The Ocular Surface 15 (2017) 511–538

Contents lists available at ScienceDirect

The Ocular Surface

journal homepage: www.theocularsurface.com

TFOS DEWS II iatrogenic report

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ARTICLE INFO

Article history:
Received 29 April 2017
Accepted 2 May 2017

Keywords:
Contact lens
Cosmetic
Drug related adverse reactions
Drug related side effects
Drug toxicity
Dry eye
Iatrogenic disease
Surgery

ABSTRACT

Dry eye can be caused by a variety of iatrogenic interventions. The increasing number of patients looking for eye care or cosmetic procedures involving the eyes, together with a better understanding of the pathophysiological mechanisms of dry eye disease (DED), have led to the need for a specific report about iatrogenic dry eye within the TFOS DEWS II.

Topical medications can cause DED due to their allergic, toxic and immuno-inflammatory effects on the ocular surface. Preservatives, such as benzalkonium chloride, may further aggravate DED. A variety of systemic drugs can also induce DED secondary to multiple mechanisms. Moreover, the use of contact lens induces or is associated with DED. However, one of the most emblematic situations is DED caused by surgical procedures such as corneal refractive surgery as in laser-assisted in situ keratomileusis (LASIK) and keratoplasty due to mechanisms intrinsic to the procedure (i.e. corneal nerve cutting) or even by the use of postoperative topical drugs. Cataract surgery, lid surgeries, botulinum toxin application and cosmetic procedures are also considered risk factors to iatrogenic DED, which can cause patient dissatisfaction, visual disturbance and poor surgical outcomes.

This report also presents future directions to address iatrogenic DED, including the need for more in-depth epidemiological studies about the risk factors, development of less toxic medications and preservatives, as well as new techniques for less invasive eye surgeries. Novel research into detection of early dry eye prior to surgeries, efforts to establish appropriate therapeutics and a greater attempt to regulate and oversee medications, preservatives and procedures should be considered.

1. Introduction

Iatrogenic disease is defined as an adverse clinical condition resulting from medical treatment by a health professional. The

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http://dx.doi.org/10.1016/j.jtos.2017.05.004
1542-0124/

word iatrogenic is derived from Greek *iatros,* physician, *genein*, to produce. Iatrogenic disease is thus a condition caused by the commission, rather than the omission, of treatment. It affects a large number of patients worldwide in all areas of medicine [1].

Dry eye can be caused by a variety of iatrogenic interventions, including topical or systemic drugs, the use of contact lenses, and ophthalmic surgical and non-surgical procedures. Recognized as important causes of dry eye disease (DED), these iatrogenic factors were addressed in the 2007 Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) Definition and Classification subcommittee report [2].

The ever-increasing number of patients undergoing ophthalmic (and non-ophthalmic) procedures, together with a better understanding of the pathophysiological mechanisms of DED, have highlighted the need for a deeper analysis of iatrogenic dry eye, and thus, TFOS DEWS II has a dedicated report on this topic [3].

In addition to providing updated scientific information regarding iatrogenic dry eye, the TFOS DEWS II report aims to increase awareness in the medical and non-medical communities with regard to preventing, or at least decreasing, the effects of iatrogenic dry eye on the ocular surface, vision, and quality of life of our DED patients.

2. Goals of the TFOS DEWS II iatrogenic subcommittee

The goals of the TFOS DEWS II Iatrogenic Dry Eye Subcommittee were to: 1) define iatrogenic dry eye; 2) identify the most important iatrogenic mechanisms of dry eye and propose an etiological classification; 3) present an updated epidemiological analysis and a comprehensive and evidence-based review of each type of iatrogenic dry eye; 4) discuss prophylaxis and recommendations for management; and 5) propose areas for future research.

3. Classification of iatrogenic dry eye

Iatrogenic dry eye can be classified as shown in Table 1.

Table 1
Classification of iatrogenic dry eye.

- I. Drug-induced
  - A. Systemic
  - B. Topical
- II. Contact lens-induced
- III. Ophthalmic surgery
  - A. Refractive surgery
  - B. Keratoplasty (PK, LK and EK)
  - C. Cataract surgery
  - D. Lid surgery
  - E. Other surgeries
    - 1. Conjunctival surgery
    - 2. Glaucoma surgery
    - 3. Vitreoretinal surgery
    - 4. Strabismus surgery
    - 5. Intrastromal corneal ring segment implantation
    - 6. Others
- IV. Non-surgical ophthalmic procedures
  - A. Botulinum toxin
  - B. Crosslinking (CXL)
  - C. Cosmetic procedures
  - D. Others
- V. Non-ophthalmic conditions
  - A. Graft-versus-host disease (GVHD)
  - B. Others

PK, penetrating keratoplasty; LK, lamellar keratoplasty; EK, endothelial keratoplasty.

4. Major causes of iatrogenic dry eye

4.1. Systemic drug-induced DED

4.1.1. Incidence and prevalence

Among the top 100 best-selling systemic drugs in the US in 2009, 22 of them possibly cause dry eye [4]. Of the 9 systemic drugs known to be secreted into the tear film, 8 have been associated with causing dry eye [4]. Most of the studies available on systemic drug-induced DED analyze only the classes of drugs, but not individual prescription drugs [4]. Overall, systemic drugs may cause dry eye secondary to decreased tear production, altered nerve input and reflex secretion, inflammatory effects on secretory glands, or direct irritation effects through secretion into the tears [5]. However, not every drug does actually reach the ocular surface structures. Rather certain drug properties and kinetics play a role in determining which drugs penetrate intraocularly, namely, lipid solubility, molecular weight, ionic state, plasma protein binding and total blood concentration [6].

Schein et al. attributed 62% of DED cases in the elderly to systemic drying medications, including nonsteroidal anti-inflammatory drugs (NSAIDs; odds ratio [OR] 1.30), diuretics (OR 1.25), vasodilators (OR 1.37), analgesics/antipyretics (OR 1.28), antiulcer agents (OR 1.44), sulfonylureas (OR 1.3), cardiac glycosides (OR 1.28), anxiolytics/benzodiazepines (OR 2.35), anti-infectives (OR 1.88), antidepressants/antipsychotics (OR 2.54), hypotensive agents (OR 1.98), and antihistamines (OR 1.67) [7].

The Beaver Dam population-based, age-adjusted, cumulative 10-year dry eye study in 3722 subjects recognized the use of systemic antihistamines and diuretics as risk factors for DED [8]. The Beaver Dam Offspring Study analyzing the prevalence of dry eye in 3275 individuals included inhaled steroid use as an additional risk factor (OR 2.04) [9]. Systemic hormones were associated with a 71% increase in the likelihood of dry eye symptoms in women under the age of 50 years (OR 1.71), as well as multivitamin use (OR 1.43) [9]. In all subjects 50 years and older, the use of benzodiazepines was also associated with dry eye (OR 2.25) [9]. Hormone replacement therapy, especially estrogen use alone (OR 1.69), was added as a risk factor for DED by the Women's Health Study, which analyzed over 25,000 postmenopausal women [10]. The Extension Blue Mountains Eye Study, which included 1174 participants aged 50 or older in Australia, confirmed corticosteroids (OR 1.6), antidepressants (OR 1.7), and hormone replacement therapy (OR 1.6) as risk factors for DED in the elderly [11]. In 25,444 US men aged 50 years and older, antidepressants (OR 1.90), antihypertensives (OR 1.15), and medications used to treat benign prostatic hyperplasia (OR 1.35) were associated with an increased risk of DED [12]. A small case-control study in male subjects taking anti-androgen therapy for prostatic disorders confirmed its added risk for the development of MGD-associated DED [13].

In the National U.S. Veterans Affairs Administration database, which includes over 2 million patients, the use of antidepressant medications (OR 1.97) and antianxiety medications (OR 1.74) was associated with an increased risk of DED [14]. The use of systemic beta-blockers was associated with worsening of dry eye in nearly 800 participants of the Women's and Physicians Health studies [15].

The systemic drugs identified by large epidemiological studies as increasing the risk for DED together with their associated ORs are listed in Table 2.

4.1.2. Systemic drugs with a known or suspected link to dry eye symptoms

The list of systemic drugs with a known or suspected link to dry eye symptoms is quite extensive. Table 3 presents a compilation of known or suspected systemic agents that have been reported to induce or exacerbate dry eye. Among other sources, this listing of drugs has been compiled from a series of extensive reviews [17–23], epidemiological studies and the key database from Fraunfelder and