Comparison of Tear Interleukin-6 level, Conjunctival Inflammation, and Tear Film Function in Daily Conventional Hydrogel and Extended Silicone Hydrogel Contact Lens Wear

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Abstract: Background: Contact lenses were increasing use worldwide. Silicone hydrogel material was proposed to be safe for overnight Soft Contact Lens wear. This study aim to evaluate IL-6 levels, conjuctival inflammation, tear function and tear menisci parameters after overnight wear of silicone hydrogel Soft Contact Lens and compare with daily wear of hydrogel SCL. A randomized controlled trial carried out in myopia subjects, treated using daily hydrogel (Nefilcon-A) SCL in one eye, and overnight silicone hydrogel (Lotrafilcon-B) SCL in the fellow eye for 14 days. The slit lamp examination, NIBUT, Schirmer test, tear menisci measured with OCT, and tear sampling for IL-6 were performed before and after SCL wear. One hundred and for eyes from 52 subjects were included. The tear IL-6 significantly increases 6.37 pg/mL in Lotrafilcon-B and 4.46 pg/mL in Nefilcon-A. There were no significant conjuctival hyperemia changes in both groups (p=1.000) nor significant correlation of tear IL-6 levels and conjunctival hyperemia (p = 0.234). The NIBUT of both groups were decrease significantly (p=0.000). The Schirmer I were not significant changes after SCL wear. The tear meniscus height were not significantly decrease in both groups. The tear meniscus area were decrease significantly 1,181.5 μm2 in the the Lotrafilcon-B group and 1,795.0 μm2 in the Nelfilcon-A group. The tear meniscus volume were decrease 0.08 μL in the the Lotrafilcon-B 0.05 μL in the Nelfilcon-A group.The correlation between NIBUT, Schirmer I test and tear menisci parameter was not significant. Two weeks of daily hydrogel and weekly silicone hydrogel SCL wear comparably increases tear IL-6, did not increase conjunctival hyperemia, decreases NIBUT, tear menisci, without significant alterations in Schirmer.

1 INTRODUCTION

Prevalence of contact lens (CL) wear is increasing with many reason.[1–3] Increasing prevalence of myopia[4,5] lead to the increase of contact lens wear. International contact lens prescribing in 2019 data[4] shows that the mean age at fitting was in early 30s (32.8 ± 14.9 years) and even younger in Asian markets. Soft contact lens (SCL) was prescribed for 87%. Conventional hydrogel SCLs were prescribe for 21% daily wear CL patients compare to 57% of silicon hydrogel for daily wear CL patients. Only 7% extended wear SCLs were prescribed by the practitioners.[5] However, due to patient's need to have good visual acuity over the time, then emerges demand on overnight or extended wear (EW) SCL.

Contact lens wear can lead to complications including corneal hypoxia, inflammation, contact lens related discomfort and dryness.[1,6] Conjunctival hyperemia was one of its inflamation signs. It was resulted by increase vascular permeability that were often ascociated with tear Interlukin (IL)-6.[7,8] Tear IL-6 level in soft contact lens wearer have been evaluated in some studies.[8–12]

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Silicone hydrogel material was developed to increase CL oxygen permeability. It is important to prevent cornea hypoxia due to overnight CL wear however, the addition of hydrophobic silicone components lower the SCL wettability and cause discomfort. Surface treatment makes SCL surface becomes more hydrophilic, more comfortable to wear, decrease dry eyes risk.6 On the other hand, contact lenses made from conventional hydrogel material need to have a high water content to increase its oxygen permeability. High water content is related to SCL dehydration and protein deposit that can cause decrease of pre- and post-lens tear layer.13–15 Such condition can cause low wettability and make tear easier be evaporated.

SCL wearing duration could also affect tear layer function. Fahmy et al16 reported that Daily Wear (DW) SCL is more comfortable than weekly/monthly wear with the same SCL. Similar result was found in SiHy SCL with increased comfort in DW rather than Extended Wear (EW).17

Evaluating tear film functions could be performed with measuring Non-Invasive Break Up Time (NIBUT), Schirmer, and tear volume.18,19 Tear meniscus could be assess non invasively with Optical Coherence Tomography (OCT). It was reported OCT have a great precision to measure tear meniscus.

As far as our knowledge, there is no prior study that evaluate the inflamation rate of SCL users with an appropriate manner of SCLs wearing schedule based on it's material oxygen permeability. The aim of this study to compare the effect of weekly wear of silicon hydrogel SCL and daily wear conventional hydrogel SCL on tear IL-6 level, conjunctival inflammation, tear film functions, and the correlation among that parameters.

2 MATERIAS AND METHODS

The subjects were recruited with inclusion criteria of low to moderate myopia (-0.50 to -6.00 Diopters) and astigmatism less than 1 diopters, subjects with 6/6 BCVA on both eyes, aged ≥18-35 years, had a good general condition and were able to undergo a follow-up procedure. The subjects with abnormal corneal topography, have a disease or history of allergic or atopic disease, NIBUT less than 10 seconds, work in exposure to chemicals, smoke, hazardous gases, and welding / flame sparks were excluded. Subjects who did not come for follow up according to the schedule determined by the researcher, resigned while the research was in progress, experiencing severe inflammation or infection in the eye, or did not use SCL according to the instructions given by the researcher consider to be drop out from the study. Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine Universitas Indonesia (N0: KET-135/UN2.F1/ETIK/PPM.00.02/2019).

Conjunctival inflammation with the was assessed based on slit lamp camera photos by 2 ophthalmologist. The assessment was carried out using the Efron Grading System.20 If there is a difference of opinion between the two assessors, the value taken is the highest grading number. Tear samples were taken before and 14 days after SCL wear. The tear IL-6 was examined at Biochemistry Laboratory Faculty of Medicine, Universitas Indonesia using the Human Interleukin-6 Elisa Kit Coma Biotech® Quote JC5607 Product No. K0331194 from Indonesian Genetics Science LLC. The NIBUT was measured with Tearscope-plus® (Keeler, Windsor, UK), determined by the time (second) of Tearscope mirres on the cornea break after blink. Schirmer I test was performed using Schirmer test strips. Tear meniscus examination was measured 3 times, 20-60 minutes, 7 days, and 14 days after using SCL by measuring tear meniscus hight (TMH) and tear meniscus area (TMA) using anterior OCT of Cirrus™-HD OCT 5000, Carl Zeiss, Germany. Manual measurement with ImageJ software was used to measure TMV. Assessments were done 3 times, 20-60 minutes, 7 days, and 14 days after using SCL. All the examiner were blinded to the type of the SCL worn by the subjects.

3 RESULTS

There were 52 subjects (104 eyes) included to this study, 10 subjects are male and 42 are female. The mean age of subjects is 22.12±1.79 years.
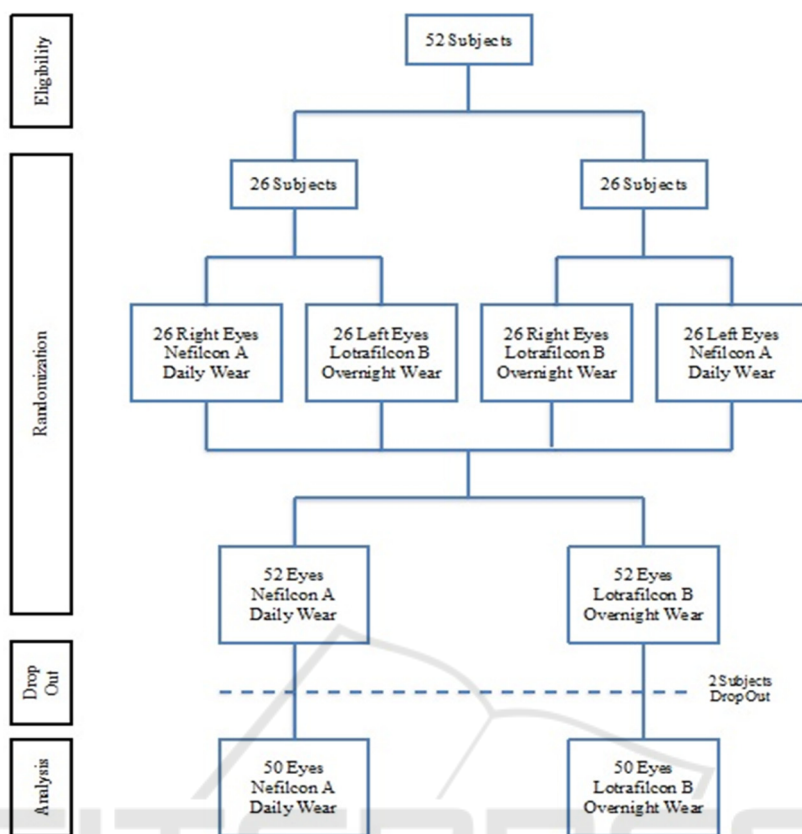
Figure 1. Scheme of Recruitment

Table 1. Clinical Characteristics data of Subjects in Two Groups

Parameter	Nefilcon A	Lotrafilcon B	P value
	Mean / Med (SD / Range)	Mean / Med (SD / Range)	
UCVA	0,40 (0,02 - 0,86)	0,50 (0,03 - 0,86)	0,386*
Spher (D)	-1,25 (-6,00 - -0,50)	-1,00 (-6,00 - -0,50)	0,169*
Cyl (D)	-0,25(-1,25 - 0,00)	-0,25 (-1,25 - 0,00)	0,399*
SCL (D)	-1,25 (-6,00 - -0,50)	-1,00 (-6,00 - -0,50)	0,059*
K1 (D)	42,93 (± 1,27)	42,92 (± 1,23)	0,697
K2 (D)	44,03 (± 1,23)	44,08 (± 1,22)	0,364
IL-6 pre (pg/ml)	1,24 (0,04 - 160,10)	0,95 (0,04 - 171,02)	0,695*
NIBUT	14,70 (± 3,72)	16,76 (± 5,05)	0,001

Table 2. The IL-6 Tear Level Before and After SCL wear between Groups

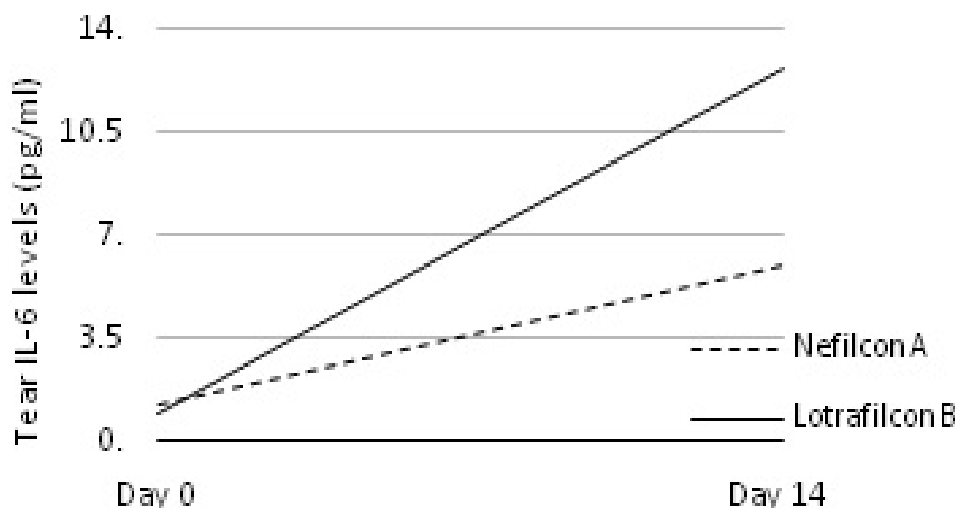| Parameter	Nefilcon A	Lotrafilcon B	P value*
	Median (Range) pg/ml	Median (Range) pg/ml	
IL-6 pre	1,24 (0,04 - 160,10)	0,95 (0,04 - 171,02)	0,695
IL-6 post	5,97 (0,07 - 698,95)	12,66 (0,11 - 1118,59)	0,101
IL-6 increase	4,46 (0,01 – 685,40)	6,37 (0,05 – 1115,8)	0,117

Figure 2. Comparison between IL-6 levels before and 14 days after daily use Neflicon A and weekly use of Lotrafilcon B

Lotrafilcon B were used in 21 eyes and 31 left eyes while Nefilcon A were used in 31 right eyes and 21 left eyes. Two subjects were dropped out due to non-compliance of SCL wear and lost to follow-up. Data analysis was carried out in 100 eyes of 50 subjects, 50 eyes with Nefilcon A daily wear and 50 eyes with Lotrafilcon B overnight wear (figure 2).

There is no significant difference in UCVA, spherical and cylindical power correction, keratometric value, and IL-6 tear levels between groups before using SCL. The NIBUT value of subjects in Lotrafilcon group was significantly higher compare to those in Nefilcon group. However the difference is not clinically significant, since the mean NIBUT value of both group are in normal range. (tabel 1).

There is a significant increase of tear IL-6 level after 14 days SCL wear in both groups (p=0.000). However, there were no significant differences in the delta IL-6 tear levels between groups as seen in Table 2. The increasing tear IL-6 levels in weekly Lotrafilcon B SCL wearer seems higher compare to those in daily Nefilcon A SCL wearer. However, the difference is not statistically signifinat. Figure 2.

There is no significant differences in conjunctival inflammation, determined with Efron's Grading System, betwen two groups of SCL wearer before and after 14 days using SCL as well (p=0.000).The difference of conjunctival inflammation changes was also not statistically significant between two groups of SCL wearer (figure 3). Table 3 and 4 shows that the correlation between tear IL-6 and conjunctival inflammation was not significant. There was significant decrease the mean

of NIBUT in both groups after 14 days SCL wear. The mean of NIBUT value changes were 3.4 seconds in Nefilcon A daily SCL wear and 4.6 seconds in Lotrafilcon B weekly SCL wear. The NIBUT decrease after 14 days Lotrafilcon weekly SCL wear was significantly greater rather than that in Nefilcon daily SCL wear (p=0.008, Wilcoxon rank test). There were no significant difference of Schirmer I change before and after SCL wear between groups, that were 0.41 mm (-6.0 – 7.0 mm) in Nefilcon A group and 0.69 mm (-10 – 10 mm) in Lotrafilcon B group (p= 0.401, Wilcoxon rank test).
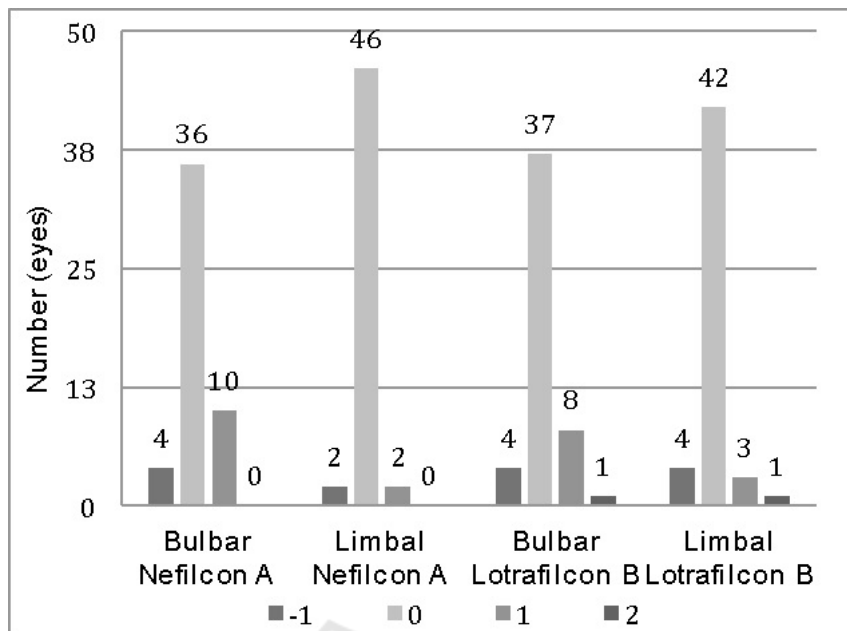
Degrees changes -1:One degree down, 0:No changes, 1:Increases by 1 degree, 2:increase by 2 degrees

Figure 3. Changes in the degree of conjunctival inflammation before and after daily use of Nefilcon A LKL and weekly use of Lotrafilcon B

Table 3. Correlation between conjunctival bulbar inflammation and changes in IL-6 levels

Conjunctival inflammation (Efron's Grade)	Nefilcon A		Lotrafilcon B		P value*
	n	Tear IL-6 Median (Range)	n	Tear IL-6 Median (Range)	
(1)	9	0,38 (0,02 - 685,40)	10	4,61 (0,06 - 230,30)	0,243
(2)	40	4,60 (0,01 - 120,46)	36	5,61 (0,05 - 1115,80)	0,905
(3)**	1	8,48 (8,48 - 8,48)	4	15,7 (2,45 - 29,77)	----

*Mann Whitney rank. ** Not tested

Table 4. Correlation between conjunctival limbal inflammation and changes in IL-6 levels

Conjunctival inflammation (Efron's Grade)	Nefilcon A		Lotrafilcon B		P value*
	n	Tear IL-6 Median (Range)	n	Tear IL-6 Median (Range)	
(0)	1	0,13(0,13 - 0,13)	0	------	----
(1)	46	4,46 (0,01 - 685,40)	47	7,03 (0,05 - 1115,8)	0,424
(2) **	3	26,5 (0,05 - 120,46)	2	1,35 (0,83 - 1,87)	----
(3) **	0	------	1	29,8 (29,8 - 29,8)	----
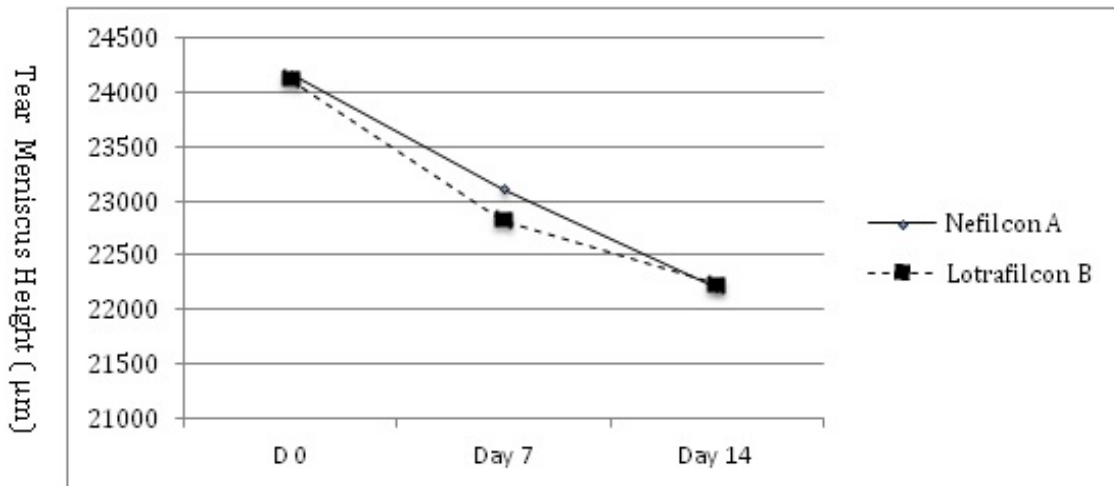
Nelfilcon A; Anova p=0.236
Lotrafilcon B; Anova p=0.476

Figure 3. Tear Meniscus Height mean value at day 0, day 7, and day 14 evaluation
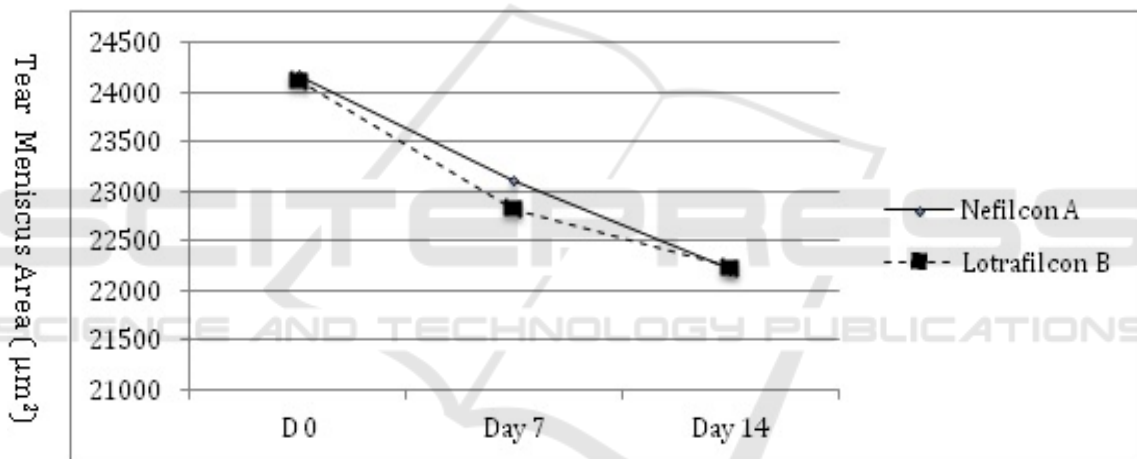
Nelfilcon A: Anova p=0.001   0 vs 7 : p=0.085   7 vs 14: p=0.116   0 vs 14: p=0.000
Lotrafilcon B: Anova p=0.003   0 vs 7 : p=0.058   7 vs 14: p=0.548   0 vs 14: p=0.003

Figure 4. Tear Meniscus Area mean value changes from initial to day 14 evaluation
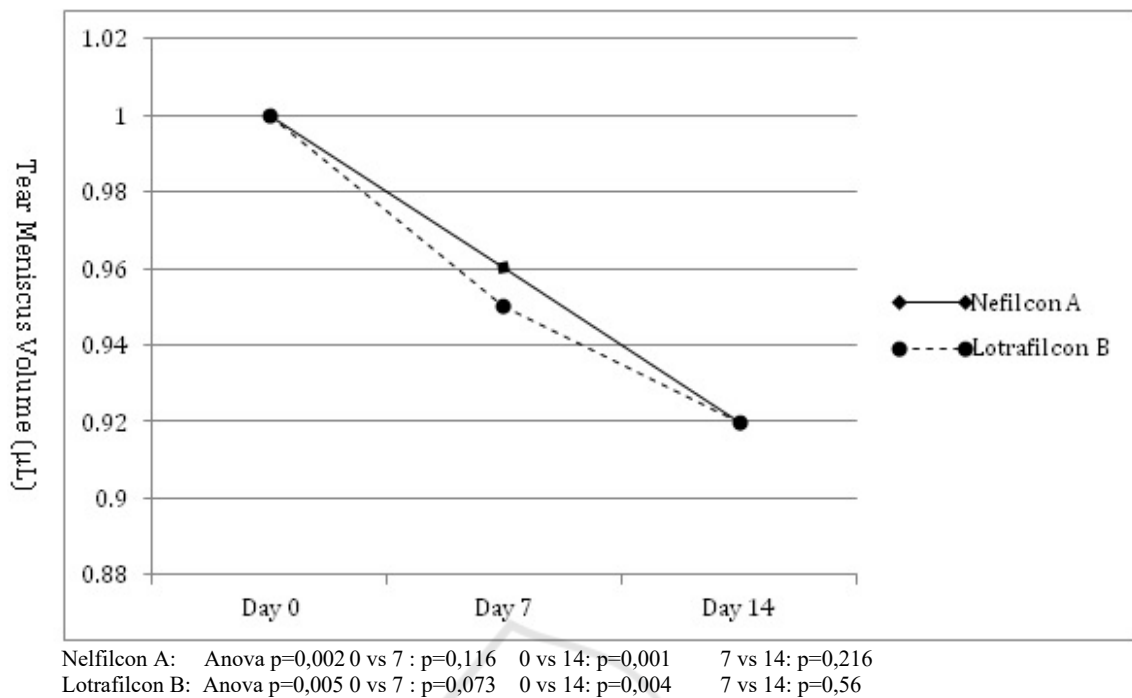
Nelfilcon A: Anova p=0,002 0 vs 7 : p=0,116   0 vs 14: p=0,001   7 vs 14: p=0,216
Lotrafilcon B: Anova p=0,005 0 vs 7 : p=0,073   0 vs 14: p=0,004   7 vs 14: p=0,56

Figure 5. TMV mean value changes from initial evaluation to day 14 evaluation

There are no significant TMH decrease in both Nelfilcon A group (p=0.236, Anova test) and Lotrafilcon B group (p=0.476, Anova test)(figure3). There is also no significant diference TMH decrease between group (p=0.556, Wilcoxon rank test).

There were significant decreases in mean of TMA value after day 14 days of SCL wear, which are 1.795,0 μm2 in Nelfilcon A group and 1,181.5 μm2 in Lotrafilcon B group (figure 4). The decreases of TMA between group have no significant difference (p= 0.898, Wilcoxon rank test).

Changes in TMV mean value on both groups were also found insignificantly different (p>0.05). Changes in TMV mean value for Nelfilcon A and Lotrafilcon B groups after 14 days are -0.08 μL and -0.05 μL. These results were statistically insignificant (p= 0.342). Figure 5 showed significant decrease of TMV after 14 days wearing SCL, while the decrease after 7 days wearing SCL was found insignificant.

Spearman correlation test was carried out in this study. It is found that neither in group Nelfilcon A or Lotrafilcon B was found significant correlation between NIBUT or Schirmer 1, both initial and final evaluation results, and TMH, TMA, and TMV both initial and final evaluation results (r < ±0,3).

4 DISCUSSION

The level of IL-6 in tears increased significantly after 14 days SCL in both groups (p=0,000). However, the difference in the increase of that was not significant between groups (p=0.117). It could be proposed that 14 days of silicon hydrogel weekly overnight SCL wear have equally effect in tear IL-6 levels increase with daily conventional hydrogel SCL wear. Poyraz et al9 found that increasing IL-6 values in conventional hydrogel SCL users and silicone hydrogel SCL wearer did not have significant differences. In Poyraz's study both SCL types were used daily.

The conjuctival hyperemia of the subjects in this study were not significantly changed before and after 14 days SCL wear, both in Nefilcon A group (p=1.000) and Lotrafilcon B group (p=1.000). Fonn et al21 reported that subjects using conventional hydrogel SCL shows significantly higher increase conjunctival injection compare to that who use silicon hydrogel SCL. The effects difference of SCL wear in Fonn's study was probably caused by both type of SCL with different Oxygen permeability were use for overnight wear. Brennan et al22   found that conventional hydrogel weekly SCL wearer showed a significant higher level of conjunctival inflammation compare to silicon hydrogel SCL wearer. Covey et al23 reported the level of inflammation in high Dk

silicone hydrogel SCL wearer were the same as in normal not wearing SCL eyes, it was grade 2 (mild), similar with our study. This suggests that 14 days of properly SCL wear did not triger a significant conjunctival inflammation yet.

There is no significant correlation between elevated tear IL-6 levels with conjunctival inflammation found in this study. Significant increase in tear IL-6 after 14 day SCL wear was not followed by an increase in conjunctival vascular injection. Same findings were reported by Enrique de Salamanca et al24 and Kalsow et al25, who suggest that an increase in cytokines on the ocular surface often occurs before the appearance of clinical symptoms. Dogru et al8 reported that 2 weeks daily use of silicone hydrogels SCL has a close relationship with increased IL-6 in tears wich is not accompanied by significant changes in the surface damage of the conjunctiva or cornea, as well as changes in keratoconjunctival cell morphology.

Soft Contact Lens wear could induce CLIDE, because it increases evaporation, disturbs tear film stability6,14 and alters tear production. Conventional hydrogel SCL may cause CLIDE due to its high water content, protein deposit, low wettability, and friction between SCL and ocular surface.6,18,26 Meanwhile, silicone hydrogel SCL that is more hydrophobic, have lower wettability, and its extended wearing could increase the risk of CLIDE.

The subjects of both groups experience significant decrease of NIBUT after 2 weeks using both SCL. This finding is similar to previous studies.8,27,28 Weekly overnight Lotrafilcon B wear dcreases NIBUT significantly greater compare to daily Nefilcon A SCL wear (p=0.008). SCL wear could intervere physiological quality of tear film due to evaporation.8,14

We found no significant changes in Schirmer I results after 14 days SCL wear in both group. Iskeleli29 also found no decrease in Schirmer I evaluation after 3 months of Lotrafilcon A and Lotrafilcon B SCL wear. Other study by Dogru et al8 found no significant decrease after 2 weeks using daily wear silicon hydrogel SCL.

There was no significant decrease of TMH after 2 weeks using both type of SCL. There was also no significant difference of TMH decrease between the two groups. This findings was similar with Santodomingo-Rubido et al11 that found no significant TMH difference between 4 groups of Silicon Hydrogel wear for 1, 3, 6, 12, and 18 months.

Tear Meniscus Area was not significanty decrease after 2 weeks using SCL, with no significant difference between groups. Wang et al30 found no significant decrease in TMA after 20 minutes using two SCL types. Wang et al used 20 adapted subjects using Balafilcon A on one eye and Galyfilcon A on the other eye.

Our study found that both daily wear conventional hydrogel and weekly silicone hydrogel SCLs waer significantly decreases TMV after 2 weeks with no significant difference between group. This is accordance to study by Wang30 that found no significance difference in TMV decrease in adapted subjects after 20 minutes and 4 hours using SCL.

We found no correlation between NIBUT and Schirmer I examination, both groups. Wang et al also found no correlation between NIBUT and tear volume which was assessed with fluorometry.31 It is proposed that NIBUT shows tear film stability, not tear quantity.

The correlation between Schirmer I and tear menisci parameters has been studied both in normal and dry eyes populations. Raj A et al32 evaluated tear menisci in normal population using Fourier Domain OCT and showed no correlation between Schirmer 1 and TMH. This result may be affected by Schirmer 1 method that used direct contact to eye so it affected secretion reflex and tear base. Meanwhile, evaluation with OCT used non-invasive method to measure tear menisci at one time.

5 CONCLUSIONS

Tear IL-6 level increased significantly after 14 days daily conventional and weekly silicone hydrogel SCL wear. The increased tear IL-6 level occur before the increase conjunctival hyperemia. The NIBUT, Schirmer I, and tear menisci parameters have each functions that can be replaced by one another. After 2 weeks of using daily wear Nefilcon A and weekly Lotrafilcon B SCLs decereases the NIBUT and Tear Meniscus Volume. It is suggested to evaluate tear stability in long term SCL wearer.

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