Jun-2023 06:17AM (UTC-0400)
Submission ID: 2115144527
File name: nosis_in_breast_cancer_patients_treated_with_docetaxel_1_2.docx (96.38K)
Word count: 3337
Character count: 22451

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

IOP Conf. Series: Journal of Physics: Conf. Series **1246** (2019) 012011 doi:10.1088/1742-6596/1246/1/012011

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

Riani Erna[1], Nur Qodir[2], Ristania[1]

[1] Ophthalmology Department, Mohammad Hoesin Hospital, Universitas Sriwijaya, Palembang, Indonesia
[2] Surgery Department, Mohammad Hoesin Hospital, Universitas Sriwijaya, Palembang, Indonesia

E-mail : rianierna@fk.unsri.ac.id

Abstract. Canalicular steno()sis caused by inflammato()ry pro()cesses in the muco()sa o()f canalicular causing thickening o()f the squamo()us epithelium, subsequently parakerato()sis and hyperkerato()sis o()f the squamo()us epithelium. The aim o()f this study was to() assess the effects o()f so()dium hyaluro()nate co()mpared with stero()id eye dro()p against the degree o()f canalicular steno()sis in breast cancer patients treated with do()cetaxel chemo()therapeutic agents. This study was a clinical trial with the rando()mized co()ntro()lled trial (RCT) o()f 80 sample during the perio()d August-O()cto()ber 2017. Bivariate analyzes used chi-square and McNemar test, and multivariate analysis used lo()gistic regressio()n with the backward metho()d. A to()tal o()f 20 samples with mo()derate degree steno()sis became mild degree and 36 samples with mild degree steno()sis became no()t steno()sis after treated with so()dium hyaluro()nate eye dro()ps. A to()tal o()f 16 samples with mo()derate degree steno()sis became mild degreeand 36 samples with mild degree steno()sis became no()t steno()sis after treated with stero()id eye dro()ps.McNemar test sho()wed a significant difference in the degree o()f steno()sis after treated with so()dium hyaluro()nate (p=0.039) and stero()id eye dro()ps (p=0.000), but chi-square test sho()wed no() significant difference in the degree o()f steno()sis between so()dium hyaluro()nate and stero()id (p=0.302). Multivariate analysis sho()wed that age, duratio()n o()f administratio()n and do()se o()f do()cetaxel effects incanalicular steno()sis. Administratio()n o()f so()dium hyaluro()nate and stero()id eye dro()ps can impro()ve the degree o()f canalicular steno()sis.

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

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 eessive 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 eretory 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	
105 mg	4	40.0	6	60.0	
125 mg	10	41.7	14	58.3	0.042
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	
105 mg	10	100.0	0	0.0	
125 mg	12	50.0	12	50.0	0.000
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 Esmaeli et al. in Texas about the docetaxel related ephiphora 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 ephiphora 4 regiments (3 months). The length of chemotherapy will affect the accumulation of the dosage used up to the occurrence of canalicular stenosis or epiphoria [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	
Steroid	18	45	22	55	0.654

*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
ModerateStenosis	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.

6. References

[1] Esmaeli B, Burnstine M A, Ahmadi M A and Prieto V G 2003 Docetaxel-induced histologic changes in the lacrimal sac and the nasal mucosa *Ophthalmic Plast. Reconstr. Surg.* **19** 305–8

[2] Esmaeli B, Ahmadi M A, Rivera E, Valero V, Hutto T, Jackson D M and Newman R A 2008 Docetaxel secretion in tears: association with lacrimal drainage obstruction *Arch. Ophthalmol.* **120** 1180–2

[3] Esmaeli B, Hortobagyi G N, Esteva F J, Booser D, Ahmadi M A, Rivera E, Arbuckle R, Delpassand E, Guerra L and Valero V 2002 Canalicular stenosis secondary to weekly versus every-3-weeks docetaxel in patients with metastatic breast cancer *Ophthalmology* **109** 1188–91

[4] Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, Chan S, Grimes D, Antón A and Lluch A 2005 Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group *J. Clin. Oncol.* **23** 4265–74

[5] Kementrian Kesehatan R I 2015 Situasi penyakit kanker *Pus. data dan Inf. kementrian Kesehatan. RI*

[6] Esmaeli B, Amin S, Valero V, Adinin R, Arbuckle R, Banay R, Do K-A and Rivera E 2006 Prospective study of incidence and severity of epiphora and canalicular stenosis in patients with metastatic breast cancer receiving docetaxel *J. Clin. Oncol.* **24** 3619–22

[7] Burstein H J, Manola J, Younger J, Parker L M, Bunnell C A, Scheib R, Matulonis U A, Garber J E, Clarke K D and Shulman L N 2000 Docetaxel administered on a weekly basis for metastatic breast cancer *J. Clin. Oncol.* **18** 1212–9

[8] Kersten R C, Bartley G B, Nerad J A, Neuhaus R W, Nowinski T S, Popham J K and Beardsley T L 2005 Orbit, eyelids and lacrimal system *Am. Acad. Ophthalmol. San Fr. CA* 254–62

[9] Esmaeli B, Valero V, Ahmadi M A and Booser D 2001 Canalicular stenosis secondary to docetaxel (taxotere): a newly recognized side effect *Ophthalmology* **108** 994–5

[10] Schmid KE, Kornek GV, Scheithauer W, Binder S. Update on ocular complications of systemic cancer chemotherapy. Surv Ophthalmol 2006; 51:19–40.

[11] Esmaeli, Bita, Vicente Valero, M Amir Ahmadi, and Daniel Booser. 2001. "Canalicular Stenosis Secondary to Docetaxel (Taxotere): A Newly Recognized Side Effect."*Ophthalmology* **108**(5): 994–95. (2001, et al.)

[12] Esmaeli B, Hidaji L, Adinin RB et al. Blockage of the lacrimal drainage apparatus as a side effect of docetaxel therapy. Cancer 2003; **98**: 504–507.

[13] Nagi KS, Meyer DR: Utilization patterns for diagnostic imaging in the evaluation of epiphora due to lacrimal obstruction: A national survey. Ophthal Plast Reconstr Surg **26**:168-171, 2010

[14] Martin M, Pienkowski T, Mackey J, et al: Adjuvant docetaxel for node-positive breast cancer. N Engl J Med **352**:2302-2313, 2005

[15] Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med **358**:1663-1671, 2008

[16] Chan A, Su C, de Boer RH, et al: Prevalence of eessive tearing in women with early breast cancer receiving adjuvant docetaxel-based chemotherapy. J Clin Oncol **31**:2123-2127, 2013
[17] Swain. SM.Chemotherapy: Updates and New Perspectives.The Oncologist. 2010 ;**15**(suppl 5) :8-17 NCCN
[18] Clinical Practice Guidelines In Oncology. Breast Cancer.V.2.2011. Available at: www.nccn.org
[19] Trudeau ME. Eisenhauer EA, Higgins BP et al. Docetaxel in Received 11 January 1999; accepted 8 April 1999. patients with metastatic breast cancer: A phase II study of the National Cancer Institute of Canada - Clinical Trials Group. J Clin Oncol 1996; **14**: 422-8.
[20] Hudis CA, Seidman AD, Crown JPA et al. Phase II and pharma- Dn E Bnasoulls ecological study of docetaxel as initial chemotherapy for metastatic Department of Medical Oncology School of Medicine breast cancer. J Clin Oncol 1996; **14**: 58-65.
[21] Wicke C, Halliday B, Allen D et all. Effect of Steroid and Retinoid in Wound Healing. Arc Surg/Vol 135, Nov. 2000.
[22] Gonul B, Kaplan B, Bilgihan K et all. Effects of epidermal growth factor in artificial tear on vitamin C levels of corneal wounded eye tissues. Eye (2001) **15**, 213-216.
[23] Pe MR, Langford JD, Linberg JV, Schwartz TL, Sondhi N. Ritleng intubation system for treatment of congenital nasolacrimal duct obstruction. Arch Ophthalmol 1998; 116:387-91.
[24] Dave TV, Ali MJ. Intubation in lacrimal surgery: Devices and Techniques. In: Ali MJ, editors. Principles and Practice of Lacrimal Surgery. India: Springer; 2015. p. 289-301.
[25] Repka MX, Chandler DL, Holmes JM, Hoover DL, Morse CL, Schloff S, Silbert DI, Tien DR; Pediatric Eye Disease Investigator Group. Balloon catheter dilation and nasolacrimal duct intubation for treatment of nasolacrimal duct obstruction after failed probing. Arch Ophthalmol 2009; **127**:633-9.
[26] Shams PN, Chen PG, Wormald PJ, Sloan B, Wilcsek G, McNab A, Selva D. Management of functional epiphora in patients with an anatomically patent dacryocystorhinostomy. JAMA Ophthalmol 2014; **132**:1127-32.
[27] Fayet B, Assouline M, Bernard J: Monocanalicular nasolacrimal duct intubation. Ophthalmology 1998; **105**:1795.
[28] Kaufman LM, Guay-Bhatia LA: Monocanalicular intubation with mini Monaca tubes for the treatment of congenital nasolacrimal duct obstruction. Ophthalmology 1998; **105**:336
[29] Goldstein S, Goldstein J, Katowitz J: Monocanalicular Stenting and Balloon Dacryoplasty Following Failed Probing for Congenital Nasolacrimal Duct Obstruction. ASOPRS Annual Meeting, 2001.

Effects Of Sodium Hyaluronate Compared with Steroid Eye Drop Against The Degree Of Canalicular Stenosis In Breast Cancer Patients Treated With Docetax

ORIGINALITY REPORT

2%	0%	2%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

MATCH ALL SOURCES (ONLY SELECTED SOURCE PRINTED)

2%

★ Riani Erna, Nur Qodir, Ristania. "Effects of sodium hyaluronate compared with steroid eye drop against the degree of canalicular stenosis in breast cancer patients treated with docetaxel", Journal of Physics: Conference Series, 2019

Publication

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	Off		

Effects Of Sodium Hyaluronate Compared with Steroid Eye Drop Against The Degree Of Canalicular Stenosis In Breast Cancer Patients Treated With Docetax