Acupuncture compared with 0.5% carboxymethyl cellulose for improving Schirmer I test and OSDI scores for treating dry eye in menopausal women

S A Apriani, D K Widya, A Srilestari* and M Susiyanti

1Departement of Medical Acupuncture, Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia.
2Departement of Ophthalmology, Faculty of Medicine, Universitas Indonesia, Jakarta, 10430, Indonesia.

*E-mail: adiningsih.srilestari@yahoo.com

Abstract. Dry eye is the most common condition reported by patients who seek ophthalmologic care and by menopausal women. Acupuncture can help improve symptoms of dry eye. Therefore, in the present study, we aimed to evaluate the efficacy of acupuncture compared with 0.5% carboxymethyl cellulose (CMC) in improving Schirmer I test and Ocular Surface Disease Index (OSDI) scores and treating dry eye in menopausal women. The study consisted of 69 menopausal women with dry eye divided into a 0.5% CMC group, a group given acupuncture once (1× acupuncture group), and a group given acupuncture twice (2× acupuncture group). In the 0.5% CMC group, patients were given one drop of CMC four times daily for 7 days. In the 1× acupuncture group, acupuncture was performed on Ex HN3 Yintang, GB 1 Tongziliao, BL1 Jingming, LI 4 Hegu, LR 3 Taichong, SP 6 Sanyinjiao, and GB 37 Guangming for 20 min. In the 2× acupuncture group, acupuncture was performed at the same points on day 1 and repeated on day 3 after the first therapy session. Evaluation was performed 1, 3, 7, and 14 days after the first therapy session. The results showed that acupuncture increased Schirmer I test scores and decreased OSDI scores. The efficacy of 0.5% CMC was 87%, that of 1× acupuncture was 91.3%, and that of 2× acupuncture was 100% in increasing Schirmer I test scores on day 7 of evaluation. The efficacy of 0.5% CMC was 91.3%, that of 1× acupuncture was 87%, and that of 2× acupuncture was 100% in decreasing OSDI scores on day 7 of evaluation. No side effects occurred in the study.

1. Introduction
Dry eye is a tear and eye surface disorder that causes discomfort, visual disturbance, and tear instability with the potential to cause eye damage. The disorder is accompanied by an increase in tear osmolarity and inflammation of the eye surface [1]. Dry eye is the most common disorder found in the field of ophthalmology [2]. The prevalence of dry eye varies between 6% and 33% in the adult population and is found more frequently in those aged >50 years [3-6]. The prevalence of dry eye in the Sumatera region was reported to be approximately 27% [7]. At the eye polyclinic for sub-immunological infection at Cipto Mangunkusumo Hospital, a dry eye prevalence of approximately 27.59% was noted in the period of May–June 2004, with the women:men ratio being approximately 7.3:1 [8]. The number of dry eye patients at the Cipto Mangunkusumo Hospital General Eye Clinic in 2010 was 625. In general, dry eye is considered a chronic disorder and is generally symptomatic,
although it can sometimes be asymptomatic [9]. Symptoms include sore, sandy, sticky, itchy, stiff, red, and stingy eyes, with a burning sensation, drowsiness, and exhaustion. These symptoms interfere with patients’ daily activities such as reading, watching television, or using a computer [10,11].

Dry eye is known to be often experienced by menopausal women [12]. Dry eye mechanisms in postmenopausal women are thought to be due to progressive degeneration in lacrimal and meibom glands induced by hormonal deficiencies, especially those of estrogen and androgens, and are affected by tissue aging [13].

Dry eye diagnosis is based on subjective and objective tests. A commonly indicated subjective examination is a specific questionnaire used to assess dry eye symptoms such as the Ocular Surface Disease Index (OSDI) questionnaire and the McMonnies questionnaire. An objective examination of dry eye is done using the Schirmer I test to assess the quantity of tears and tear break-up time to assess quality of the tear layer [14].

Dry eye therapy in menopausal women is aimed at improving the stability of the tear layer (LAM) to relieve complaints of ocular irritation quickly; for example, using emulsion drops containing lipids in water [15,16]. A study by Putri NE mentions the use of 0.5% carboxymethyl cellulose (CMC) in treating dry eye experienced by postmenopausal women and improving the OSDI questionnaire score; however, when compared with baseline, there was no significant difference [17]. Causative therapy using hormone replacement therapy was not satisfactory. A study by Kuschu et al. showed that a combination of estrogen and medroxyprogesterone hormone replacement therapy for 6 months in postmenopausal women was not able to resolve complaints of ocular irritation or TF BUT and Schirmer I test scores significantly [18].

Based on the principles of traditional Chinese medicine, dry eye is not considered a disease but a syndrome associated with the liver, namely the deficiency of liver Yin, excess of liver Yang or disruption of Fire liver. The principle of using acupuncture to overcome dry eye complaints is based on achieving balanced functioning of the liver [19].

Previous acupuncture studies to resolve dry eye showed satisfactory results. A descriptive study by Kyle et al. on 17 dry eye patients evaluated using OSDI assessment and treated using 1× acupuncture at ST1 Jingming point, Tongziliao GB1, and BL 2 Cuanzhu, and 4-Hz electrical stimulation at Taichong LR3 point, LR8 Ququan, LR 14 Qimen, and GB 1 Tongziliao bilaterally for 15 mins found an improvement of 88% [20]. Richard et al. reported four case studies of xerophthalmia treatment using acupuncture on the index finger in the meridian region of the colon, 3–4 mm above the Shangyang 1 LI point, and on the Zero, Shenmen, and salivary glands on the ear bilaterally. The results showed that artificial tear drop usage could be reduced in these patients from every 10 mins to once or twice daily [21].

The mechanism of acupuncture action on dry eye experienced by postmenopausal women was found to be related to its pathophysiology, involving disturbance in androgen hormones, estrogens, and hormones in the hypothalamic–pituitary axis affecting the role of lacrimal gland production and the meibom glands [4,5,12]. Acupuncture was found to resolve the dry eye experienced by menopausal women through local effects by improving cell metabolism, and through central effects stimulating the function of the optic nerve from the retina to the visual cortex [22]. It also activates the hypothalamus-hypophysis which releases endorphin beta into the blood and cerebrospinal fluid [23]. Endogenous peptide opioid compounds including beta-endorphins play a role in releasing Gonadotropin Releasing Hormone (GnRH) in the hypothalamus either directly or indirectly [23].

An experimental study concluded that the effect of acupuncture in regulating the hypothalamic–pituitary–ovarian (HPO) axis occurs through the activation of the hypothalamic–pituitary–adrenal (HPA) axis which enhances the synthesis and secretion of adrenal steroid hormones such as androgens that can be transformed into estrogens and lead to negative feedback on estrogen levels in the HPO axis [23].

Previous studies using hormone replacement therapy in menopausal women suffering from dry eye have shown unsatisfactory results. Use of artificial tears, comprising 0.5% CMC, is symptomatic therapy that should be used for prolonged periods, and the use of acupuncture to treat dry eye has
shown favorable results. However, acupuncture studies have not conducted an objective and subjective assessment of dry eye experienced by menopausal women. The present study aimed to determine the effect of acupuncture on improving Schirmer I test results and OSDI scores in the treatment of dry eye in menopausal women.

2. Methods
The research design of this study was that of a quasi-experimental clinical trial. The population of the study consisted of postmenopausal women suffering from dry eye who visited the immunology infection polyclinic subsection of the Department of Ophthalmology at Cipto Mangunkusumo Hospital. The acceptance criteria were the lack of menstruation for 12 months–5 years, Schirmer I test scores of 5–10 mm, OSDI scores > 23, and willingness to provide informed consent and participate in the study schedule until completion.

Subjects were divided into three groups: group A received artificial tears comprising 0.5% CMC as one drop four times daily for 7 days; group B received 1× acupuncture therapy with an acupuncture needle of size 0.18 × 13 mm at Ex HN3 Yintang point, GB 1 Tongziliao, BL1 Jingming, and with a needle of size 0.25 × 25 mm at point LI 4 Hegu and LR 3 Taichong, with a needle of size 0.25 × 40 mm on SP6 Sanyinjiao and GB 37 Guangming, with all points receiving bilateral insertions. Insertion was done until the sensation of matchmaking was felt, and stimulation was performed every 5 min. The needles were allowed to remain for 20 mins and then removed. Group C received 2× acupuncture therapy at the same point as group B on days 1 and 3 (Table 1).

Table 1. Treatment Schedule

| Groups | Treatments | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 14 |
|--------|------------|------|------|------|------|------|------|------|-------|
| A      | Sch I      | Sch I| CMC  | Sch I| OSDI | CMC  | CMC  | CMC  | Sch I |
| (CMC 0.5%) | OSDI      | OSDI | CMC  | OSDI | OSDI | OSDI | OSDI | OSDI | OSDI  |
| B      | Sch I      | Sch I| OSDI | Sch I| OSDI | OSDI | OSDI | OSDI | Sch I |
| (Acp 1×) | OSDI      | OSDI | OSDI | OSDI |      |      |      |      |       |
| C      | Sch I      | Sch I| OSDI | Sch I| OSDI | OSDI | OSDI | OSDI | OSDI  |
| (Acp 2×) | OSDI      | OSDI | OSDI | OSDI |      |      |      |      |       |

ACP: Acupuncture
CMC: Carboxymethyl Cellulose 0.5%

Notes:
Sch I: Schirmer I test
OSDI: Ocular Surface Disease Index

Subjects were considered to have dropped out if they did not follow the research procedure until completion or continued using eye drops following acupuncture therapy.

Type I error (α) was set at 5% resulting in Za = 1.96; study power was set at 90% resulting in Zβ = 1.28; S was the standard deviation of the OSDI value (library18); S = 0.2.

As a result, the number of subjects per group was 21 people.

Objective assessment in this study was done using the Schirmer I test, which is an examination that uses the Schirmer paper (Clement Clarke Int'l Ltd, Edinburgh Way, Essex, UK). Subjective assessment
was done with a translated OSDI questionnaire, which is used in the clinic of the Department of Ophthalmology Cipto Mangunkusumo Hospital. The data collected in the study are presented in the form of tables and diagrams with narration. Statistical analysis was performed using the package SPSS version 17.00. To compare the Schirmer I test data and OSDI scores in all three therapy groups, one-way ANOVA was used with the Kruskal–Wallis test depending on the data distribution. To compare the Schirmer I test data and OSDI scores in each group before and after therapy, repeated ANOVA with the Wilcoxon test was used depending on the data distribution. The significance value was set at $p \leq 0.05$.

The study was conducted after the approval of the Health Research Ethics Committee of Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital with No. 410 / PT02.FK / ETIK / 2010. All study subjects agreed to participate by signing informed consent forms which stated that secrecy is guaranteed and disclosure is voluntary.

3. Results
The study was conducted during October–December 2010 in 69 menopausal women experiencing dry eye at the eye polyclinic of Cipto Mangunkusumo Hospital Jakarta (Table 2). All patients participated in observations per the schedule, i.e., before treatment, on days 1, 3, 7, and 14 after treatment.

| Table 2. Characteristics of Subjects |
|--------------------------------------|
| Groups                               | CMC 0.5% | 1× ACP | 2× ACP |
|                                      | n = 23   | n = 23 | n = 23 |
| Age*                                 | 53.826 ± 2.806 | 52.608 ± 2.606 | 54.304 ± 2.098 |
| Amenore*                             | 3.313 ± 0.919 | 2.826 ± 0.886 | 3.087 ± 0.702 |
| Schirmer I **                        | 6.478 ± 1.441 | 6.087± 1.755 | 5.869 ± 1.713 |
| OSDI                                 | 33.00 ± 4.274 | 33.13 ± 5.011 | 33.39 ± 4.802 |

*p\text{in year}, **p\text{in millimeters (mm)}

The graph on Fig. 1 above shows that after the treatment on day 1 in each group, there was an increase in Schirmer I test scores. ANOVA results showed that compared to baseline, Schirmer I test scores in the 0.5% CMC group, the 1× group acupuncture group, and the 2× group acupuncture increased significantly on days 1 (p-value 0.004), 3 (p-value 0.000), and 14 (p-value 0.000).

The success rate of 0.5% CMC in improvement of OSDI scores on day 7 after treatment was 91.3%, with 21 people showing improvement and two people not showing improvement. In the 1× acupuncture group, 87% improvement was seen in OSDI scores, with 20 people experiencing improvement and three people not showing improvement. In the 2× acupuncture group, 100% showed improvement in OSDI scores (Figure 2).

The adverse effect of visual blur shortly after the use of 0.5% CMC drops was felt by one patient and was only reported on day 1 of evaluation. Complaints of itching or pain after dripping were not reported until the end of the study. No subject experienced a drop-out due to adverse events. The subjects were not given additional medication to overcome the complaints but were educated regarding maintenance of eyelid hygiene.
4. Discussion

This study was conducted using a quasi-experimental design among 69 menopausal women experiencing dry eye. The patients were divided into three groups; group A receiving 0.5% CMC as eye treatment (control), group B who received 1× acupuncture therapy, and group C who received 2× acupuncture therapy.
In the control group, after CMC 0.5% on day 1, mean improvement in Schirmer I test scores continued to increase until day 7 compared with baseline. In the 1× acupuncture group, the average Schirmer I test score increased from day 1 to day 3, but the mean improvement decreased on day 7 with further decreases until day 14. This shows that the 1× acupuncture led to improvement in the maximum Schirmer I test score on day 3 and declined until day 14, despite not returning to baseline before needle usage. These effects of 1× acupuncture are consistent with the theory that acupuncture effects last up to 3–4 days [24].

The 2× acupuncture group’s mean improvement in Schirmer I test scores increased from day 1 until day 7. On day 14, the score decreased but remained better than the score before treatment. These assessments show that the improvement in Schirmer I test scores is best when compared between the three groups. The 2× acupuncture resulted in improving mean value of Schirmer I test scores compared with 1× acupuncture. For optimal dry eye therapy, acupuncture should be done more frequently.

Schirmer I test scores on day 3 after treatment in the 2× acupuncture group were higher than those in the 1× acupuncture group. This was due to differences in test timings. According to Bayoan et al., disadvantages of the Schirmer I test when performed at different times and performed by different people can result in varying Schirmer I test scores [25].

In the assessment of OSDI score, the success rate of 2× acupuncture was 100% (23 individuals), that of 0.5% CMC group was 91.3% (21 individuals), and that of 1× acupuncture was 87% (20 individuals). ANOVA showed no significant difference. Therefore, 2× acupuncture, 1× acupuncture and 0.5% CMC were equal in resolving subjective complaints. The results were better than those obtained by Kyle et al. in 17 dry eye patients using single acupuncture at ST1, GB1, and BL2 points with 4 Hz stimulation at LR3, LR8, LR 14, and GB1 bilaterally for 15 mins, which showed 88% improvement. Therefore, selection of different acupuncture points and frequency affects improvement in OSDI scores.

In treating dry eye, acupuncture has been thought to play a significant role in local and central pathways (hypothalamus). The pricking of acupuncture points locally creates micro injury to tissues that stimulates cell membranes by increasing their permeability ultimately leading to the accumulation of Na and K ions at the two sides of the cell membrane (intra and extra cellular). This leads to excitation of sensory receptors and somatic afferent fibers (Aδ and C fibers) [24].

, nociceptive stimulation turns into a nociceptive impulse via several local substances such as histamine, serotonin, kinin, lymphokines, leukotriene, and prostaglandins and other peptides which play a role in affecting myelin in the peripheral afferent fibers and transduction of nociceptive information, repairing damaged tissue, causing dilatation of capillaries, activation of leukocytes, release of prostaglandins and other chemical mediators causing local clinical phenomena such as inflammation, swelling, redness, itching, and warmth in the puncture area. Because this local reaction is a small inflammatory reaction, it would involve endogenous opioid synthesis, whose antinociceptive effects are prolonged to 3–4 days after acupuncture therapy.

Through central effects, acupuncture could improve the optic nerve status by stimulating optic nerve function from the retina to the visual cortex and activate the hypothalamus of the pituitary through the activation of the hypothalamic–pituitary–adrenal (HPA) axis function. The selected acupuncture points are traversed by innervation that affects optics such as n. opthalmica, n. fascialis and n. trigemine. It is therefore likely that acupuncture improves optic nerve status.

The experimental studies concluded that the effect of acupuncture in regulating the HPO occurs through activation of the HPA axis, which increases synthesis and secretion of adrenal steroid hormones such as androgens that are subject to change to estrogen, and provide negative feedback on estrogen in the HPO axis. Further, acupuncture can increase release of beta-endorphins in the central nervous system to inhibit excessive secretion of GnRH and LH [26]. It is therefore expected that acupuncture may help overcome dry eye symptoms, with one mechanism through the above pathway.

The adverse effects of blurry eyes due to 0.5% CMC eye drops occurred only the first time. Because these side effects did not continue, no patients dropped out in this group. In the acupuncture
group, there were no side effects such as hematoma, pain after treatment, or persistent itching at the pricked site.

Current treatment of dry eye in menopausal women involves use of artificial tears as symptomatic therapy, which is used continuously for prolonged periods with minimal side effects. 0.5% CMC has anionic properties that increase the mucoadhesive strength of a substance and extend the contact time (retention) on the ocular surface. These drugs will usually harden and feel sticky when dry, often causing crusting on the user's eyelids [27]. Hormone replacement therapy has been studied by Kuscu et al., but the results showed ineffectiveness of the therapy. The presence of systemic side effects such as breast tenderness, water retention, nausea, leg pain, and headaches further decrease the quality of life of hormone replacement therapy users [17]. Acupuncture therapy in the present study showed an effect equivalent to 0.5% CMC use in improving Schirmer I test and OSDI scores. There were no side effects of acupuncture during the study. In summary, our results showed that acupuncture can be used as a therapy for treating dry eye experienced by menopausal women.

5. Conclusions
Acupuncture had an effect in increasing Schirmer I test scores and decreasing OSDI scores. The success rate of 0.5% CMC was 87%, that of 1× acupuncture 91.3%, and that of 2× acupuncture was 100% on Schirmer I test scores on day 7 of evaluation post-treatment. The success rate of 0.5% CMC was 91.3%, that of 1× acupuncture was 87%, and that of 2× acupuncture was 100% in OSDI scores on day 7 of evaluation post-treatment.

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