Glaucoma and dry eye disease: the role of preservatives in glaucoma medications

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Abstrak

Glaukoma adalah penyebab kebutaan yang ireversibel dengan prevalensi yang kian meningkat. Sebagian besar penderita glaukoma juga mengalami mata kering. Mata kering merupakan efek samping tersering akibat obat tetes mata topikal berpengawet benzalkonium klorida pada penderita glaukoma. Selain itu, glaukoma dan mata kering memiliki faktor risiko yang sama, yaitu usia lanjut dan jenis kelamin wanita. Mata kering pada penderita glaukoma perlu ditangani segera karena menyebabkan ketidaknyamanan, mengurangi kepatuhan berobat, dan menurunkan tingkat keberhasilan terapi. Penanganan mata kering pada penderita glaukoma dapat dilakukan melalui penggunaan obat tanpa pengawet benzalkonium klorida, kombinasi obat yang mengandung dengan yang tidak mengandung pengawet untuk mengurangi paparan, pemberian air mata buatan, dan pembedahan untuk mengurangi kebutuhan obat anti glaukoma topikal. ***(Med J Indones 2011; 20:302-5)***

Abstract

Glaucoma is a common cause of irreversible blindness with increasing prevalence. Some of glaucoma patients will also experience dry eye. Dry eye is the most frequent side effect related to benzalkonium chloride (BAC)-containing eye drop used for glaucoma patients. In addition, glaucoma and dry eyes have shared risk factors that are old age and female. Dry eye among glaucoma patients need to be treated promptly as it produces discomfort, reduces patients' compliance and decreases success rate of glaucoma therapy. Dry eye symptoms can be treated by applying preservative-free eye drop, giving combination of preservative containing and preservative-free eye drop to reduce BAC exposure, prescribing artificial tear and conducting surgery to minimize or eliminate the need of topical medication. ***(Med J Indones 2011; 20:302-5)***

Keywords: *benzalkonium chloride, dry eye, glaucoma*

Glaucoma is an optic neuropathy that can cause visual field defects and irreversible blindness. According to World Health Organization (WHO), glaucoma is the third most common cause of blindness in the world.[1] It is estimated that the number of people living with glaucoma worldwide will grow from 60.5 million in 2010 to 79.6 million in 2020.[2] Glaucoma is most commonly found among women (59%) and Asian races (49%).[2] Primary open angle glaucoma (POAG) is the most common form of glaucoma and caused by trabecular blockage that inhibits aqueous humor excretion and increases intraocular pressure (IOP).[3] Increased intraocular pressure (IOP) remains as major risk factor for developing glaucoma. Pharmacological therapy as the first-line treatment is directed towards maintaining the IOP at normal level to preserve vision.[3-5]

Beside vision loss, some of glaucoma patients will also experience dry eye. Erb *et al*.[6] reported that 52.6% of glaucoma patients also experienced dry eye. Another study by Schmier *et al.*[7] concluded that dry eye was more common in glaucoma patients (16.5%) than in non-glaucoma patients (5.6%). There are several factors predicted to be accountable for the concurrence. First, glaucoma and dry eye appear to have shared risk factors that are women and old age. Second, long term use of eye drops with preservatives in glaucoma patients can disrupt tear production resulting in dry eye.[6] Pisella *et al.*[8] stated that dry eye symptoms are more frequently found in glaucoma patients treated with benzalkonium chloride (BAC)-containing eye drops.

The co-existence of glaucoma and dry eye will negatively influence treatment and the course of disease. Dry eye symptoms will cause discomfort and lower patients' compliance, thus reducing the effectiveness of therapy. Long-term exposure to preservatives in the eye drops is also known to cause sustained inflammation and decreased success rate of glaucoma surgery.[8] Therefore, it is important to diagnose and treat dry eye to improve adherence and success rate of glaucoma therapy. In this review, we will address glaucoma treatment, dry eye and the pathophysiology, and treatment of dry eye in glaucoma patients.

Glaucoma Treatment

According to the European Glaucoma Society (EGS) guideline, the first line treatment for lowering IOP in glaucoma is pharmacological therapy. There are two primary mechanisms for lowering the IOP. The first is by decreasing the production of aqueous humor with beta blockers (timolol, betaxolol, carteolol, metipranolol) and carbonic anhidrase inhibitors (brinzolamide, dorzolamide). The second is by increasing aqueous humor excretion through the trabecular and uveoscleral

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pathways using prostaglandin derivatives (latanoprost, travoprost, tafluprost), sympathomimetic and cholinergic/parasympathomimetic drugs (pilocarpine).[5]

Most eye drops for glaucoma therapy contain preservatives in their formulation to prevent microbial contamination and to maintain the active ingredients so that they will withstand changes for a longer period of time.[8,9] Recent research showed that the use of preservatives, particularly BAC, is associated with greater side effects. The most frequent side effect is dry eye due to long-term exposure to the preservative.[7,8]

Dry Eye

The international Dry Eye Workshop 2007 defines dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[7,10,11]

Two main causes of dry eye are deficiency of aqueous component in tear film (aqueous tear-deficient dry eye/ADDE) and excessive evaporation (evaporative dry eye/EDE) that involves tear hyperosmolarity and tear instability.[12] Aqueous tear-deficient dry eye is caused by failure of lacrimal gland in producing tears. Damage in the acinus or dysfunction of the lacrimal gland will result in reduced tear secretion and tear volume. Although the evaporation rates from the ocular surface occurs at normal rates, tear hyperosmolarity occurs because its production is reduced. Tear hyperosmolarity will lead into ocular surface inflammation through activation of inflammation cascade involving mitogen-activated protein (MAP) kinase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway and release of inflammatory mediators such as interleukin (IL) 1α and 1β, tumor necrosis factor (TNF)-α, and matrix metalloproteinase (MMP)-9. Inflammation will lead to apoptosis of epithelial cells, reduction of goblet cells and disturbance in mucin expression; all of which will result in tear instability. Tear instability will deteriorate hyperosmolarity state and trigger activation of more inflammatory cascades.[10,13] Evaporative dry eye develops as a result of excessive tear evaporation from the ocular surface without abnormality in lacrimal gland function. Excessive tear evaporation also results in tear hyperosmolarity that promotes a series of inflammatory process as mentioned above.[10,13]

The pathophysiology of dry eye in glaucoma patients

The IOP, ocular perfusion and tear production are regulated by autonomic nervous system. Dysfunction of the autonomic nervous system results in disturbance of IOP and basal tear production.[14] Kuppens *et al.*[15] reported that ADDE is the probable mechanism underlying the decreased basal tear production in glaucoma. It is also reported that there is lower basal tear turnover rate in patients with primary open angle glaucoma (POAG) receiving no therapy, that is 22% and 27% lower compared to patients with ocular hypertension and healthy patients, respectively.[15]

Old age and women are identified as the shared risk factors of glaucoma (particularly POAG) and dry eye. In normal population, aging leads to pathological changes of lacrimal duct such as periductal fibrosis, interacinar fibrosis, loss of paraductal blood vessel and acinar cell atrophy. Those pathological changes account for disturbance in tear dynamics and is a primary disease referred as age-related dry eye (ARDE).[10] Decreased tear production usually occurs in accordance with increased age, particularly after entering the sixth decade.[11]

Women, specifically those entering postmenopausal period, are at higher risk for developing both glaucoma and dry eye due to hormonal changes. Primary open angle glaucoma is the most common type of glaucoma found in postmenopausal women, especially among those entering the postmenopausal period at earlier age.[16-18] Low level of 17β-estradiol, a form of estrogen hormone, results in reduced level activity of nitric oxide (NO) synthase III enzyme and NO level in the endothelial cells. As the consequences, the relaxation of trabecular meshwork is prevented and IOP escalates.[17] Progesterone is known for its antagonist action on glucocorticoid, a hormone that is capable of increasing IOP. Both progesterone and glucocorticoid receptors are found in trabecular meshwork. Low progesterone level will reduce its receptor-binding competition with glucocorticoid in trabecular meshwork and increase IOP.[17]

Androgen regulates Meibomian gland function and influences the structure as well as function of the lacrimal gland. Androgen deficiency in elderly (both men and women) and postmenopausal women is responsible for Meibomian gland dysfunction and EDE.[7,12] Sex hormones also regulate the number of conjunctival goblet cells, as indicated by a study showing that oral contraception user has more conjunctival goblet cells.[7] However, the benefit of hormone replacement therapy is still questionable because the use of estrogen alone is also associated with an increased risk for dry eye.[12]

Another problem faced by glaucoma patients is the long-term use of multiple topical medications that mostly contain BAC. Long term exposure to BAC induces toxic response on the ocular surface, proinflammatory and

proapoptotic effects to conjunctival cells, conjunctival inflammation, and mucus cells damage. Damage of epithelial cells also occurs thus result in epithelial punctata keratitis, which disturbs the wetting of ocular surface.[10,19-22] Xiong *et al.*[9] reported that there was a significant reduction of Schirmer Score that represents decrease in tear production, goblet cells number, and goblet cell-specific mucin-5subtype AC (MUC5AC) on rabbit eyes instilled with eye drops preserved with BAC.

Other disadvantages of topical medication usage for more than three years are inferior fornix shortening as a result of conjunctival fibrosis along with increased number of subepithelial fibroblast, macrophage, lymphocyte, and mast cell.[22,23] Herschler *et al*.[24] stated that prolonged use of eye drops may alter fibroblast inhibition properties of aqueous humor.[22,24] Benzalkonium chloride exposure is also related with increased incidence of stromal corneal edema.[25] Benzalkonium chloride is claimed to be capable of causing hyperpermeability and cell death in concentration as low as 0.0001%. It can induce cell apoptosis in lower concentration, while in higher concentration it can lead to cell necrosis.[26] Benzalkonium chloride is a quaternary ammonium with detergent properties that can modify the lipid phase in tear film.[19] Many studies showed that the use of preservative-free eye drops increased the stability of tear film, reduced epithelial permeability, and prevented corneal stromal damage.[25]

Treatment of dry eye in glaucoma patients

One treatment strategy for treating dry eye in glaucoma patients is by avoiding the use of BAC-containing topical medication. Horsley et al.[27] reported improvement of tear break-up time (TBUT), a method to determine the stability of the tear film, after patients were converted to BAC-free prostaglandin eye drops. The mean occurrence of corneal staining and ocular surface disease index (OSDI) were also reduced.[27] OSDI is a survey that consists of 12 questions to document the symptoms of dry eye and follow their progression. Henry et al.[28] reported OSDI reduction, hyperemia improvement, and better IOP control among glaucoma patients receiving preservative-free prostaglandin eye drop.

When BAC exposure is inevitable, it is advisable to maintain the dose of BAC-preserved eye drop at minimal yet effective level. The strategy can be done by using eye drop with lower concentration of BAC or administrating combination therapy between BAC-containing and preservative-free eye drops to lower BAC exposure. However, the combination strategy can not always be applied to all patients. Some patients need only single regimen of eye drop at a dose higher than dose provided by available combination regimen.[29] Artificial tear may also be considered as an eligible alternative. Artificial tear can significantly improve reliability and visual field index of glaucoma patients undergoing visual field examination.[30]

Another option is surgery. Surgery may provide a good solution since it is able to reduce or even eliminate the need of topical anti-glaucoma medication. Surgical procedures, such as laser trabeculoplasty can be used as monotherapy or as additional therapy to topical medication, especially for glaucoma patients with pigment dispersion syndrome or pseudoexfoliation. Trabeculectomy or shunt installment may serve as alternative procedures that are able to lower IOP without further BAC exposure. However, the risk of developing infection after surgery limits the benefit of surgical procedures. The decision of whether to conduct surgical procedures or not should be based on careful consideration regarding risk-benefit ratio.[29]

In conclusion, some glaucoma patients also experience dry eye, which can be resulted from the use of BAC-containing topical medication.

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